CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210251Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA 210251 Uni-Review

Application Type	NDA
Application Number(s)	210251
Priority or Standard	Priority
Submit Date(s)	June 10, 2017
Received Date(s)	June 12, 2017
PDUFA Goal Date	February 12, 2018
Division/Office	DAVP/OAP
Review Completion Date	February 6, 2018
Established Name	Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) Fixed-Dose Combination
(Proposed) Trade Name	BIKTARVY®
Pharmacologic Class	Bictegravir is an integrase strand-transfer inhibitor (INSTI), emtricitabine and tenofovir alafenamide are nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)
Applicant	Gilead Sciences
Formulation(s)	FDC Tablet
Dosing Regimen	Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.
Recommendation on Regulatory Action	Approval

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPV= Division of Pharmacovigilance
DRISK=Division of Risk Management

Glossary

3TC	lamivudine
ABC	abacavir
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse reaction
AE	adverse event
ART	antiretroviral therapy
ARV	antiretroviral
BIC	bictegravir
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
BIC/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CC_{50}	50% cytotoxic concentration
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CPE	cytopathic effect
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
ddI	didanosine
DMC	data monitoring committee
DRV	darunavir
DTG	dolutegravir
ECG	electrocardiogram
eCTD	electronic common technical document
$eGFR_{CG}$	estimated glomerular filtration rate by Cockcroft-Gault
EC_{50}	effective concentration inhibiting viral replication by 50%
EOP2	End of Phase 2
EVG	elvitegravir
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	Fixed-Dose Combination
FTC	emtricitabine

GCP	good clinical practice
GRMP	good review management practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
ICH	International Conference on Harmonization
IN	HIV-1 integrase
IND	Investigational New Drug
INSTI	HIV-1 integrase strand transfer inhibitor
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LTR	HIV-1 long terminal repeat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MOI	multiplicity of infection
NDA	new drug application
NME	new molecular entity
NNRTI	HIV-1 non-nucleoside reverse transcriptase inhibitor
NRTI	HIV-1 nucleos(t)ide reverse transcriptase inhibitor
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBMC	peripheral blood mononuclear cell
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PI	HIV-1 protease inhibitor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	HIV-1 protease
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
RT	HIV-1 reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SBR	Stay on Baseline Regimen
SOC	Body System Organ Class

TAF	tenofovir alafenamide
TAM	thymidine analogue-associated mutation
TEAE	treatment emergent adverse event
TEADR	treatment emergent adverse reaction
TFV	tenofovir

1 Executive Summary – Division and Office Level Concurrence

This NDA for bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) fixed- dose combination tablets for oral use is submitted by Gilead Sciences. B/F/TAF includes bictegravir, a new integrase strand transfer inhibitor and emtricitabine and tenofovir alafenamide, previous approved nucleos(t)ide reverse transcriptase inhibitors. This NDA has been reviewed by the multi-disciplinary review team. Each discipline has recommended approval of this NDA, and we concur with those recommendations. B/F/TAF tablets will be approved as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of B/F/TAF.

The applicant has submitted four adequate and well-controlled trials that provide substantial evidence of efficacy for the indication approved. B/F/TAF is safe for its intended use with an adverse event profile similar to other drug products in the integrase strand transfer inhibitor class or containing F/TAF. We concur that identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance. The overall Benefit Risk is favorable. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Uni-Review document, the Quality Assessment Review, and the Benefit Risk Summary.

1.1. Product Introduction

The Applicant, Gilead Sciences, submitted NDA 210251 for BIKTARVY, a fixed dose combination (FDC) tablet intended to provide a complete treatment regimen for HIV-1 infection dosed once daily. BIKTARVY contains bictegravir (BIC), an integrase strand transfer inhibitor of human immunodeficiency virus type-1 (HIV-1), emtricitabine (FTC) and tenofovir alafenamide (TAF), two approved HIV-1 nucleos(t)ide reverse transcriptase inhibitors (NRTIs). Of the three component drugs, only bictegravir has not been previously approved either alone or in combination with other antiretrovirals.

Bictegravir inhibits viral replication by blocking the integrase enzyme responsible for insertion of viral genome into host cell DNA. Raltegravir, elvitegravir, and dolutegravir are three other integrase strand transfer inhibitors (INSTIs) currently marketed for HIV-1 treatment. Bictegravir, a new molecular entity, will be the fourth INSTI added to this mechanistic class.

Bictegravir will not be manufactured by itself, but rather as a fixed dose combination (FDC) with emtricitabine and tenofovir alafenamide, both nucleos(t)ide analogues.

Established name:	Bictegravir (GS-9883)
NDA Classification Code:	New molecular entity (Type 1, 4)
Pharmacologic Class:	Integrase strand transfer inhibitor
Fixed Dose Combination:	Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF)
Trade Name:	BIKTARVY®
Proposed Indication:	Treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.
Dosage Form:	50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide
Dosage and Regimen:	One tablet taken orally once daily with or without food

1.2. Conclusions on the Substantial Evidence of Effectiveness

Forty-eight-week data from the two adequate and well-controlled Phase 3 trials, 1489 and 1490, included in this application provide substantial evidence of effectiveness to support approval of B/F/TAF for treatment of HIV-1 infection in adults as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history. The efficacy of B/F/TAF was demonstrated in Trials 1489 (NCT02607930) and 1490 (NCT02607956), both 48 week, blinded, randomized active-controlled, non-inferiority trials in HIV-1 infected treatment naïve subjects. In Trial 1489, the proportion of subjects with HIV RNA <50 copies at Week 48 was 92.4% in the B/F/TAF treatment group and 93% in the abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) group [adjusted treatment difference and 95% CI: -0.6% (-4.8%, 3.6%)]. In Trial 1490, the proportion of subjects with HIV RNA <50 copies at Week 48 was 89.4% in the B/F/TAF treatment group and 92.9% in the dolutegravir/emtricitabine/tenofovir alafenamide (DTG/F/TAF) group [adjusted treatment difference and 95% CI: -3.5% (-7.9%, 1.0%)]. The lower bound of 2-sided 95.002% CI of the rate difference (B/F/TAF – active-control) was -4.8% in Trial 1489 and -7.9% in Trial 1490, which is

greater than -12%, the pre-specified non-inferiority (NI) margin. Therefore, B/F/TAF demonstrated non-inferiority to the active-control regimens, ABC/DTG/3TC in Trial 1489 and DTG/F/TAF in Trial 1490.

Forty eight week data from the two additional adequate and well-controlled Phase 3 trials, 1844 and 1878, included in this application provide substantial evidence of effectiveness as required by law 21 CFR 314.126(a)(b) to support approval of B/F/TAF for treatment of HIV-1 infection in adults as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of B/F/TAF. The efficacy of B/F/TAF was demonstrated at 48 weeks in two trials in virologically suppressed HIV-1 infected subjects, Trials 1844 (NCT0260312) and 1878 (NCT02603107). Trial 1844 is a blinded, randomized active-controlled, non-inferiority trial; Trial 1878 is an open-labelled, randomized active controlled, non-inferiority trial. In Trial 1844, the proportion of subjects with HIV RNA ≥ 50 copies/ml at Week 48 were 1.1% in the B/F/TAF treatment group and 0.4% in the abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) group [adjusted treatment difference and 95% CI: 0.7% (-1.0%, 2.8%)]. In Trial 1878, the proportion of subjects with HIV RNA ≥ 50 copies/ml at Week 48 were 1.7% in the B/F/TAF treatment group and 1.7% in the Stay on Baseline Regimen (SBR) group [adjusted treatment difference and 95% CI: 0.0% (-2.5%, 2.5%)]. In Trials 1844 and 1878, the upper bounds of 2-sided 95% CI of the rate difference (B/F/TAF – active-control) based on HIV-1 RNA ≥50 copies/mL at Week 48 were 2.8% and 2.5%, respectively, which is less than 4%, the pre-specified NI margin. Therefore, B/F/TAF is non-inferior to the active-control regimens, ABC/DTG/3TC in Trial 1844 and boosted ATV- or boosted DRV- based regimens in Trial 1878.

The most common adverse reactions occurring in five percent or greater of treatment-naïve subjects on B/F/TAF were diarrhea, nausea and headache; the safety findings were similar in subjects who were virologically- suppressed at baseline. The safety profile of B/F/TAF is acceptable for the intended populations and supportive of a favorable benefit-risk profile for the indication. All disciplines were in agreement with the approval of B/F/TAF and no outstanding issues were identified that would preclude approval. In summary, B/F/TAF for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of B/F/TAF, demonstrates a favorable benefit-risk profile with acceptable evidence to recommend approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Bictegravir inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. This new drug, bictegravir, will be co-formulated in a fixed dose combination (FDC) pill with emtricitabine and tenofovir alafenamide, two approved nucleos(t)ide reverse transcriptase inhibitors (NRTIs) of the HIV-1 virus.

As reported by the CDC, the estimated incidence of new HIV-1 diagnoses in the US in 2016 was 39,782 among adults and children.[1] The goal of HIV treatment is to durably suppress plasma HIV RNA, preserve and restore the immune system, and reduce HIV-associated morbidity. INSTIs in combination with two NRTIs have become a preferred component of HIV treatment as recommended by the HIV treatment guidelines.[2]

Two on-going randomized, active-controlled, Phase 3 trials, Trials 1489 and 1490, were conducted in HIV-1 treatment naïve subjects with 48-week data were presented for this NDA application. Efficacy rates were comparable in the treatment arms. In Trial 1489, the proportion of subjects with HIV RNA <50 copies at Week 48 were 92.4% in the B/F/TAF treatment group and 93% in the abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) group. In Trial 1490, the proportion of subjects with HIV RNA <50 copies/ml at Week 48 were 89.4% in the B/F/TAF treatment group and 92.9% in the dolutegravir/emtricitabine/tenofovir alafenamide (DTG/F/TAF) group. The lower bound of 2-sided 95.002% CI of the rate difference (B/F/TAF – active-control) was -4.8% in Trial 1489 and -7.9% in Trial 1490, which is greater than -12%, the pre-specified non-inferiority (NI) margin. Therefore, B/F/TAF demonstrated non-inferiority to the active-control regimens, ABC/DTG/3TC in Trial 1489 and DTG/F/TAF in Trial 1490.

Two on-going randomized, Phase 3 trials, Trials 1844 and 1878, were conducted in HIV-1 adults to evaluate replacing the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of B/F/TAF. Trial 1844 is a blinded, randomized active-controlled, non-inferiority trial; Trial 1878 is an open-labelled, randomized active controlled, non-inferiority trial. In Trial 1844, the proportion of subjects with HIV RNA ≥ 50 copies/ml at Week 48 were 1.1% in the B/F/TAF treatment group and 0.4% in the abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) group. In Trial 1878, the proportion of subjects with HIV RNA ≥ 50 copies at Week 48 were 1.7% in the B/F/TAF treatment group and 1.7% in the Stay on Baseline Regimen (SBR) group. In Trials 1844 and 1878, the upper bounds of 2-sided 95% CI of the rate difference (B/F/TAF – active-control) based on HIV-1 RNA ≥50 copies/mL at Week 48 were 2.8% and 2.5%, respectively, which is less than 4%, the pre-specified NI margin. Therefore, B/F/TAF is non-inferior to the active-control regimens, ABC/DTG/3TC

in Trial 1844 and boosted ATV- or boosted DRV- based regimens in Trial 1878.

The safety data submitted with this NDA application demonstrate a favorable safety profile. Generally, subjects tolerated B/F/TAF well, with a discontinuation rate due to adverse events of 1-2%. The adverse reactions that occurred in at least two percent of the pooled naïve treatment groups on B/F/TAF included nausea, headache, fatigue, dizziness, and insomnia. Other important risks including vomiting, flatulence, dyspepsia, abdominal pain, rash, depression, suicide ideation, suicide attempt, and depression suicide, occurred in fewer than two percent of subjects, and in some cases, resulted in study drug discontinuation. The safety profile was similar in the virologically suppressed population; however, the incidence of these adverse reactions was generally lower.

In conclusion, approval of B/F/TAF, as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components is fully supported by available evidence and analysis of efficacy and safety.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The estimated incidence of new HIV-1 diagnoses in the US in 2016 was 39,782 among adults and children.[1] • The goal of HIV treatment is to durably sustain plasma HIV RNA suppression, preserve and restore the immune system, and reduce HIV-associated morbidity.	If untreated, HIV is a life-threatening condition, one that affects a large population. Potential consequences of untreated HIV are morbidity and mortality. HIV infection is a significant public health concern.
Current Treatment Options	• INSTIs in combination with two NRTIs have become a preferred component of HIV treatment as recommended by the DHHS guidelines. • HIV therapy is often lifelong. • FDCs are convenient options for treatment. • TAF and TDF are prodrugs of Tenofovir (TFV). TAF results in a lower serum exposure of TFV.	The HIV treatment armamentarium would benefit from another unboosted INSTI option that may mitigate treatment side effects. The HIV treatment armamentarium would

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Two NRTIs, TDF and Abacavir, in current FDC HIV treatment options are associated with treatment limiting adverse reactions.	benefit from different NRTI options in FDC that may mitigate treatment side effects.
Benefit	• The efficacy in HIV-1 treatment naïve subjects was established in two Phase 3 clinical trials for HIV treatment naïve subjects with a total of 634 subjects with 48-week data presented. Overall, 89-92% of subjects who took B/F/TAF had undetectable HIV-1 viral load at Week 48. • The efficacy in HIV-1 virologically suppressed subjects was established in two Phase 3 clinical trials for HIV treatment naïve subjects with a total of 572 subjects with 48-week data presented. Overall, less than two percent of subjects experienced virologic failure on B/F/TAF at Week 48. • Trial 1490 enrolled subjects with an estimated glomerular filtration rate by Cockcroft Gault ($eGFR_{CG}$) ≥ 30 mL/min because both B/F/TAF and DTG + F/TAF, the comparator, do not require dose adjustment down to an $eGFR_{CG}$ of 30 mL/min. • Select INSTIs can have a high genetic barrier to resistance. • Bictegravir does not require pharmacokinetic enhancement (boosting) with a CYP3A inhibitor	B/F/TAF was non-inferior to ABC/DTG/3TC and DTG+F/TAF in HIV-1 treatment naïve adults at 48 weeks. B/F/TAF was non-inferior to ABC/DTG/3TC and SBR (which was a boosted protease inhibitor regimen) at 48 weeks. If approved, B/F/TAF will provide another unboosted INSTI FDC treatment option, in addition to ABC/DTG/3TC. Less drug interactions are expected with unboosted regimens. B/F/TAF provides an unboosted INSTI FDC option for patients with $eGFR_{CG}$ of ≥ 30 mL/min. The currently approved unboosted INSTI FDC option, ABC/DTG/3TC, is limited to HIV patients with $eGFR_{CG}$ of ≥ 50 mL/min. Minimal resistance to bictegravir and B/F/TAF was observed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety data submitted with this NDA demonstrate a favorable safety profile. The adverse drug reactions (ADRs) that occurred in at least two percent of subjects on B/F/TAF in the pooled treatment naïve trials include nausea, headache, fatigue, dizziness, and insomnia. Other important risks that were treatment limiting and occurred in less than two percent of subjects include vomiting, flatulence, dyspepsia, abdominal pain, rash, depression, suicide ideation, suicide attempt, and depression suicide. The safety profile of B/F/TAF was similar in the virologically suppressed population; however, the incidence of the ADRs was generally lower in the virologically suppressed population compared to the treatment-naïve population. • Grade 3 or 4 elevations of amylase, AST, creatine kinase, neutrophils and LDL-cholesterol in the treatment naïve population occurred in a similar number of subjects across treatment arms. • Grade 1 or 2 elevation in bilirubin occurred in 12% of subjects in the pooled naïve trials and less frequently in the virologically suppressed population.	Generally, B/F/TAF is safe and well tolerated.
Risk Management	• Because TAF and TDF are both prodrugs of TFV, the TAF prescribing information will include safety information contained in the current TDF label: o Though no cases of new or worsening renal impairment occurred in the Phase 3 trials, Section 5 of the B/F/TAF label will include a warning regarding new and worsening renal impairment consistent with other TAF containing products. • Section 5 will also include a warning for lactic acidosis/severe hepatomegaly with steatosis per class labeling with NRTIs.	Safety considerations can be adequately described in the label. No risk management beyond standard pharmacovigilance is warranted based on this review.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Boxed Warning and Section 5 will include a warning regarding severe acute exacerbation of hepatitis B in patients who have discontinued B/F/TAF (due to anti-HBV activity of F/TAF).	

2 Therapeutic Context

2.1. Analysis of Condition

The World Health Organization (WHO) states approximately 37 million people were living with HIV globally in 2016.[3] In the United States, at the end of 2015, an estimated 1.1 million persons aged 13 or older were living with HIV infection, including an estimated 162,500 persons whose infections had not been diagnosed.[4] Additionally, as reported by the Centers for Disease Control (CDC), the number of new HIV-1 infections in the US in 2016 was 39,782 among adults and children.[1] Currently, antiretroviral therapy (ART) for treatment of HIV-1 infection in treatment-naïve or treatment-experienced patients, without history of virologic failure, is generally comprised of a combination with at least three antiretroviral (ARV) medications, two of which belong in the nucleos(t)ide reverse transcriptase inhibitor (NRTI) class. The third agent is selected from non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), or integrase strand transfer inhibitors (INSTI) classes.

The goal of HIV treatment is to durably suppress HIV viral load, preserve and restore the immune system, and reduce HIV-associated morbidity. ART has provided HIV-infected patients with improved long-term survival. Effective viral load suppression can also provide the public health benefit of decreased HIV transmission.

Treatment of HIV infection has dramatically improved since the mid-1990s, after the introduction of the use of highly active antiretroviral therapy. Despite such progress, the need continues for development of new ARV drug products, new fixed dose combination (FDC) products, and new regimens because of the ongoing epidemic in parts of the world. A need for better tolerated regimens also exists. The introduction of FDC drug products has allowed for simpler ARV regimens, increasing the likelihood of adherence and thereby improving treatment outcomes. Availability of new regimens such as complete three drug regimen FDCs have also allowed patients to switch if they are not tolerating their current regimens or have 'pill fatigue' from multiple pill regimens. For example, a publication by the Antiretroviral Therapy Cohort Collaboration (2013) finds among the 21,000+ patients in a European and North American cohort who are on their first combination antiretroviral therapy (cART) regimen, more than half modified or interrupted their first cART regimen because of either adverse events or toxicities of cART, desire for simplification of the regimen, or due to patient choice.[4] These observations suggest a need for continued development of new products and/or regimens. Complete regimen FDCs may be convenient for patients with HIV/AIDS.

The Department of Health and Human Resources Guidelines for the Use of Antiretroviral Agents in Adults and Adolescent Living with HIV state that integrase strand transfer inhibitors (INSTIs) plus 2-NRTIs are a preferred ART regimen for initial therapy based on durable virologic

efficacy, favorable tolerability and toxicity profiles, and ease of use (Guidelines for the Use of Antiretroviral Agents in Adults and Adolescent Living with HIV, Table 6).[5] B/F/TAF will provide another once daily FDC complete HIV-1 treatment regimen that fulfills the INSTI plus 2-NRTIs preferred ART regimen by the DHHS guidelines.

2.2. Analysis of Current Treatment Options

Excluding fixed drug combinations (FDC) or different formulations, 28 drugs are approved for the treatment of HIV-1 infection. Standard of care involves the administration of multiple drugs targeting different events in the viral life cycle. Based on the mechanism of action on the life cycle of HIV-1, the drugs are classified into six mechanistic drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 inhibitors, and integrase strand transfer inhibitors (INSTI). Table 1 below summarizes the approved antiretroviral drugs. Cobicistat (co) is available as a pharmacokinetic booster that increases exposure of protease inhibitors and elvitegravir, an INSTI.

Table 1: Currently Approved ARV Drugs for the Treatment of HIV Infection

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx EC®
	Zalcitabine (ddC)	Hivid®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Tenofovir disoproxil fumarate (TDF)	Viread®
	Tenofovir alafenamide (TAF)[1]	
	Emtricitabine (FTC)	Emtriva®
NNRTI	Nevirapine (NVP)	Viramune®
	Efavirenz (EFV)	Sustiva®
	Etravirine (ETR)	Intelence®
	Rilpivirine (RPV)	Edurant®
Protease Inhibitor	Indinavir (IDV)	Crixivan®
	Nelfinavir	Viracept®
	Saquinavir, (hard gel, soft gel)	Invirase®, Fortavase®
	Fosamprenavir (FPV)	Lexiva®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Atazanavir (ATV)	Reyataz®
	Darunavir (DRV)	Prezista®

	Tipranavir	Aptivus®
Integrase Inhibitor	Raltegravir (RAL)	Isentress®
	Elvitegravir[2]	
	Dolutegravir (DTG)	Tivicay®
CCR5 receptor antagonist	Maraviroc (MVC)	Selzentry®
Fusion/entry Inhibitor	Enfuvirtide (T-20)	Fuzeon®
Pharmacokinetic Enhancers[3]	Ritonavir (r)	Norvir®
	Cobicistat (co)[4]	

Source: Individual Product labeling
*Please refer to the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents for discussion on the safety and efficacy evidence considered for selecting preferred regimens in treatment-naïve patients and in patients who are virologically suppressed and are switching regimens
[1]TAF is approved for the treatment of HIV infection as part of FDC products - Descovy® (FTC/TAF), Odefsey® (FTC/RPV/TAF), and Genvoya® (elvitegravir/cobicistat/FTC/TAF). The single agent TAF (Vemlidy®) is indicted for the treatment of chronic Hepatitis B.
[2] Elvitegravir is approved as part of FDC product only- Stribild® (elvitegravir/cobicistat/FTC/TDF), Genvoya® (elvitegravir/cobicistat/FTC/TAF).
[3] Pharmacokinetic enhancers do not have direct antiviral activity
[4]Cobicistat is approved as part of FDC products- Genvoya®, Prezcobix® (darunavir/cobi) and Evotaz® (atazanavir/cobi)

Currently, three FDA approved INSTIs are available. Selected details of INSTI options are in Table 2 below.

Table 2: Approved INSTIs

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues
Raltegravir	Treatment of HIV-1	2007	bid or qd with new 2017 formulation	Rash, including Stevens-Johnson Syndrome Nausea Headache Diarrhea Pyrexia CPK elevation, muscle weakness, and rhabdomyolysis Insomnia Depression and suicidal ideation+
Elvitegravir	Treatment-experienced HIV-1; Use	2014*	qd	Nausea Diarrhea Depression and suicidal

	in combination with other drugs			ideation+
Dolutegravir	Treatment-naïve or treatment-experienced HIV-1	2013	qd for treatment naïve bid for selected integrase resistance	Hypersensitivity reactions (including rash) Insomnia Headache Depression and suicidal ideation+

Source: _Product labeling; qd = once daily, bid = twice daily

*2014 is year when approved as a new formulation standalone product, but approved as a component of the FDC Stribild earlier

+Rare; usually with pre-existing psychiatric conditions

FDCs with INSTIs are available and selected details are listed in the **Table 3** below.

Table 3: FDCs Containing INSTIs (All Dosed One Pill Once A Day)

Product (s) Name	Relevant Indication	Year of Approval	Important Safety and Tolerability Issues
Stribild®[1]	Treatment-naïve HIV-1; Virologically suppressed HIV-1	2012	Renal warnings for TDF Drug -Drug Interactions (DDI) from cobicistat
Triumeq®[2]	Treatment of HIV-1 infection	2014	Screen for HLA-B*5701 before therapy; Abacavir component is associated with possible increased cardiovascular risk
Genvoya®[3]	Treatment-naïve HIV-1; Virologically suppressed HIV-1	2015	Renal warnings for TAF DDI from cobicistat

1. Stribild® contains elvitegravir, cobicistat, TDF, and FTC
2. Triumeq® contains dolutegravir, ABC, and 3TC
3. Genvoya® contains elvitegravir, cobicistat, TAF, and FTC

Per the Department of Health and Human Services Guidelines for Use of Antiretroviral Agents in Adults and Adolescents Living with HIV the following is recommended, alternative and other antiretroviral options for treatment-naïve patients. [4]

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI + 2 NRTIs:

- DTG/ABC/3TC[a] **(AI)**—if HLA-B*5701 negative
- DTG + tenofovir[b]/FTC[a] (**AI** for both TAF/FTC and TDF/FTC)
- EVG/c/tenofovir[b]/FTC (**AI** for both TAF/FTC and TDF/FTC)
- RAL[c] + tenofovir[b]/FTC[a] (**AI** for TDF/FTC, **AII** for TAF/FTC)

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred

Boosted PI + 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) + tenofovir[b]/FTC[a] (**AI** for DRV/r and **AII** for DRV/c)
- (ATV/c or ATV/r) + tenofovir[b]/FTC[a] **(BI)**
- (DRV/c or DRV/r) + ABC/3TC[a] **—if HLA-B*5701–negative (BII)**
- (ATV/c or ATV/r) + ABC/3TC[a] **—if HLA-B*5701–negative and HIV RNA <100,000 copies/mL** (**CI** for ATV/r and **CIII** for ATV/c)

NNRTI + 2 NRTIs:

- EFV + tenofovir[b]/FTC[a] (**BI** for EFV/TDF/FTC and **BII** for EFV + TAF/FTC)
- RPV/tenofovir[b]/FTC[a] **(BI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**

INSTI + 2 NRTIs:

- RAL[c] + ABC/3TC[a] **(CII)—if HLA-B*5701–negative and HIV RNA < 100,000 copies/mL**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used:[d]

- DRV/r + RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**
- LPV/r + 3TC[a] (BID)[e] **(CI)**

Recommended Initial Regimens for Most People with HIV

[a] 3TC may be substituted for FTC, or vice versa, if a non–fixed-dose NRTI combination is desired.
[b] TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.
[c] RAL can be given as 400 mg BID or 1200 mg (two 600-mg tablets) once daily.
[d] Several other NRTI-limiting treatment strategies are under investigation. See the section titled Selected Strategies That Are Under Evaluation and Not Yet Recommended below for discussion regarding these regimens.
[e] LPV/r plus 3TC is the only boosted PI plus 3TC regimen with published 48-week data in a randomized controlled trial in ART-naive patients. Limitations of LPV/r plus 3TC include twice-daily dosing, high pill burden, and greater rates of gastrointestinal side effects than other PIs

Source: Department of Health and Human Services Guidelines for Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

If approved, the NME bictegravir, combined with F/TAF as a FDC formulation, will provide another option for a complete one tablet once daily treatment regimen for treatment of adults with HIV-1 infection. Because B/F/TAF is not boosted with cobiscistat, it has the advantage of less drug-drug interactions than Stribild or Genvoya®.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BIKTARVY (B/F/TAF) fixed-dose combination (FDC) tablet is not currently marketed in the United States or elsewhere.

3.2. Summary of Pre-submission/Submission Regulatory Activity

April 28. 2014: IND 121318, the initial application, was received for bictegravir (GS-9883, BIC), single agent. Based on the results of the Phase 1 trials under this IND, the Sponsor stated their intent is to co-formulate bictegravir as a fixed-dose combination with other ARV's as a complete regimen for the treatment of HIV-1.

May 4, 2015: IND 125589 was submitted in the United States to investigate B/F/TAF FDC as a complete regimen for the treatment of HIV-1 infection. The initial application opened with clinical trial, GS-US-141-1233, to evaluate the relative bioavailability of the investigational B/F/TAF FDC tablet versus bictegravir (BIC) single agent plus F/TAF FDC tablets.

October 21, 2015: Under IND 125589, an EOP2 meeting was held via teleconference to discuss the B/F/TAF development program. To facilitate the meeting discussions the Sponsor provided Week 12 interim data from their Phase 2, randomized, double-blinded, active-controlled trial (GS-US-141-1475) to assess the safety, tolerability, and efficacy of a once-daily regimen containing BIC+F/TAF versus DTG+F/TAF in HIV-1-infected ART-naive adults. A high-level summary of Week 24 supporting data from this same trial was later provided, albeit in advance of this EOP2 meeting to support discussions. Briefly, FDA agreed that in general the pre-clinical and clinical trials were sufficient to support initiation of the planned Phase 3 trials (two trials in treatment naive HIV-1 subjects and two trials in virologically suppressed HIV-1 subjects). FDA objected to the inclusion of adolescents in clinical trials until the safety and efficacy of B/F/TAF in the adult population is adequately established.

April 4, 2016: Under IND 125589 the Sponsor submitted a new Phase 2/3 pediatric protocol (GS-US-380-1474), to evaluate the pharmacokinetics, safety, and antiviral activity of B/F/TAF FDC in HIV-1 infected virologically suppressed adolescents and children. The trial was designed in sequential cohorts: Cohort 1 (12 to < 18 years of age and > 35 kg) and Cohort 2 (6 < 12 years of age). The Sponsor initiated this pediatric trial in September 2016.

November 4, 2016: Under IND 125589**,** the Sponsor submitted a request for a Type-B Pre-New Drug Application (Pre-NDA) Meeting. Following review of the information provided and questions posed by the Sponsor, the meeting was denied as FDA was not in receipt of sufficient data to facilitate constructive discussion for several important questions included in the meeting request.

November 10, 2016: Under IND 125589, the Sponsor submitted a request for Fast Track Designation for B/F/TAF FDC citing the potential to significantly improve tolerability and patient adherence and therefore maximize suppression of viral replication and minimize the emergence of HIV-1 resistance and for the potential to fulfill unmet medical needs in the pediatric population by offering a complete regimen for younger pediatric patients. On December 9, 2016, FDA denied this request as insufficient information was provided to support that B/F/TAF provided for an unmet medical need for the treatment of HIV-1.

January 26, 2017: Under IND 125589, FDA provided written responses to a November 21, 2016, Type C Meeting request to review of the Sponsor's NDA submission plans and key content for B/F/TAF. FDA generally agreed to the Sponsor's proposed submission strategy. There were no requests or agreements for late component submissions once the original NDA is received by the FDA.

March 1, 2017: The Sponsor notified FDA of their intent to use a Tropical Disease Priority Review Voucher at the time of their planned NDA submission for B/F/TAF, scheduled for June 2017.

(b) (4)

June 12, 2017: The Sponsor submitted NDA 210251 for B/F/TAF FDC tablets for the treatment of HIV-1 infection in adults who are HIV-1 ART-naive or virologically suppressed with no known mutations associated with resistance to the individual components of B/F/TAF. This submission was accompanied with a Tropical Disease Voucher for priority review consideration.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Six sites were selected for clinical inspection. These sites were selected primarily on their relatively high enrollment. In addition, three of the six sites (Sites #698, #2106, and #2728) were identified as having investigators or sub-investigators with disclosable financial interests (see Section 15.2). The details of the site information and trial number evaluation follows:

- Site #2106. Trial 1498. PI; Olayemi Osiyemi; Triple O Research Institute, P.A.; West Palm Beach, FL, USA. This site had 19 subjects screened and 19 randomized.
- Site #11791. Trial 1489. PI: Louise Charest, Clinique Medicale L'Actuel, Montreal, Quebec, Canada. This site had 16 subjects screened and 12 randomized.
- Site #986. Trial 1490. PI: Ellen Koenig, Instituto Dominicano de Estudios Virologicos (IDEV), Santo Domingo, Dominican Republic. This site had 52 subjects screened, 45 subjects randomized, and one discontinued.
- Site #11678. Trial 1490. PI: Mezgebe Berhe, North Texas Infectious Diseases Consultants, P.A., Dallas, TX, USA. This site had 16 subjects screened, 14 randomized, and two discontinued.
- Site #2728. Trial 1844. PI: Anthony Mills, Mills Clinical Research, Los Angeles, CA, USA. This site had 27 subjects screened, 24 randomized, and one discontinued.
- Site #698. Trial 1844. PI: Edwin DeJesus, Orlando Immunology Center, Orlando, FL, USA. This site had 15 subjects screened and 14 randomized.

OSI review was completed and none of the above site inspections indicated serious deviations or findings that would affect the validity or reliability of the submitted data.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No
Sufficient controls to insure safety and efficacy of the commercial product: Yes

B/F/TAF fixed-dose combination tablets are an immediate-release oral dosage form containing 50 mg of bictegravir (BIC, B), 200 mg of emtricitabine (FTC, F), and 25 mg of tenofovir alafenamide (TAF). The tablets are capsule-shaped, film-coated purplish-brown, debossed with "GSI" on one side of the tablet and "9883" on the other side. The quantitative composition of the tablets is listed in the sponsor's table below. See FDA product quality review for additional details.

Table 4: Quantitative Composition of BIKTARVY (B/F/TAF) Tablets

Components	Unit Formulation (mg/tablet)	% w/w	Quality Standard	Function
(b) (4)				
Bictegravir Sodium[a]	52.45[b]	(b) (4)	In-house	Active ingredient
Microcrystalline Cellulose[a]	(b) (4)		NF, Ph. Eur.	(b) (4)
Croscarmellose Sodium			NF, Ph. Eur.	
Magnesium Stearate			NF, Ph. Eur.	
(b) (4)			---	---
Emtricitabine[a]	200.00		In-house	Active ingredient
Tenofovir Alafenamide Fumarate[a]	28.04[c]		In-house	Active ingredient
(b) (4)			NF, Ph. Eur.	(b) (4)
			NF, Ph. Eur.	
			NF, Ph. Eur.	
			---	---
			---	---
Film-Coat				
(b) (4)				
a (b) (4)				
b 52.45 mg of bictegravir sodium is equivalent to 50 mg of bictegravir free acid.				
c 28.04 mg of tenofovir alafenamide fumarate is equivalent to 25 mg of tenofovir alafenamide free base.				
d (b) (4)				
e				
f				

Source: Excerpt from 3.2.P.1 Description and Composition of the Drug Product in NDA 210251

4.3 Devices and Companion Diagnostic Issues

Not Applicable.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

The nonclinical safety profile of BIC was evaluated in: safety pharmacology studies in rats and monkeys; repeat-dose toxicology studies in mice, rats and monkeys for up to 4, 26, and 39 weeks, respectively; at least 2-week toxicology studies in rats to qualify impurities; phototoxicity studies in mouse fibroblasts and pigmented rats; fertility and pre- and post-natal developmental studies in rats; embryo-fetal developmental studies in rats and rabbits; genetic toxicology studies (Ames, *in vitro* chromosomal aberration and *in vivo* rat micronucleus assays); and a carcinogenicity study in transgenic mice. In addition, numerous *in vitro* and *in vivo* nonclinical pharmacokinetic studies evaluating the absorption, distribution, metabolism and excretion of BIC have been conducted in mice, rats, dogs, and monkeys, and a rat carcinogenicity study with BIC is currently in progress. Nonclinical safety studies for F/TAF to support the FDC were reviewed previously. Refer to the Pharmacology/Toxicology reviews for NDA-021500, NDA-208464, and NDA-208215 for a detailed summary of FTC, TAF, and F/TAF nonclinical data, respectively.

Pharmacokinetics:

The steady-state volume of distribution (V_{ss}) following intravenous infusion of BIC was 0.09 to 0.22 L/kg in rats, dogs and monkeys, values lower than total body water. BIC had moderate-to-high oral bioavailability (42-74% in rats, monkeys and dogs) with rapid absorption, reaching maximal plasma concentrations (C_{max}) within 4 hours postdose. BIC was highly bound to plasma protein (>98%) in all species examined and had wide tissue distribution in rodents. BIC concentrations in tissues were lower than in blood, but had minimal partitioning into erythrocytes with a blood to plasma ratio close to 0.6. BIC was mainly eliminated through metabolism by the liver followed by excretion into feces (>40%) and urine (<20%). In a rat pre/post-natal study, BIC was detected in the plasma of neonates on lactation day 10, indicating transfer through milk; BIC exposure in maternal rats was up to 2.8-times higher than in pups.

Safety Pharmacology:

No significant effects on neurologic (modified Irwin test) or respiratory parameters (plethysmography) were observed in male rats following single oral doses of BIC up to 300 mg/kg. In addition, no significant cardiovascular effects on hemodynamic or

electrocardiographic parameters were noted for up to 75 hours post-dose in telemetry-monitored male monkeys given single oral doses of BIC up to 1000 mg/kg. BIC did not significantly inhibit hERG current *in vitro* until it reached a concentration of 7.1 µM (10.3%; estimated IC_{50} is >7.1 µM). No cardiovascular events were observed in clinical trials with the FDC.

Repeat-Dose Toxicology Studies:

The hepatobiliary system (with gastrointestinal intolerance) was identified as the target organ of toxicity in repeat-dose toxicology studies in mice, rats, and monkeys administered BIC doses up to 100, 300, and 1000 mg/kg/day for 1, 6 and 9 months, respectively. In monkeys, BIC administration of 1000 mg/kg resulted in non-adverse emesis and reversible elevations of ALT (290%), and adverse irreversible liver lesions with microscopic correlates (hyperplasia with immune infiltration). Based on these findings, the NOAEL in monkeys was 200 mg/kg/day (AUC_{0-24} 709 µg*hr/mL). In rats, there were no treatment related effects up to the highest dose examined (AUC_{0-24} 1830 µg*hr/mL). In mice, BIC administration of 1000 mg/kg resulted in substantially decreased body weight gain with liver injury (depleted glycogen). Based on these findings, the NOAEL in mice was 100 mg/kg/day (AUC_{0-24} 1180 µg*hr/mL). BIC exposures at these doses in mice, rats, and monkeys were 12, 18, and 7 times the exposure in humans at the recommended human dose for the FDC B/F/TAF (AUC of 102 µg*hr/mL in humans).

Genetic Toxicology and Carcinogenicity:

BIC was not mutagenic or clastogenic as tested in the Ames assay up to 5000 µg/plate, the *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes up to 500 µg/mL, and the *in vivo* rat micronucleus assay up to day 14 of 300 mg/kg/day. A 6 month carcinogenicity transgenic rasH2 mouse study had no findings suggestive of turmorigenic potential, and a 2 year rat study is currently on-going.

Reproductive Toxicology:

BIC exposure was not associated with effects on fertility. Daily oral doses of BIC to rats for 14 days (females) or 28 days (males) prior to cohabitation and during cohabitation had no effects on male or female reproductive performance, on the estrous cycle or sperm, or on embryo/fetal viability. The NOEL for fertility and early embryonic development in rats is 300 mg/kg/day (AUC_{0-t} 3650 µg*hr/mL), the highest dose tested in the study. When compared to human BIC exposure following administration of the FDC, the margin of exposure for BIC is ~36-times.

Developmental toxicity studies were conducted in rats and rabbits. There were no effects on maternal or embryo-fetal development in rats, and the NOEL was 300 mg/kg/day. In rabbits, administration of oral BIC at 1000 mg/kg/day to pregnant females during organogenesis resulted in maternal toxicity (decreased food consumption and body weight loss) and concomitant fetal toxicity (abortion and reduced body weight). While the suspected cause of abortion was severe maternal toxicity, marked autolysis prevented evaluation of the fetuses, so malformations could not be ruled out as a potential cause for abortion. This finding occurred at exposures, based on AUC (138 µg*hr/mL), approximately similar to (1.35 times) the

projected clinical exposure of BIC following administration of the FDC. Based on these findings, the NOAEL for maternal toxicity and embryofetal development in the rabbit was 300 mg/kg/day (AUC_{0-24}= 60.3 µg*hr/mL). This AUC is below the AUC expected following administration of the FDC (0.59 times).

BIC maternal exposure was not associated with clear effects on pre- and postnatal development. BIC at doses up to 300 mg/kg/day in pregnant rats had no maternal or fetal effects on behavior/development. The F_1 generation had mild decreased reproductive performance, but the relationship to BIC exposure was unclear. This finding was considered nonadverse as the reduced performance was within historical control data range. These animals had approximately 30% the exposure of BIC observed in the F_0 females on lactation day 10. BIC maternal (F_0) exposure (lactation day 10: AUC_{0-24} 3100 µg*h/mL) at the maternal and F1 offspring NOAEL in the pre- and postnatal development study was ~31-times higher than the mean clinical exposure with the FDC.

Other Toxicology:

BIC was nonphototoxic, noncorrosive and nonirritating to skin, and a moderate eye irritant. BIC also showed no potential for sensitization.

RECOMMENDATION

The sponsor has provided sufficient nonclinical safety information on bictegravir to support approval for marketing in the U.S as a component in the fixed-dosed combination B/F/TAF (BIKTARVY). With respect to the FDC of B/F/TAF, no specific overlapping toxicity of potential significant clinical concern was identified in animals.

5.2 Referenced NDAs, BLAs, DMFs

Some GS-9883 nonclinical safety studies, including safety pharmacology, ADME, repeat-dose toxicology, genetic toxicology, and reproductive toxicology studies have been reviewed by Dr. Mark Powley under INDs 121318 (BIC) and 125889 (B/F/TAF), and are summarized (as appropriate) in sections of this review. Complete reviews of all pivotal studies for BIC are included within the review text. FTC and TAF have been fully reviewed under NDAs 021500 (Emtriva®; FTC), 208464 (Vemlidy®; TAF), and 208215 (Descovy®; FTC/TAF).

5.3 Pharmacology

5.3.1 Primary pharmacology

BIC

BIC, a novel strand transfer inhibitor of HIV-1 integrase, has shown antiviral activity across all HIV-1 clinical isolates with mean and median EC_{50} values of 0.60 and 0.55 nM, respectively. HIV-2 was similarly susceptible to BIC with an EC_{50} value of 1.1 nM.

B/F/TAF
The combination of BIC, FTC, and TAF was found to be highly synergistic with respect to antiviral activity and had no evidence of cross-antagonism in vitro, supporting the use of these agents in combination in HIV-1 infected patients. The resistance profiles of the individual agents are distinct and non-overlapping. Additional complete details of the pharmacodynamics of BIC and B/F/TAF can be found in the clinical virology review.

5.3.2 Secondary Pharmacology

BIC
Molecular Target Screen of GS-9883 (PC-141-2029)
BIC was evaluated against a panel of mammalian enzymes, ion channels, and receptors for potential off-target activity, and no significant responses (≥ 50% inhibition or stimulation) were observed at 10 µM BIC.

Cytotoxicity of GS-9883 in Multiple Cell Lines (PC-141-2042)
The cytotoxicity of GS-9883 was evaluated in two hepatic cell lines (Huh7 and HepG2), a prostate carcinoma cell line (PC-3), normal lung fibroblasts (MRC-5), and primary human hepatocytes from two independent donors following five days of BIC exposure. GS-9883 had no observed cellular cytotoxicity. CC_{50} value s for GS-9883 in the tested cell types ranged from 34 to > 100 µM. Overall, BIC has low cellular cytotoxicity.

Antiviral Activity of GS-9883 against Non-HIV Viruses (PC-141-2043)
GS-9883 was tested against hepatitis B and C viruses, influenza A virus, human rhinovirus and respiratory syncytial virus in cell-based assays. GS-9883 did not display selective in vitro antiviral activity against any of these viruses up to the highest concentration tested (44 µM).

B/F/TAF
Due to the low potential for off-target activity and cytotoxicity by each component, no additional secondary pharmacology studies were deemed necessary.

5.3.3 Safety Pharmacology

BIC
Effects of GS-9883 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (PC-141-2049)
To examine the in vitro effect of GS-9883 on potassium ion channels, GS-9883 at concentrations of 0.8 and 7.1 µM were evaluated on the hERG (human ether-à-go-go-related gene) channel current. GS-9883 inhibited hERG current by 1.0 ± 0.4% at 0.8 µM and 10.3 ± 1.2% at 7.1 µM versus 0.8 ± 0.4% (n = 3) in control. hERG inhibition was statistically significant at 7.1 µM

compared to vehicle control. The IC50 for the inhibitory effect of GS-9883 on hERG potassium current is estimated to be greater than 7.1 µM. Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by 87.5 ± 2.9% (n = 2), confirming the sensitivity of the test system.

Cardiovascular Safety Pharmacology Evaluation of GS-9883 Administered by Oral Gavage to Male Telemetry-Instrumented Conscious Nonhuman Primates (PC-141-2046)
To evaluate the potential cardiovascular effects of GS-9883, male cynomolgus monkeys (n=4) were administered each dose via oral gavage using a Latin square design on days 1, 8, 15, and 22. Each monkey received vehicle and GS-9883 at doses of 30, 100 and 1000 mg/kg. No GS-9883-related mortality, morbidity, or effects on body weight/food consumption were noted. Assessments of cardiovascular function were based on hemodynamic and electrocardiographic (ECG) parameters where telemetry data was continuously recorded for at least 60 minutes prior to dosing and through approximately 75 hours post-dose. Plasma levels at 8 hours postdose confirmed all monkeys were exposed to test article. No GS-9883 related effects were noted on qualitative or quantitative ECG or hemodynamic parameters. Based on these results, the NOEL for cardiovascular parameters is 1000 mg/kg.

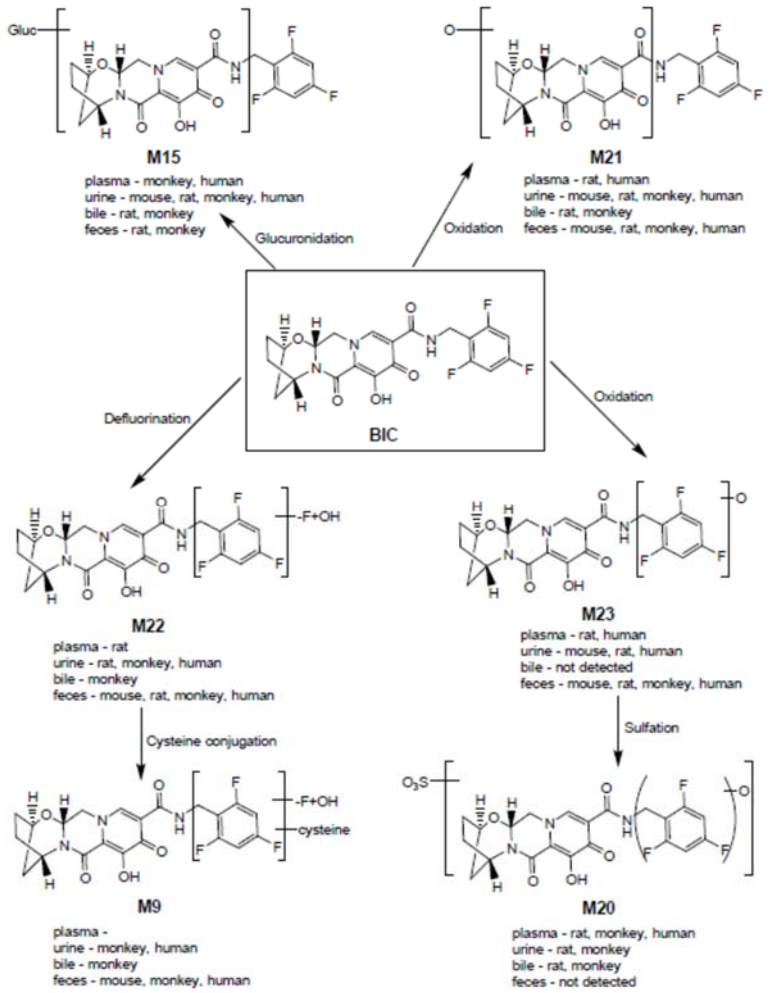
Central Nervous System Safety Pharmacology Evaluation of GS-9883 following Oral Administration to Male Rats (PC-141-2047)
To evaluate the neurological effects of GS-9883, forty male Crl:WI (Han) rats were randomized to five groups (eight rats/group) and administered a single dose by oral gavage of vehicle or GS-9883 at dose levels of 10, 30, 100, or 300 mg/kg. Neurological assessments were collected approximately 3, 7.5, 24 (Day 2), 48 (Day 3), 72 (Day 4), and 144 (Day 7) hours postdose in a modified Irwin battery, including home cage, hand-held, open-field, and elicited response observations. No effects related to GS-9883 were observed for clinical signs or body temperature. No neurological effects related to GS-9883 were evident during the modified Irwin observational battery. Based on these results, the NOEL for neurological function in rats is 300 mg/kg.

Respiratory Safety Pharmacology Evaluation of GS-9883 Using Head-Out Plethysmography following Oral Gavage Administration to Male Rats (PC-141-2048)
To evaluate the respiratory effects of GS-5816, forty male Crl:WI (Han) rats were randomized to five groups (eight rats/group) and administered a single dose by oral gavage of vehicle or GS-9883 at dose levels of 10, 30, 100, or 300 mg/kg. Plethysmography data, including tidal volume, respiration rate, and minute volume, were collected continuously for 30 minute segments prior to dosing, beginning 2 hours through 8 hours postdose, and as a single segment 24- (Day 2), 48- (Day 3), 72- (Day 4), and 144-hour (Day 7) postdose . Plethysmography parameters were analyzed as 30-minute averages from 2 through 8 hours postdose. All rats survived until the scheduled sacrifice and no mortality, morbidity, or signs of toxicity were observed. No GS-9883-related changes in respiration rate, tidal volume, or minute volume were observed. Based on these results, the NOEL for respiratory function in rats is 300 mg/kg.

B/F/TAF
No combination safety pharmacology studies were performed as no component had biologically meaningful vital organ effects. Thus, the combination is unlikely to have significant effects on the respiratory, CNS, or cardiovascular systems.

5.4 ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Single Dose Pharmacokinetic Study of GS-9883 in Male Cynomolgus Monkeys (AD-141-2281)</td><td>Table 5: Pharmacokinetic Parameters Following a Single IV or Oral Dose of GS-9883 to Male Cynomolgus Monkeys
<table><tr><th rowspan="2">Parameter</th><th colspan="2">Route of Administration</th></tr><tr><th>IV Infusion</th><th>Oral</th></tr><tr><td>Dosage (mg/kg)</td><td>0.5</td><td>1</td></tr><tr><td>T_{max} (h)</td><td>0.55 ± 0.06</td><td>0.83 ± 0.29</td></tr><tr><td>Plasma C_{max} (nM)</td><td>11500 ± 173</td><td>16600 ± 4540</td></tr><tr><td>MRT (h)</td><td>4.16 ± 0.93</td><td>ND</td></tr><tr><td>$t_{1/2}$ (h)</td><td>3.58 ± 0.23</td><td>3.26 ± 0.50</td></tr><tr><td>Plasma AUC_{last} (nM•h)</td><td>49000 ± 12200</td><td>72100 ± 39300</td></tr><tr><td>Plasma AUC_{inf} (nM•h)</td><td>49400 ± 12400</td><td>72500 ± 39500</td></tr><tr><td>CL (L/h/kg)</td><td>0.024 ± 0.007</td><td>ND</td></tr><tr><td>V_{ss} (L/kg)</td><td>0.095 ± 0.010</td><td>ND</td></tr><tr><td>F (%)</td><td>ND</td><td>73.8 ± 40.3</td></tr></table>Predicts moderate to high human oral bioavailability</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>In Vitro Protein Binding Determination of GS-9883 by Equilibrium Dialysis (AD-141-2287)</td><td>Table 6: Protein Binding of GS-9883 in Plasma from Different Species
<table><tr><th>Matrix</th><th>Conc. (µM) [a]</th><th>Free Fraction (%)[b]</th></tr><tr><td>Human Plasma</td><td>2</td><td>0.25 ± 0.01</td></tr><tr><td>Beagle Dog Plasma</td><td>2</td><td>1.24 ± 0.06</td></tr><tr><td>Sprague-Dawley Rat Plasma</td><td>2</td><td>0.01 ± 0.00</td></tr><tr><td>Cynomolgus Monkey Plasma</td><td>2</td><td>0.31 ± 0.01</td></tr><tr><td>Rhesus Monkey Plasma</td><td>2</td><td>0.32 ± 0.02</td></tr></table></td></tr>
<tr><td>Pharmacokinetics, Absorption, Distribution, and Excretion of 14C-GS-9883 Following a Single Oral</td><td>Radioactivity was widely distributed to most tissues, except the brain and testis(es) (0.25 hours postdose)
Maximum concentration (C_{max}) by 1 hour postdose
Radioactivity remained 168 hours postdose
Tissue/plasma ratio: 0.6</td></tr>
</table>

Type of Study	Major Findings
Administration to Rats (AD-141-2276)	
Metabolism	
Single oral administration of [^{14}C]BIC to mouse, rat, monkey and human (AD-141-2304, AD-141-2277, AD-141-2299, GS-US-141-1481)	 **Figure 1: Proposed Biotransformation Pathway of Bictegravir Based on Metabolite Identification in Plasma, Urine, Bile, and Feces Following Oral Administration**
Excretion	
Pharmacokinetics, Absorption, and Excretion of 14C-GS-9883 Following Oral Administration to	Overall recovery from intact monkeys: 80.4% Feces: 40.9% Urine: 20.8% Overall recovery from bile duct cannulated monkeys: 86.0% Feces: 20.3%

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Intact and Bile Duct-Cannulated Monkeys (AD-141-2298)</td><td>Bile: 39.7%
Urine: 15.2%

Reason for incomplete recovery: Unclear</td></tr>
<tr><td>TK data from general toxicology studies
Monkey: 39-week repeat oral dose
• 0, 30, 200, 1000 mg/kg, daily
• Samples collected predose, 0.25, 0.5, 1, 2, 4, 6, 12, and 24 hrs postdose
• TX-141-2032</td><td>Accumulation: None
Dose proportionality: Less Than
Table 7: Toxicokinetic Parameters for GS-9883 in Monkey Plasma Day 1 and Weeks 13 and 39
<table>
<tr><th>Interval</th><th>Dose Group</th><th>Dose Level (mg/kg/day)</th><th>Sex</th><th>C_{max} (µg/mL)</th><th>T_{max} (hr)</th><th>AUC_{0-t} (µg·hr/mL)</th></tr>
<tr><td>Day 1</td><td>2</td><td>30</td><td>M</td><td>40.1</td><td>2.29</td><td>280</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>24.6</td><td>2.86</td><td>243</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>32.3</td><td>2.57</td><td>262</td></tr>
<tr><td></td><td>3</td><td>200</td><td>M</td><td>43.4</td><td>3.43</td><td>514</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>55.1</td><td>4.86</td><td>797</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>49.2</td><td>4.14</td><td>655</td></tr>
<tr><td></td><td>4</td><td>1000</td><td>M</td><td>97.3</td><td>5.78</td><td>1450</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>111</td><td>5.33</td><td>1520</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>104</td><td>5.56</td><td>1480</td></tr>
<tr><td>Week 13</td><td>2</td><td>30</td><td>M</td><td>30.2</td><td>2.71</td><td>288</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>25.1</td><td>3.07</td><td>254</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>27.7</td><td>2.89</td><td>271</td></tr>
<tr><td></td><td>3</td><td>200</td><td>M</td><td>66.7</td><td>4.29</td><td>855</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>59.7</td><td>4.29</td><td>664</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>63.2</td><td>4.29</td><td>760</td></tr>
<tr><td></td><td>4</td><td>1000</td><td>M</td><td>112</td><td>4.89</td><td>1540</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>89.8</td><td>5.11</td><td>1180</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>101</td><td>5.00</td><td>1360</td></tr>
<tr><td>Week 39</td><td>2</td><td>30</td><td>M</td><td>28.3</td><td>2.25</td><td>248</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>24.4</td><td>2.50</td><td>253</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>26.4</td><td>2.38</td><td>251</td></tr>
<tr><td></td><td>3</td><td>200</td><td>M</td><td>67.8</td><td>2.00</td><td>595</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>70.4</td><td>3.00</td><td>823</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>69.1</td><td>2.50</td><td>709</td></tr>
<tr><td></td><td>4</td><td>1000</td><td>M</td><td>104</td><td>4.67</td><td>1450</td></tr>
<tr><td></td><td></td><td></td><td>F</td><td>109</td><td>4.67</td><td>1750</td></tr>
<tr><td></td><td></td><td></td><td>MF</td><td>106</td><td>4.67</td><td>1600</td></tr>
</table></td></tr>
<tr><td>Rat: 26-week repeat oral dose
• 0, 5, 30, and 300 mg/kg, daily
• Samples collected predose, 0.25, 0.5, 1, 2, 4, 8,</td><td>Accumulation: With LD only
Dose proportionality: Less Than
Table 8: Toxicokinetic Parameters for GS-9883 in Rat Plasma Day 1, 90, and 181</td></tr>
</table>

Type of Study	Major Findings
12, and 24 hrs postdose • *TX-141-2031*	

Interval	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-24} (µg·hr/mL)
Day 1	2	5	M	19.4	2.00	341
			F	22.9	1.00	436
			MF	21.1	2.00	387
	3	30	M	82.4	2.00	1420
			F	113	1.00	1870
			MF	87.8	2.00	1640
	4	300	M	143	1.00	2380
			F	185	1.00	3530
			MF	164	1.00	2920
Day 90	2	5	M	33.5	1.00	460
			F	72.4	0.500	1420
			MF	50.4	0.500	938
	3	30	M	75.0	2.00	1040
			F	162	2.00	2810
			MF	119	2.00	1930
	4	300	M	92.7	1.00	1880
			F	212	8.00	4570
			MF	152	1.00	3230
Day 181	2	5	M	28.8	0.500	457
			F	70.0	4.00	1290
			MF	45.9	4.00	873
	3	30	M	76.9	2.00	1010
			F	169	2.00	2910
			MF	123	2.00	1960
	4	300	M	100	2.00	1830
			F	213	0.500	4680
			MF	152	0.500	3250

TK data from reproductive toxicology studies

A Dose Range-Finding Embryo-Fetal Development Study of GS-9883-01 by Oral Gavage in Rats (Study no. TX-141-2034)

Table 9: Toxicokinetic Parameters for GS-9883 in Pregnant Rat Plasma DG7 and DG17

Interval	Dose Group	Dosage (mg/kg/day)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng·hr/mL)	C_{last} (ng/mL)	T_{last} (hr)	AR
DG 7	2	5	27200	6.00	464000	15300	24.0	NA
	3	30	94800	6.00	1940000	55200	24.0	NA
	4	300	171000	6.00	3360000	104000	24.0	NA
DG 17	2	5	80100	6.00	1630000	63800	24.0	3.51
	3	30	164000	6.00	3080000	88900	24.0	1.58
	4	300	180000	0.500	3650000	127000	24.0	1.08

NA = Not applicable; AR = Accumulation ratio

NOAEL from Definitive Study: 300 mg/kg/day
Safety Margin: 36

A Dose Range-Finding Embryo-Fetal Development Study of GS-9883-01 by Oral Gavage in Rabbits (Study no. TX-141-2038)

Table 10: Toxicokinetic Parameters for GS-9883 in Pregnant Rabbit Plasma DG7 and DG19

Type of Study	Major Findings

Interval	Dose Group	Dose Level (mg/kg/day)		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng·hr/mL)	C_{last} (ng/mL)	T_{last} (hr)	AR
DG7	2	100	Mean	3410	3.33	17000	1550	6.67	
			SD	873	1.15	9000	395	2.31	
			N	3	3	3	3	3	
	3	300	Mean	4080	10.7	62500	3070	20.0	
			SD	378	11.5	29200	1720	6.93	
			N	3	3	3	3	3	
	4	1000	Mean	9620	17.3	146000	8610	24.0	
			SD	1440	11.5	32700	3190	0	
			N	3	3	3	3	3	
DG19	2	100	Mean	3960	4.00	38500	1420	16.0	3.45
			SD	317	0	9300	374	6.93	3.38
			N	3	3	3	3	3	3
	3	300	Mean	4050	2.75	60300	1510	24.0	1.23
			SD	458	2.17	9790	435	0	0.869
			N	3	3	3	3	3	3
	4	1000	Mean	11000	3.33	138000	4600	24.0	0.979
			SD	1110	4.04	25800	2080	0	0.298
			N	3	3	3	3	3	3

AR = Accumulation Ratio ([AUC_{0-t} DG 19] / [AUC_{0-t} DG 7])

NOAEL from Definitive Study: 300 mg/kg/day
Maternal and fetal toxicity including abortion at HD
Safety Margin: 0.59

5.5 Toxicology

5.5.1 General Toxicology

Study title/ number: 39-Week Oral Gavage Toxicity and Toxicokinetic Study with GS-9883-01 in Cynomolgus Monkeys with a 13-Week Interim Sacrifice and a 4-Week Recovery Phase (Study no. TX-141-2032)

Key Study Findings

- Adverse effects included hepatobiliary injury (increased ALT as well as gross and microscopic lesions in bile and liver) with emesis
- Based on the absence of adverse effects in the mid-dose, the NOAEL was 200 mg/kg/day (AUC_{0-t} = 709 µg·hr/mL; C_{max} = 69.1 µg/mL).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes, with exception of test article characterization and stability

Methods

Dose and frequency of dosing:	0, 30, 200, 1000; daily
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) hydroxypropyl methylcellulose and 0.1% (w/w) Tween 20 in reverse osmosis water; adjusted to pH 7.5 to 8.5 following Week 14.

Species/Strain: monkey/cynomolgus (b) (4)

Number/Sex/Group: 7
Age: 30 to 47 months
Satellite groups/ unique design: 2 Recovery animals in C and HD
Deviation from study protocol affecting interpretation of results: minor with no impact on study integrity

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	HD: Emesis/vomitus (3,M); non-adverse
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	HD: +290% ALT, reversible; non-adverse
Urinalysis	Unremarkable
Gross Pathology	HD: Liver lesions, irreversible; adverse (microscopic correlates)
Organ Weights	Unremarkable
Histopathology **Adequate battery:** Yes	HD: Liver findings (bile duct hyperplasia; hepatocyte hyperplasia, regeneration, and immune infiltration [neutrophils]), partial reversibility; adverse

C: control; LD: low dose; MD: mid dose; HD: high dose.

Study title/ number: 26-Week Oral Gavage Toxicity and Toxicokinetic Study with GS-9883 in Han Wistar Rats (Study no. TX-141-2031)

Key Study Findings

- Non-adverse increase in phosphorus (15-33%) was noted in high-dose animals
- Based on the absence of adverse effects in any dose group, the NOAEL was 300 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 3250 µg·hr/mL; C_{max} = 152 µg/mL).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes, with exception of test article characterization and stability

Methods

Dose and frequency of dosing: 0, 5, 30, 300; daily
Route of administration: Oral
Formulation/Vehicle: 0.5% (w/w) hydroxypropyl methylcellulose and 0.1% (w/w) Tween 20 in reverse osmosis water

Species/Strain:	Rats/Han Wistar (b) (4)
Number/Sex/Group:	20 C/HD and 15 LD/MD
Age:	6 to 7 weeks
Satellite groups/ unique design:	5 Recovery animals in C and HD; 9 Toxicokinetic
Deviation from study protocol affecting interpretation of results:	minor with no impact on study integrity

Observations and Results: changes from control

Parameters	Major findings
Mortality	No GS-9883 related; Seven (5 accidental, 2 tumor-related)
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	HD: +15-33% Phosphorus, reversible; non-adverse
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology **Adequate battery:** Yes	Unremarkable

C: control; LD: low dose; MD: mid dose; HD: high dose.

General toxicology; additional studies
Repeat-Dose Studies
4-Week Oral Gavage Qualification Toxicity and Toxicokinetic Study with GS-9883 in Han Wistar Rats (Study no. TX-141-2043)
Oral administration of GS-9883 (free acid) at dose levels of 100 and 300 mg/kg/day and GS-9883-01 (sodium salt) at 300 mg/kg/day for 4 weeks was well-tolerated and no treatment-related findings were noted. Minor (15%) increased phosphorus in high-dose females was considered non-adverse. Based on the absence of adverse effects in any dose group, the NOAEL was 300 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 4440 µg·hr/mL for GS-9883; $AUC_{0\text{-}24\ hr}$ = 4190 µg·hr/mL for GS-9883-B).

2-Week Oral Gavage Toxicity and Toxicokinetic Study with GS-9883 in Han Wistar Rats with Bone Marrow Micronucleus Assay (Study no. TX-141-2029)
Oral administration of GS-9883 at dose levels of 0, 10, 30, 100, and 300 mg/kg/day for 2 weeks was well-tolerated and no treatment-related findings were noted. Minor decreases in red blood cells and hematocrit in high-dose females with increased phosphorus in high-dose males were considered incidental and non-adverse. Microscopic lesions were noted in the brain and

spinal cord and attributed to tissue processing. Based on the absence of adverse effects in any dose group, the NOAEL was 300 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 2970 µg·hr/mL; C_{max} = 150 µg/mL).

2-Week Oral Gavage Investigative Toxicity Study with GS-9883 in Male Han Wistar Rats (Study no. TX-141-2033)
No GS-9883 related effects were noted following oral administration at 0 and 300 mg/kg/day for 2 weeks to male rats. Results of this study confirm that the microscopic brain and spinal cord lesions, noted in Study no. TX-141-2029, were due to tissue processing.

2-Week Oral Gavage Toxicity and Toxicokinetic Study with GS-9883 in Cynomolgus Monkeys (Study no. TX-141-2030)
Oral administration of GS-9883 at dose levels of 0, 30, 100, and 1000 mg/kg/day for 2 weeks was well-tolerated and no treatment-related findings were noted. A non-adverse decrease in CYP1A activity was noted in high-dose males. Based on the absence of adverse effects in any dose group, the NOAEL was 1000 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 1090 µg·hr/mL; C_{max} = 79.1 µg/mL).

4-Week Oral Gavage Dose Range-Finding Toxicity and Toxicokinetic Study with GS-9883-01 in 001178-W (Wild Type) RasH2 Mice (Study no. TX-141-2042)
Oral administration of GS-9883 at dose levels of 0, 30, 100, and 1000 mg/kg/day for 4 weeks was well-tolerated and treatment-related findings were limited to males receiving 1000 mg/kg/day. Minor decreased body weight and slightly increased glucose (16%) in high-dose males were considered non-adverse. Based on the absence of adverse effects in any dose group, the NOAEL was 1000 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 2330 µg·hr/mL; C_{max} = 158 µg/mL).

Single-Dose Studies
No formal single-dose toxicity studies with GS-9883 have been conducted. Doses up to 1500 mg/kg in mice, 1000 mg/kg in rats, and 1000 mg/kg in monkeys were well-tolerated in single-dose PK studies (Studies AD-141-2307, AD-141-2286, and AD-141-2284, respectively).

5.5.2 Genetic Toxicology

In Vitro
Bacterial Reverse Mutation Assay Plate Incorporation Method with GS-9883 (Study no. TX-141-2026)
Key Study Findings: Negative
GLP compliance: Yes, with exception of test article characterization and stability
Test system: Strains TA98, TA100, TA1535, TA1537, and WP2uvrA; up to 5000 ug/plate; +/- S9
Study is valid: Yes

Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes with GS-9883 (Study no. TX-141-2027)
Key Study Findings: Negative
GLP compliance: Yes, with exception of test article characterization and stability
Test system: Human peripheral blood lymphocytes; up to 500 ug/mL; +/-S9
Study is valid: Yes

In Vivo
2-Week Oral Gavage Toxicity and Toxicokinetic Study with GS-9883 in Han Wistar Rats with Bone Marrow Micronucleus Assay (Study no. TX-141-2029)
Key Study Findings: Negative
GLP compliance: Yes, with exception of test article and positive control characterization as well as test article stability
Test system: Rat, bone marrow micronuclei; 14 oral doses up to 300 mg/kg]
Study is valid: Yes

5.5.3 Carcinogenicity

6-Month rasH2 Transgenic
26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study of GS-9883-01 in 001178-T (Hemizygous) rasH2 Transgenic Mice (TX-141-2047)
Key Study Findings: No significant change to survival rate or production of dose-dependent carcinogenic effects. A single incidental finding ($p \leq 0.05$) of combined hemangioma and hemangiosarcoma tumors were noted in spleen, bladder, uterus, and vagina of mid-dose female mice.

GLP compliance: Yes, with exception of test article characterization and stability
Definitive Doses: Males: 0, 5, 15, 100 mg/kg/day; Females: 10, 30, 300 mg/kg/day
FDA Dose Concurrence: Yes, Based on findings of study TX-141-2042.
NOAEL ($AUC_{0\text{-}24}$ µg*h/mL): 100 (1560) and 300 (2340) mg/kg/day, respectively
Safety Margin: NA

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
An Oral (Gavage) Study of Fertility and Early Embryonic Development to Implantation of GS-9883-01 in Sprague Dawley Rats (Study no. TX-141-2039)
Key Study Findings

- Based on a lack of adverse findings at any dose, the NOAEL for male fertility, female fertility and early embryonic development was 300 mg/kg/day.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 5, 30, and 300 mg/kg; daily
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) hydroxypropylmethylcellulose (HPMC) and 0.1% (w/w) Tween® 20 in reverse osmosis deionized water (pH 8.0 ± 0.5)
Species/Strain:	rat/Crl:CD(SD) Sprague Dawley (from (b) (4)
Number/Sex/Group:	25
Study design:	Males: 28 days before cohabitation to scheduled sacrifice (61-62 total doses). Females: 14 days before cohabitation until GD 7 (22-35 total doses) and sacrificed on GD 15.
Deviation from study protocol affecting interpretation of results:	No

Embryo-Fetal Development

An Oral Gavage Embryo-Fetal Development Study with GS-9883-01 in Sprague Dawley Rats (Study no. TX-141-2036)

Key Study Findings

- Based on a lack of adverse findings in at any dose, the NOAEL for maternal toxicity and embryofetal development was 300 mg/kg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 5, 30, and 300 mg/kg; daily
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) hydroxypropylmethylcellulose (HPMC) and 0.1% (w/w) Tween® 20 in reverse osmosis membrane-processed deionized water (pH 8.0 ± 0.5)
Species/Strain:	rat/Crl:CD(SD) Sprague Dawley (from (b) (4)

	(b) (4)
Number/Sex/Group:	21
Study design:	daily from GD 7 to 17; sacrificed on GD 21
Deviation from study protocol affecting interpretation of results:	No

An Embryo-Fetal Development Study of GS-9883-01 by Oral Gavage in Rabbits (Study no. TX-141-2037)

Key Study Findings

- Adverse effects included abortion, clinical signs (fecal changes, thin body, and hypothermia), decreased body weight and food consumption in dams as well as decreased fetal body weights.
- Two high-dose dams aborted and were sacrificed early. While the suspected cause of abortion was severe maternal toxicity (decreased food consumption and body weight loss), malformations cannot be ruled out as marked autolysis prevented evaluation.
- Based on a lack of adverse findings in the mid-dose group, the NOAEL for maternal toxicity and embryofetal development was 300 mg/kg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 100, 300, and 1000 mg/kg; daily
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) hydroxypropylmethylcellulose (HPMC) and 0.5% (w/w) Tween® 20 in reverse osmosis membrane-processed deionized water (pH 8.0 ± 0.5)
Species/Strain:	rabbit/New Zealand White (from (b) (4)
Number/Sex/Group:	21
Study design:	daily from GD 7 to 19; sacrificed on GD 29
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	HD: 2 dams aborted and euthanized (GD25 and GD26); fetuses were not able to be evaluated for malformations (cannibalized/autolysis)

Clinical Signs	HD: Fecal changes, thin body, and hypothermia
Body Weights	HD: -7.1%

Prenatal and Postnatal Development

An Oral (Gavage) Study of the Effects of GS-9883-01 on Pre- and Postnatal Development, Including Maternal Function in Sprague-Dawley Rats (Study no. TX-141-2045)

Key Study Findings

- Non-adverse finding of reproductive performance parameters in the F_1 generation; uncertain relationship to treatment (because values were consistent with historical control range)
- Based on the lack of adverse effects at any dose level, the NOAEL for F_0 maternal toxicity, F_1 neonatal/developmental toxicity, F1 parental systemic toxicity, and F2 neonatal/early postnatal toxicity was 300 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 3100 µg·hr/mL and C_{max} = 156 µg/mL in F_0 females on LD10; $AUC_{0\text{-}24\ hr}$ = 1120 µg·hr/mL and C_{max} = 48 µg/mL in F_1 pups on PND10).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 2, 10, 300 mg/kg; daily
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) hydroxypropylmethylcellulose (HPMC) and 0.1% (w/w) Tween® 20 in reverse osmosis membrane-processed deionized water (pH 8.0 ± 0.5)
Species/Strain:	rat/Crl:CD(SD) (from (b) (4)
Number/Sex/Group:	25
Satellite groups:	3/C, 9/Dose Groups; Toxicokinetic
Study design:	Pregnant females (F_0) were dosed daily from GD 6 through LD 20 or GD 24 (if no delivery) A subset of offspring (F_1) were allowed to cohabitate and necropsied on LD 4, post-mating Day 25, or post-cohabitation Day 25 F_1 offspring (F_2) were sacrificed on PND 4.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	Unremarkable
F1 Generation	**Table 11: Reproductive Performance in Rat F1 Generation** Dosage Level (mg/kg/day) / [redacted] HC[a] Parameter: 0 / 2 / 10 / 300 / Mean (Range) Male Mating Index (%)[b]: 100.0 (24) / 100.0 (25) / 100.0 (25) / 95.7 (22) / 95.6 (84.0-100.0) Female Mating Index (%)[b]: 100.0 (24) / 100.0 (25) / 100.0 (25) / 95.8 (23) / 98.0 (92.0-100.0) Male Fertility Index (%)[b]: 100.0 (24) / 100.0 (25) / 100.0 (25) / 82.6 (19) / 90.2 (60.0-100.0) Female Fertility Index (%)[b]: 100.0 (24) / 100.0 (25) / 100.0 (25) / 83.3 (20) / 92.9 (60.0-100.0) Male Copulation Index (%)[b]: 100.0 (24) / 100.0 (25) / 100.0 (25) / 86.4 (19) / 93.9 (71.4-100.0) Female Conception Index (%)[b]: 100.0 (24) / 100.0 (25) / 100.0 (25) / 87.0 (20) / 93.6 (65.2-100.0) Estrous Cycle Length (days) (n): 4.3 (23) / 4.3 (24) / 4.3 (23) / 3.9 (21) / 4.3 (4.0-5.0) Pre-Coital Interval (days) (n): 2.4 (24) / 3.2 (25) / 2.7 (25) / 2.5 (23) / 3.2 (2.3-4.8) [a] = [redacted] historical control data [b] = Presented as percentage confirmed, with number of animals confirmed in parentheses.
F2 Generation	Unremarkable

5.5.5 Other Toxicology Studies

Local Tolerance

In general, it appears that BIC has little-to-no local tolerance liability. The only assessment that had a potential positive finding was the Ocular Irritation Study in Bovine Corneas (TX-141-2060). BIC elicited an in vitro irritancy score of 27.58 with a 4-hour incubation and was predicted to be moderately irritating.

Impurity Qualification

Potential impurities from starting material in the manufacturing process were evaluated in genotoxicity studies (TX-141-2041 and TX-141-2048). Results indicate that [redacted] were not genotoxic. Specified impurities were also present in the drug lots used in 2-week, 4-week, and 26-week rat studies (TX-141-2029, TX-141-2043, and TX-141-2031; described in the repeat-dose toxicity studies). Using NOAELs established in these studies, qualified impurity levels are adequate to support the proposed specifications. Summary information is provided in the sponsor's table below.

Table 12: Qualification Summary for Specified Impurities in BIC Sodium

Name	Maximum Observed in Toxicological Studies (%)	NOAEL (mg/kg/day)	Qualified Level (%)	Batch Number	Toxicological Study Number
[redacted]	[redacted]	[redacted]	(b) (4)	10069-75-03	TX-141-2043
				9883-01-XA-1	TX-141-2031
				5972-146-27	TX-141-2029
				5972-146-27	TX-141-2029
				5972-146-27	TX-141-2029
				10069-75-03	TX-141-2043
				10069-75-03	TX-141-2043
				5972-146-27	TX-141-2029
				10069-75-03	TX-141-2043

Source: Excerpt from 2.3.S.4 Control of Drug Substance, Page 16, Table 8

6 Clinical Pharmacology

6.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 210251. The clinical pharmacology information submitted in the application supports the approval of BIKTARVY Fixed Dose Combination (FDC) tablets as a complete regimen for the treatment of HIV-1 in adults.

6.2 Summary of Clinical Pharmacology Assessment

Please note that the review primarily focuses on BIC because the clinical pharmacology information of F and TAF (as individual products and as F/TAF FDC) has been previously reviewed.

6.2.1 Pharmacology and Clinical Pharmacokinetics

Table 13: ADME Profiles of the Components of BIKTARVY

		BIC	F	TAF
Absorption				
T_{max} (h)[a]		2.0–4.0	1.5–2.0	0.5–2.0
Effect of food[b]	AUC ratio	1.24 (1.16, 1.33)	0.96 (0.93, 0.99)	1.63 (1.43, 1.85)
	C_{max} Ratio	1.13 (1.06, 1.20)	0.86 (0.78, 0.93)	0.92 (0.73, 1.14)
Distribution				
% bound to human plasma proteins		>99	<4	~80
Blood-to-plasma ratio		0.64	0.6	1.0
Elimination				
$t_{1/2}$ (h)[c]		17.3 (14.8, 20.7)	10.4 (9, 12)	0.51(0.45, 0.62)
Metabolism				
Metabolic pathway(s)		CYP3A[d] UGT1A1[d]	Not significantly metabolized	Cathepsin A[e] (PBMCs) CES1 (hepatocytes)
Excretion				
Major route of elimination		Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urine[f]		35	70	<1
% of dose excreted in feces[f]		60.3	13.7	31.7

PBMCs=peripheral blood mononuclear cells; CES1=carboxylesterase 1

a. Values reflect administration of BIKTARVY with or without food.

b. Values refer to geometric mean ratio [high-fat meal/ fasting] in PK parameters and (90% confidence interval). High fat meal is approximately 800 kcal, 50% fat.

c. $T_{1/2}$ values refer to median (Q1, Q3) terminal plasma half-life. The active metabolite of TAF, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. BIC and 13 metabolites were identified in human plasma. [^{14}C] BIC was the major circulatory radioactive component and M20 (hydroxy-BIC-sulfate) and M15 (BIC-glucuronide) were the major metabolites in plasma, accounting for 67.9%, 20.1%, and 8.6%, respectively, of the plasma $AUC_{0\text{-}72h}$ of total radioactivity.

e. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes.

f. Dosing in mass balance studies: single dose administration of [^{14}C] BIC; single dose administration of [^{14}C] FTC after multiple dosing of FTC for ten days; TAF (single dose administration of [^{14}C] TAF.

6.2.2 Dose Selection, Population Pharmacokinetics and Pharmacodynamics

Dose selection

Dose selection of BIC for the Phase 3 trial was based on a dose-ranging monotherapy study (GS-US-141-1219) and a relative bioavailability study (GS-US-141-1233). In Study GS-US-141-1219, once-daily doses of single-agent BIC (5, 25, 50, or 100 mg) administered for 10 days led to dose-dependent decreases in HIV-1 viral load (Table 14). Based on a predicted protein-adjusted inhibitory quotient of 95% (paIQ95, in vitro protein-adjusted concentration that results in 95% inhibition), single-agent BIC 75 mg was predicted to provide near-maximal virologic response with a paIQ95 value of approximately 20 (Table 15). In Study GS-US-141-1233, the FDC formulation containing BIC 50 mg, F 200 mg and TAF 25 mg was found to result in similar BIC exposure (within the protocol-defined 70% to 143% boundary of equivalence) compared to BIC 75 mg + F/TAF (200/25 mg) under fasted conditions.

Table 14: Time Weighted Average Change from Baseline up to Day 11 (DAVG11) in Plasma HIV-1 RNA (log10 copies/mL)

	GS-9883 5 mg (N=3)	GS-9883 25 mg (N=4)	GS-9883 50 mg (N=4)	GS-9883 100 mg (N=4)	Placebo (N=4)
$DAVG_{11}$[a]					
N	3	4	4	4	4
Mean (SD)	-0.92 (0.104)	-1.33 (0.174)	-1.37 (0.310)	-1.61 (0.256)	-0.01 (0.144)
95% CI	(-1.18 , -0.66)	(-1.61 , -1.06)	(-1.87 , -0.88)	(-2.01 , -1.20)	(-0.24 , 0.22)
Median	-0.87	-1.33	-1.45	-1.57	0.02
Q1, Q3	-1.04, -0.85	-1.46, -1.20	-1.61, -1.13	-1.77, -1.44	-0.11, 0.10
Min, Max	-1.04, -0.85	-1.54, -1.13	-1.63, -0.96	-1.95, -1.34	-0.21, 0.12
Pairwise p-values[b]					
vs. Placebo	<.001	<.001	<.001	<.001	
vs. GS-9883 100 mg	<.001	0.097	0.15		
vs. GS-9883 50 mg	0.016	0.81			
vs. GS-9883 25 mg	0.026				

Source: Applicant's study report of GS-US-141-1219, Page 56, Table 9-1

Table 15: Trough Plasma Concentrations at Steady State Following BIC Administration Under Fasting Conditions and Corresponding Protein-Adjusted IQ95 Values

GS-9883 dose	n	Median (range) $C_{tau, ss}$ (ng/mL)	Median (range) $paIQ_{95}$[a]
5 mg	4	206.5 (146.0 to 342.0)	1.3 (0.9 to 2.1)
25 mg	4	797.5 (714.0 to 1900.0)	4.9 (4.4 to 11.7)
50 mg	4	2170.0 (852.0 to 3020.0)	13.4 (5.3 to 18.6)
100 mg	4	4190.0 (3730.0 to 5970.0)	25.9 (23.0 to 36.9)

Source: Applicant's study report of GS-US-141-1219, Page 71, Table 10-5

Population PK analysis

The population PK model reasonably describes the PK data pooled from 8 clinical trials in both healthy subjects and HIV patients. Only the dose of 50 mg for BIC was used in the population PK analysis. The model was used to estimate PK parameters for exposure-response analysis. The final population PK model included body weight on CL and Vc, health status (healthy subjects or HIV patients) on Vc, and proton pump inhibitors (PPI) on Ka. Final parameter estimates for BIC are listed in Table 16.

Table 16: Summary of final population PK parameters

Parameter	Parameter Description		Population Estimate (RSE%)	Percent Change from Typical	Inter-Individual Variability (RSE%)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr)	Subject with 80 kg body weight	0.504 (0.88%)	—	27.4 (5.11%)
$exp(\theta_1+\theta_5)$		Subject with 5%tile body weight	0.428	-15.1	
		Subject with 95%tile body weight	0.601	19.2	
$exp(\theta_2)$	Apparent central volume, Vc/F (L)	HIV patient with 80 kg body weight	12.5 (1.62%)	—	11.1 (26.8%)
$exp(\theta_2+\theta_6)$		HIV patient with 5%tile body weight	9.80	-21.5	
		HIV patient with 95%tile body weight	16.2	29.7	
$exp(\theta_2+\theta_7)$		HV with 80 kg body weight	11.6	-7.30	
$exp(\theta_3)$	Absorption rate constant, k_a (1/hr)	Subject without PPI usage	2.60 (7.04%)	—	124 (10.9%)
$exp(\theta_3+\theta_8)$		Subject with PPI usage	1.139	-56.2	
$exp(\theta_4)$	Lag time Tlag (hr)		0.235 (1.70%)	—	—
$\omega_{(CL,Vc)}$	Covariance between CL/F and Vc/F		0.021 (17.8%)		—
σ	Residual error		29.2 (3.53%)		—

Source: Applicant's population PK report for BIC, Page 32, Table 6

Although body weight, health status, and concomitant administration of PPIs are statistically significant covariates on the PK, they did not have a clinically significant impact on BIC exposure (AUC_{tau}, C_{max} and C_{tau}). It is worth noting that PPI in the population PK model was a binary covariate without further clarification such as how PPI was used, thus limited information was provided.

Pharmacodynamics

Exposure-response analysis for efficacy

The E-R relationship for efficacy was evaluated in ART-naive HIV-infected subjects in the Phase 3 Studies (GS-US-380-1489 and GS-US-380-1490) using BIC exposures derived from the population PK model. The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48, as determined by the US FDA-defined snapshot algorithm. A total of 624 subjects were included in the exposure-efficacy analysis accounting for 98.4% patients receiving BIC/F/TAC tablets. The results showed that no

exposure-response relationship was identified for the primary efficacy endpoint and the response rate was consistently high at four exposure quantiles.

Table 17: Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Population Predicted Quartiles of BIC Exposures in ART-Naive HIV-Infected Subjects based on Studies 1489 and 1490

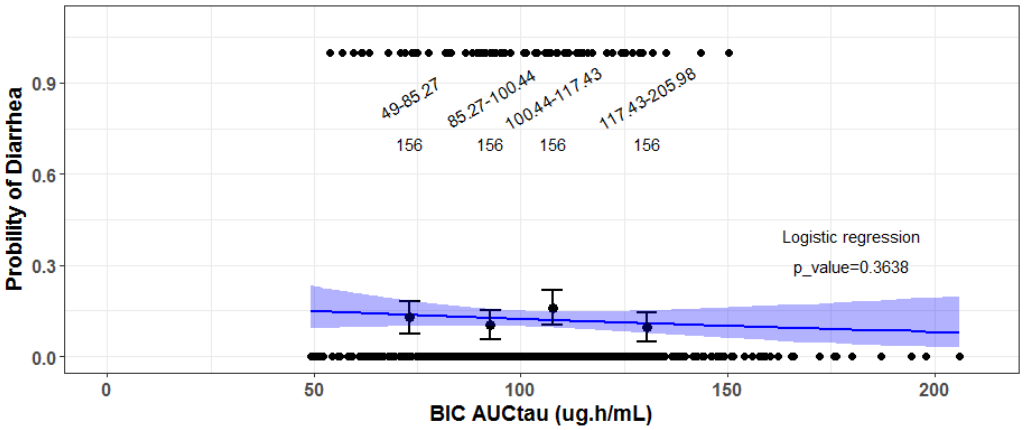
Quantile of BIC AUCtau at Week 48 (ng·h/mL)	No. of subjects	%patients with HIV-1 RNA levels < 50 copies/mL at Week 48
Q1 (≥49173.5-85291.0)	156	93
Q2 (≥85291.0 -100462.8)	156	92
Q3 (≥100462.8-117682.2)	156	89
Q4 (≥117682.2-205983.0)	156	94

Source: Reviewer's analysis

Exposure-response analysis for safety

The exposure-safety relationships for BIC were evaluated in ART-naive HIV-infected subjects in Phase 3 Trials (Trials 1489 and 1490) who received B/F/TAF using BIC exposure estimates (AUCtau and Cmax) derived from population PK modeling. Two safety endpoints were analyzed including diarrhea and headache, as the event rates of both endpoints were more than 10%. A total of 624 subjects were included in exposure-safety analysis accounting for 98.4% patients receiving BIC/F/TAC tablets with 76 subjects (12.2%) experiencing diarrhea and 77 subjects (12.3%) experiencing headache in the treatment arm over 48 weeks. These two AEs were not experienced with F or TAF.

Figure 2: Exposure-response analysis for probability of diarrhea for BIC



Source: Reviewer's analysis

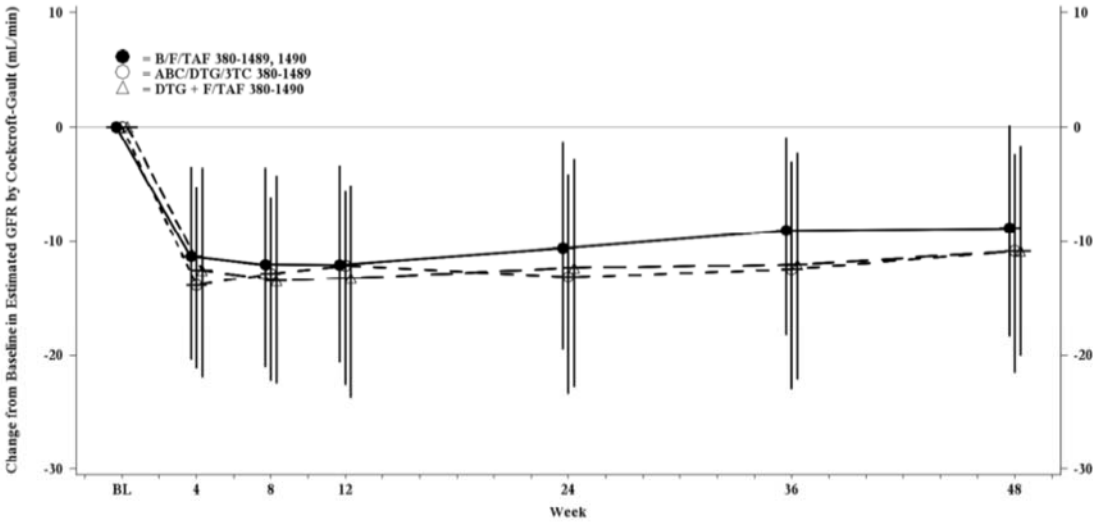
The results suggest no significant exposure-response relationship was identified between AUC_{tau} and probability of diarrhea. A similar result was obtained for probability of headache in which the logistic regression showed that the p value was 0.913.

In summary, the exposure-response relationships for efficacy and safety show the current dose (50 mg) of BIC would provide a sufficient high exposure for efficacy and a reasonable safety profile.

Effect of BIC on serum creatinine via inhibition of renal transporters

BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) in vitro (IC_{50} values of 0.42 µM and 8.04 µM, respectively). Co-administration of BIKTARVY with drugs that are substrates of OCT2 and MATE1 may increase their plasma concentrations. Creatinine, an endogenous marker, often assessed in clinical practice to monitor renal function, is a substrate of several renal transporters such as Organic Cation Transporters (OCTs) and Multi-Drug and Toxin Extrusion Transporters (MATEs). Hence, inhibition of these transporters by BIC may result in decreased active renal secretion of creatinine and a subsequent increase in serum creatinine without underlying renal toxicity. In fact, dose dependent changes in serum creatinine were observed in the drug development program; in trial GS-US-141-1218, after multiple dose administration of BIC for 14 days, serum creatinine change at day 14 (relative to baseline) ranged from 0.05 mg/dL for the 5 mg cohort to 0.18 mg/dL for the 300 mg cohort. In addition, across the Phase 3 development program, changes from baseline in serum creatinine and estimated creatinine clearance were also observed as shown in Figure 3.

Figure 3: Median (Q1, Q3) change from baseline in estimated creatinine clearance (ml/min) by visit in treatment naïve trials (GS-US-380-1489 and GS-US-380-1490)



BL = Baseline; Reference line represents no change from baseline (ie, y = 0).

Source: Summary of Clinical Safety, Page 62

To assess whether the increase in serum creatinine was because of renal injury, the applicant assessed the actual glomerular filtration rate (aGFR) by measuring the systemic clearance of intravenously administered iohexol (Trial GS-US-141-1487). The systemic clearance of iohexol was similar between baseline (day -1) and various assessment days, indicating no change in the aGFR after administration of BIC 75 mg relative to placebo as shown in Table 18.

Table 18: Mean (% CV) pharmacokinetic parameters of iohexol on various days after administration of BIC 75 mg or placebo

Day		BIC 75 mg	Placebo
-1	AUC_{inf} (µg*hr/mL)	424.8 (11.3)	432.2 (8.6)
	CL (mL/min)	128.6 (12.1)	125.6 (8.7)
7	AUC_{inf} (µg*hr/mL)	425.6 (11.8)	409.4 (10.4)
	CL(mL/min)	128.5 (13.2)	133 (9.7)
14	AUC_{inf} (µg*hr/mL)	426.2 (10.4)	417.1 (10.4)
	CL(mL/min)	127.9 (11)	130.6 (10.6)
21	AUC_{inf} (µg*hr/mL)	431.8 (11.9)	423.4 (10.7)
	CL(mL/min)	126.6 (12.4)	128.7 (10.8)

Source: prepared by the reviewer based on information provided on page 58 of the final study report.

An increase in serum creatinine from baseline relative to placebo was observed as shown in Table 19.

Table 19: Mean (95 %) baseline serum creatinine and changes from baseline by study day for 14 days of once daily BIC 75 mg or placebo

Study Day	Serum Creatinine (mg/dL) (mean [95 % CI])	
	BIC 75 mg (N = 20)	Placebo (N= 20)
Baseline (day -1)	1.1 [1, 1.2]	1.1 [1, 1.2]
Change at day 7	0.1 [0.1, 0.2]	0 [-0.1, 0.1]
Change at day 14	0.1 [0, 0.1]	-0.1 [-0.1, 0]
Change at day 21	0 [0, 0.1]	0 [-0.1, 0]

Source: prepared by the reviewer based on information provided on page 63 of the final study report

Of note, the magnitude of change in serum creatinine observed on day 14 (relative to baseline) in Trial GS-US-141-1487 and the magnitude of change in serum creatinine observed in treatment naïve subjects at week 48 (relative to baseline) is similar (approximately 0.1 mg/dL). Further, there are several published articles that describe the same phenomena (no change in actual GFR but increase in serum creatinine [hence decrease in estimated creatinine clearance] due to inhibition of renal transporters) for

several other drugs including another integrase inhibitor, dolutegravir[1]. Overall, based on the totality of information, increase in serum creatinine observed after administration of BIC can be attributed to the inhibitory effect of BIC on renal transporters that mediate the renal elimination of creatinine. Inhibition of renal transporters by BIC can also help to explain the increase in metformin exposures (metformin is a substrate of OCT2 and MATE1).

6.2.3 Therapeutic Individualization

Intrinsic Factors:

Table 20: Effect of Intrinsic Factors on the Pharmacokinetics of BIC*

Intrinsic Factor	Clinical Recommendation	Rationale for Recommendation
Renal Impairment	BIKTARVY can be administered to subjects with estimated CrCL greater than or equal to 30 mL/min. BIKTARVY is not recommended for use in subjects with severe renal impairment (estimated CrCL 15-29 mL/min).	• Based on comparison of unbound (not bound to plasma proteins) exposures, the unbound systemic exposure of BIC in subjects with severe renal impairment (estimated CrCL 15-29 mL/min) was similar to the unbound systemic exposure of BIC in subjects with normal renal function. • Results from the mass balance trial showed that only 1.3 % of the orally administered BIC is excreted unchanged through the renal route. • TAF (when given alone) can be given to subjects with estimated CrCL ≥ 15 mL/min, however, BIKTARVY is not recommended for use in subjects with severe renal impairment (estimated CrCL 15-29 mL/min) because BIKTARVY is a fixed dose combination (FDC) product and F is not approved for use in subjects with estimated CrCl< 30 mL/min.

[1] Arya V et al, J Clin Pharmacol, 2013, 54 (3), 279-281; Chu X et al, Clin Pharmacol Ther, 2016, 100 (5), 437-440; Mathialagan S et al, J Pharm Sci, 2017, 106 (9), 2535-2541.

GS-9883 PK Parameter	GLSM: Severe Renal Impairment (Test) (N = 10)	GLSM: Normal Renal Function (Reference) (N = 8)	GLSM Ratio, % (90% CI)
Total AUC_{inf} (h•ng/mL)	120,378.98	165,738.64	72.63 (48.80, 108.1
Total AUC_{last} (h•ng/mL)	119,198.88	164,570.16	72.43 (48.54, 108.0
Total C_{max} (ng/mL)	5582.27	6950.43	80.32 (59.56, 108.3
Free AUC_{inf} (h•ng/mL)[a]	797.32	802.98	99.29 (79.49, 124.0
Free AUC_{last} (h•ng/mL)[a]	789.50	797.32	99.02 (79.24, 123.7
Free C_{max} (ng/mL)[a]	36.97	33.67	109.80 (87.46, 137.

a Free AUC_{last}, free AUC_{inf}, and free C_{max} were calculated based on unbound plasma GS-9883 (PK parameter × percentage unbound GS-9883 ÷ 100 for each subject).

Source: final clinical study report of trial GS-US-141-1479, page 55

Hepatic Impairment	BIKTARVY can be administered to subjects with mild hepatic impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B). BIKTARVY is not recommended for use in subjects with severe hepatic impairment (Child-Pugh C).	• Based on comparison of unbound BIC exposures, the mean BIC exposure decreased by approximately 23% in subjects with moderate hepatic impairment as compared with normal matched control subjects. The difference between decrease in total and free BIC exposures appears to be driven by the increase in free fraction of BIC in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function. • BIC AUC_{inf} or C_{max} vs Child-Pugh scores did not indicate any trend (albeit based on a limited number of subjects) between systemic exposure of BIC and hepatic function.

BIC PK Parameter	GLSM: Moderate Hepatic Impairment (Test) (N = 10)	GLSM: Healthy Control (Reference) (N = 10)	%GLSM Ratio (90% CI)
AUC_{inf} (h•ng/mL)	99085.41	168779.84	58.71 (41.28, 83.50)
C_{max} (ng/mL)	4798.52	7557.17	63.50 (49.80, 80.96)
C_{24} (ng/mL)	1336.05	2591.06	51.56 (30.96, 85.87)
Free AUC_{inf} (h•ng/mL)	786.84	1028.05	76.54 (56.48, 103.71)
Free C_{max} (ng/mL)	38.11	46.03	82.78 (64.98, 105.45)

GLSM = geometric least-squares mean
Free PK parameter is calculated as: Mean unbound fraction (%) * PK Parameter /100 for a single subject.

Source: final clinical study report of trial GS-US-141-1478, page 52

*: Although the renal impairment trial and hepatic impairment trial were conducted using BIC alone, the recommendations shown in the table above also take into account the approved clinical recommendations pertaining to the use of Descovy® in patients with either renal impairment or hepatic impairment.

Extrinsic Factors: *(Drug-Drug Interactions and Effect of Food)*

The *in vitro* interaction potential of BIC, TAF and FTC with various enzymes and transporters is described in the table below:

Table 21: In vitro interaction potential of BIC, TAF and FTC with various enzymes and transporters

		BIC	F	TAF
Substrate	Enzymes	CYP3A UGT1A1	Primarily renally excreted by a combination of glomerular filtration and tubular secretion. Not significantly metabolized and does not affect enzymes and transporters.	Cathepsin A[2] (PBMCs) CES1 (hepatocytes)
	Transporters	P-gp and BCRP		P-gp, BCRP, OATP1B1, OATP1B3. Not a substrate of OAT1 and OAT3
Inhibition	Enzymes	Not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP26, CYP3A4, UGT1A1. Weak mechanism based inhibitor of CYP3A[1]		Not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1. Weak inhibitor of CYP3A4 *in vitro*; not an inhibitor of enzymes *in vivo*[3]
	Transporters	Not an inhibitor of OATP1B1, OATP1B3, OCT1, BSEP, OAT1, OAT3 Inhibitor of OCT2 and		Not an inhibitor of P-gp

		MATE1		
Induction	Enzymes	weak inducer of CYP3A *in vitro*[1]		not an inducer of CYP3A *in vivo*[3]

[1]BIKTARVY is not anticipated to either inhibit or induce CYP enzymes *in vivo* based on the DDI results with midazolam.
[2]In vivo, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In vitro studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes.
[3]Per the prescribing information of Descovy®.

Table 22: **Clinical Recommendations Related to Extrinsic Factors**

Extrinsic Factor	**Clinical Recommendation**	**Rationale for Recommendation**
Drug-Drug Interactions	Co-administration of BIKTARVY with **dofetilide** is contraindicated	Dofetilide is a substrate of OCT2 and MATE transporters and a narrow therapeutic index drug. Co-administration of BIKTARVY (BIC is an inhibitor of OCT2 and MATE transporters) with dofetilide may increase dofetilide plasma concentrations which can lead to serious and/or life threatening events.
	Co-administration of BIKTARVY with **rifampin** is contraindicated	BIC is a substrate of CYP3A and UGT1A1 enzymes and P-glycoprotein (P-gp) transporters. Co-administration of BIC (given without F/TAF) with rifampin decreased the mean BIC C_{max} and AUC by 28% and 75%, respectively. The decrease in BIC exposure may result in loss of therapeutic effect of BIKTARVY® and development of resistance.
	Co-administration of BIKTARVY with **rifabutin** is not recommended	Co-administration of BIC (given without F/TAF) with rifabutin (an inducer of CYP3A and P-gp) decreased the mean BIC C_{max} and AUC by 20% and 38%, respectively. The decrease in BIC exposure may result in loss of therapeutic effect and development of resistance. Of note, although the concentrations of BIC decrease when given with either rifampin or rifabutin, it is the difference in the magnitude of decrease in BIC exposures (mean AUC of BIC decreased by 75% with rifampin and 38% with rifabutin) which forms the basis of difference in clinical recommendations.
Effect of	BIKTARVY can be	Relative to administration of BIKTARVY under

Extrinsic Factor	Clinical Recommendation	Rationale for Recommendation
Food	administered with or without food	fasting conditions, administration of BIKTARVY with a moderate-fat meal (600 calories; 27% calories from fat) and high-fat meal (800 calories; 50% calories from fat) increased the mean systemic exposure (AUC_{inf}) of BIC (by approximately 25% with moderate-fat meal and high-fat meal) and TAF (by approximately 48% with a moderate fat meal and 67% with a high-fat meal). The mean exposures of F were not significantly affected. The increase in the mean systemic exposure BIC and TAF is not expected to be clinically relevant because BIKTARVY was administered without regard to food in the Phase 3 trials and no major adverse events were observed.

Note: The applicant evaluated the potential for DDI between BIKTARVY with atazanavir (ATV; CYP3A and UGT1A1 inhibitor) and atazanavir/cobicistat (ATV/Cobi; inhibitor of UGT1A1, CYP3A4, and P-gp). ATV increased the mean AUC of BIC by 315 % and ATV/Cobi increased the mean AUC of BIC by 305%. It is important to note that BIKTARVY is a complete regimen for the treatment of HIV-1 infection, therefore, DDI information with other antiretroviral drugs will not be incorporated in the prescribing information of BIKTARVY.

Clinical Recommendations Related to Use of BIKTARVY with Medications Containing Polyvalent Cations

The applicant conducted Trial GS-US-380-3909 to evaluate the effect of simultaneous administration of maximum strength antacid (each 5 mL of antacid oral suspension contains 400 mg of aluminum hydroxide, 400 mg of magnesium hydroxide, and 40 mg of simethicone; the highest recommended dose regimen (20 mL suspension) was used in the trial), calcium or iron supplements on the systemic exposures of BIC (when given as BIC/F/TAF). Further, the applicant evaluated the effect of staggered administration of BIC/F/TAF FDC and antacid compared to administration of BIC/F/TAF FDC alone on the PK of BIC. Based on the review of the information from the DDI trial and considering that antacids and supplements are available over-the-counter and commonly used by HIV-1 infected patients, the applicant was asked to share their perspective on several dosing scenarios that were not evaluated in Trial GS-US-380-3909.

Table 23 shows the magnitude of change in AUC of BIC with different dosing scenarios with AL/Mg containing antacids and supplements, applicant's proposed recommendation and the final recommendation.

Table 23: Magnitude of change in AUC of BIC under various dosing scenarios with AL/Mg containing antacid and supplements, applicant's proposed recommendation and the final recommendation

(b) (4)

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(b) (4)

The applicant accepted the Division's proposal and the final prescribing information reflects the feedback provided to the applicant.

7 Statistical and Clinical Evaluation

7.1 Sources of Clinical Data and Review Strategy

7.1.1 Table of Clinical Trials

The primary trials that support the safety and efficacy of the B/F/TAF (50/200/25 mg) FDC are two Phase 3 trials in HIV-1 infected, treatment-naïve adults (GS-US-380-1489 and GS-US-380-1490) and two Phase 3 trials in HIV-1 infected, virologically suppressed adults (GS-US-380-1844 and GS-US-380-1878). The Applicant also submitted data from a supportive Phase 2 trial of BIC 75 mg + F/TAF in HIV-1 infected treatment-naïve adults (GS-US-141-1475). The Phase 2 and Phase 3 Trials used to support the application are summarized in
Table 24. For a discussion of the pharmacokinetic trials, including drug-drug interaction trials, please refer to Section 6 Clinical Pharmacology.

Table 24: Clinical Trials Relevant to NDA 210251

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Trials to Support Efficacy and Safety							
GS-US-380-1489 (Trial 1489)	MC, R, DB, AC (48 wks)	B/F/TAF (N=300) Vs. ABC/DTG/3TC (N=300)	**Primary:** The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis (FDA-defined snapshot algorithm); **Secondary:** The change from baseline in log10 HIV-1 RNA and CD4+ cell count at Weeks 48	This is an on-going trial and planned for 144 weeks.	631 subjects were randomized and 2 were not dosed. The FAS has 629 subjects.	HIV-1 infected, antiretroviral treatment-naïve (TN) adult subjects.	122 study centers in 9 countries: 2 in Belgium, 8 in Canada, 1 in the Dominican Republic, 6 in France, 3 in Germany, 3 in Italy, 10 in Spain, 8 in the United Kingdom (UK), and 81 in the United States (US).
GS-US-380-1490 (Trial 1490)	MC, R, DB, AC (48 wks)	B/F/TAF (N= 300) Vs. DTG +F/TAF (N=300)	**Primary:** The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis (FDA-defined snapshot algorithm); **Secondary:** The	This is an on-going trial and planned for 144 weeks	657 subjects were randomized and 12 were not dosed. The FAS has 645 subjects.	HIV-1 infected, antiretroviral treatment-naïve (TN) adult subjects.	126 study centers in 10 countries: 6 in Australia, 2 in Belgium, 6 in Canada, 1 in the Dominican Republic, 4 in France, 8 in Germany, 3 in

			change from baseline in log10 HIV-1 RNA and CD4+ cell count at Weeks 48				Italy, 8 in Spain, 11 in the United Kingdom (UK), and 77 in the United States (US).
GS-US-380-1844 (Trial 1844)	MC, R, DB, AC (48 wks)	B/F/TAF (N=280) Vs. ABC/DTG/3TC (N=280)	**Primary:** The percentage of subjects with virologic failure (plasma HIV-1 RNA ≥ 50 copies/mL) at Week 48 as defined by the modified US FDA snapshot algorithm; **Secondaries:** The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis (FDA-defined snapshot algorithm); The change from baseline in log10 HIV-1 RNA and CD4+ cell count at Weeks 48	This is an on-going trial and planned for 96 weeks	567 subjects were randomized and 4 were not dosed. The FAS has 563 subjects.	HIV-1 infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen (of DTG + ABC/3TC or the FDC ABC/DTG/3TC) for ≥ 3 months prior to screening.	96 study centers in 9 countries: 3 in Australia, 1 in Belgium, 5 in Canada, 4 in France, 8 in Germany, 1 in Italy, 7 in Spain, 3 in the United Kingdom (UK), and 64 in the United States (US; including Puerto Rico).
GS-US-380-1878 (Trial	MC, R, DB, AC (48 wks)	B/F/TAF (N=260) Vs.	**Primary:** The percentage of subjects with virologic failure (plasma HIV-1 RNA ≥	This is an on-going trial and planned for 96 weeks	578 subjects were randomized and 1 was not dosed.	HIV-1 infected adult subjects who are virologically suppressed (HIV-1	121 study centers in 10 countries: 68 in the United

1878)		Ritonavir or cobicistat boosted ATV- or DRV- plus FTC/TDF or ABC/3TC (N=260)	50 copies/mL) at Week 48 as defined by the modified US FDA snapshot algorithm; **Secondaries:** The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis (FDA-defined snapshot algorithm); The change from baseline in log10 HIV-1 RNA and CD4+ cell count at Weeks 48		The FAS has 577 subjects.	RNA < 50 copies/mL) on a regimen consisting of ritonavir or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months prior to screening	States, 14 in United Kingdom (UK), 12 in Germany, 7 in Australia, 6 in Canada, 6 in France, 3 in Spain, 2 in Belgium, 2 in Italy, and 1 in the Dominican Republic.
Phase 2 Trial to Support Safety							
GS-US-141-1475	MC, R, DB, AC (48 wks)	Randomized 2:1 ratio to the following: Group 1: BIC 75 mg + F/TAF (200/25mg) + placebo to match DTG 50 mg QD without regard to food Group 2: DTG 50 mg +	Primary: The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 as defined by the FDA snapshot analysis (FDA-defined snapshot algorithm)	48 weeks followed by optional open-label extension in which all subjects receive B/F/TAF FDC	98 subjects were randomized. The FAS has 98 subjects	HIV-1 infected, antiretroviral treatment-naïve (TN) adult subjects.	22 sites in the US

		F/TAF (200/25 mg) + placebo to match BIC 75 mg QD without regard to food					

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled
Source: Reviewers created

7.1.2 Review Strategy

Data Sources

This application was submitted in eCTD format and was entirely electronic. The sources of data used for evaluation of the efficacy and safety of B/F/TAF included protocols, final study reports, statistical analysis plans, the integrated summaries of efficacy and safety, and datasets (in both Study Tabulation Data Module (STDM) and Analysis Data Model (ADaM) formats). The links for the sources of data are provided below:

\\CDSESUB1\evsprod\NDA210251\0000\m5\datasets\gs-us-1489
\\CDSESUB1\evsprod\NDA210251\0000\m5\datasets\gs-us-1490
\\CDSESUB1\evsprod\NDA210251\0000\m5\datasets\gs-us-1844
\\CDSESUB1\evsprod\NDA210251\0000\m5\datasets\gs-us-1878

Data and Analysis Quality

Overall, the quality of the submitted data was adequate for the four trials. SAPs were submitted prior to unblinding. Reviewer guides and annotated SAS programs were included in the submission.

7.2 Review of Relevant Individual Trials Used to Support Efficacy

7.2.1 Trials 1489 and 1490 in HIV-1 Treatment Naïve Subjects

Trial Design and Endpoints

Trial 1489 is an ongoing phase 3, randomized, double-blind study to evaluate Bictegravir/Emtricitabine/Tenofovir Alafenamide versus Abacavir/Dolutegravir/Lamivudine in HIV-1 infected, antiretroviral treatment-naïve (TN) adults. The planned study duration is 144 weeks; however, the current NDA only provides the interim Week 48 results.

Following a screening period, eligible subjects were randomized in a 1:1 ratio to one of the following two treatment groups:

- **Treatment Group 1:** FDC of bictegravir 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) + placebo to match FDC of abacavir 600 mg/ dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) administered orally, once daily, without regard to food (n=300)

- **Treatment Group 2:** FDC of abacavir 600 mg/dolutegravir 50 mg/ lamivudine 300 mg (ABC/DTG/3TC) + Placebo to match FDC of bictegravir 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) administered orally, once daily, without regard to food (n=300)

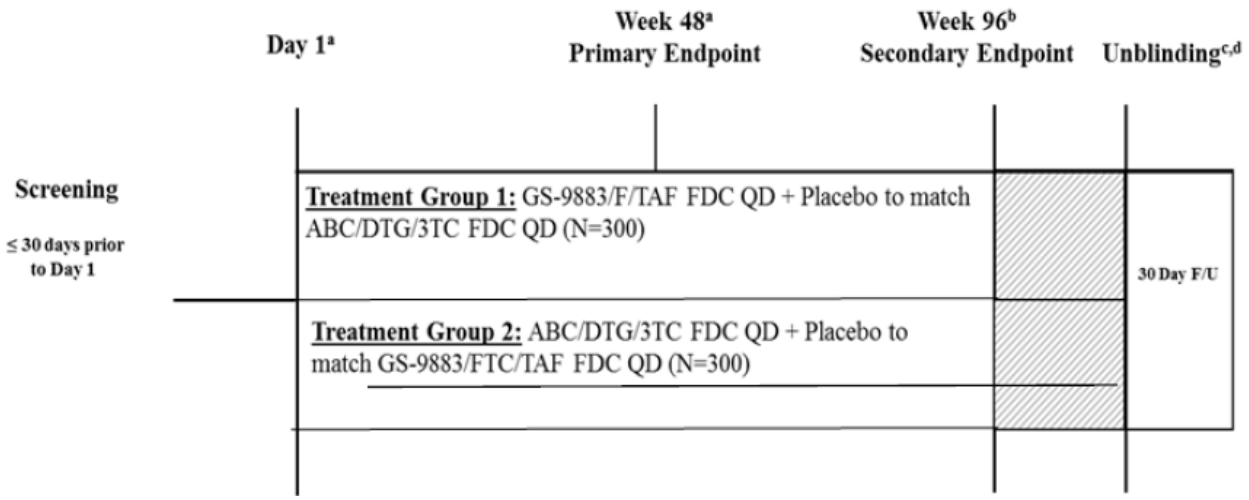


Figure 4: Study Schema for Trial 1489
Source: Applicant's CSR

Trial 1490 is an ongoing phase 3, randomized, double-blind study to evaluate Bictegravir/Emtricitabine/Tenofovir Alafenamide versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 infected, antiretroviral treatment-naïve adults. The study schema is the following:

Eligible subjects were randomized in a 1:1 ratio to one of the following two treatment groups:

- **Treatment Group 1:** FDC of bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) + Placebo to match dolutegravir 50 mg and Placebo to match FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) administered orally, once daily, without regard to food (n=300)

- **Treatment Group 2:** Dolutegravir 50 mg + FDC of emtricitabine 200 mg/tenofovir alafenamide 25 mg (F/TAF) + Placebo to match FDC of GS-9883 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (GS-9883/F/TAF) administered orally, once daily, without regard to food (n=300)

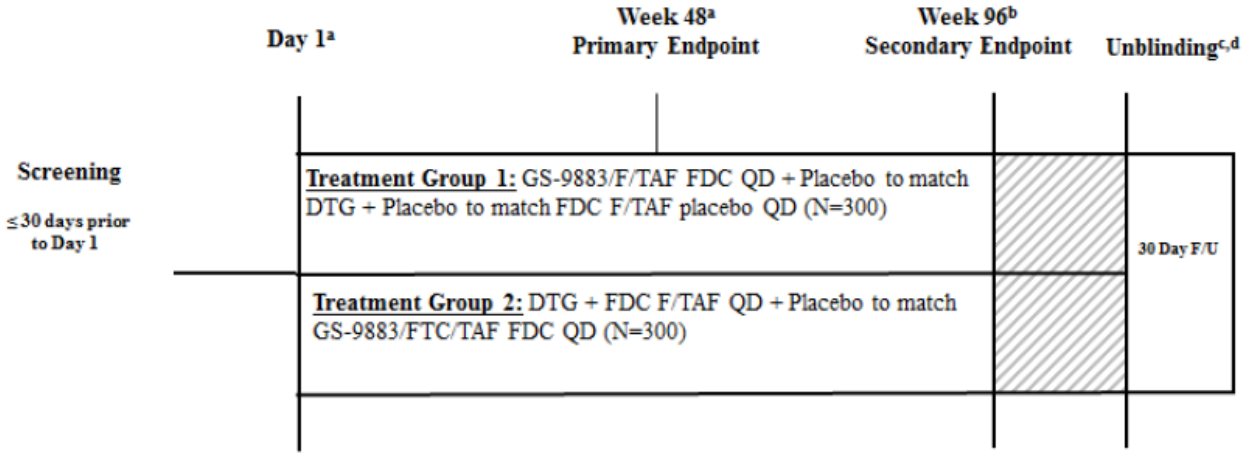


Figure 5: Study Schema for Trial 1490

Source: Applicant's CSR

The study design features of the two trials were nearly identical, except for the differences in the active control groups as described above.

Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL) at the screening visit, CD4+ cell count (< 50 cells/µL, 50 - 199 cells/µL, or ≥ 200 cells/µL) at the screening visit, and region (US vs. Ex-US) at randomization.

Trial Hypotheses:

- **Null hypothesis:** The B/F/TAF group (Treatment Group 1) was at least 12% lower than the active-control group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL ("response rate", as determined by the US FDA-defined snapshot algorithm) at Week 48.

- **Alternative hypothesis:** The B/F/TAF group (Treatment Group 1) was less than 12% lower than the active-control group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48.

Primary Efficacy Endpoint: Proportion of subjects who achieved HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA snapshot algorithm.

Selected Secondary Endpoints:

- The proportion of subjects who achieve HIV-1 RNA < 20 copies/mL at Weeks 48 as defined by the US FDA snapshot algorithm

- The change from baseline in log_{10} HIV-1 RNA and CD4+ cell count at Weeks 48

Sample Size Calculation:

The Applicant calculated the sample size assuming a response rate of 91% in both arms (based on Gilead Studies GS-US-292-0104 and GS-US-292-0111), a 12% non-inferiority (NI) margin, and a one-sided 0.025 significance level. Based on these assumptions, a total of approximately 600 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups was expected to achieve at least 95% power to rule out a non-inferiority margin of 12% in Week 48 response rate (HIV-1 RNA < 50 copies/mL as defined by the US FDA snapshot algorithm) difference between the 2 treatment groups. For trials in the HIV-1 treatment-naïve population, a 12% NI margin is considered clinically acceptable.

Key Inclusion Criteria in Trials 1489 and 1490:

1. Age ≥ 18 years old
2. Antiretroviral treatment naïve (≤ 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) except the use for PrEP (pre-exposure prophylaxis) or PEP (post-exposure prophylaxis), up to one month prior to screening
3. HIV RNA ≥ 500 copies/mL at the screening visit
4. Life expectancy ≥ 1 year
5. Normal ECG (or, if abnormal not clinically significant)
6. AST and ALT ≤ 5X ULN and Total bilirubin ≤ 1.5X ULN or normal direct bilirubin
7. Serum amylase ≤ 5X ULN or if it is greater than 5X ULN, lipase must be ≤ 5X ULN
8. Adequate hematologic function (absolute neutrophil count ≥ 750/mm3; platelets ≥ 50,000/mm3; hemoglobin ≥ 8.5 g/dL
9. Females of childbearing potential must agree to utilize protocol recommended contraceptive methods or be non-heterosexually active or practice sexual abstinence from screening, throughout the duration of the study period, and for 30 days following the last dose of study drug.
10. Male subjects who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception throughout the study period and for 90 days following the last dose of study drug.

Inclusion criteria in the naïve trials differed in three ways: sensitivity to NRTIs that were possible treatment regimens, renal function parameters, and HLA-B*5701 allele screening. In Trial 1489, the screening genotype of local genotype ≤ 90 days prior to screening visit must show sensitivity to FTC, TFV, 3TC, and ABC; while in Trial 1490, the genotypes must show sensitivity to FTC and TFV. In Trial 1489, the estimated glomerular filtration rate (eGFR) had to

be ≥ 50 mL/min according to the Cockcroft-Gault (CG) formula; while in Trial 1490, the $eGFR_{CG}$ had to be ≥ 30 mL/min. Additionally, in Trial 1490, all subjects must have had a negative screening HLA-B*5701 allele test because abacavir was a treatment option.

Key Exclusion criteria in Trials 1489 and 1490:

- Any opportunistic infection indicative of Stage 3 HIV within 30 days prior to screening
- Any serious infection requiring parenteral antibiotic or antifungal within 30 days
- Acute hepatitis within 30 days
- Decompensated cirrhosis
- Active tuberculosis infection
- Malignancy except some skin cancers and cutaneous KS not anticipated to require systemic therapy
- Women who are pregnant or breastfeeding
- Subjects taking any of the following disallowed medications:
  alfuzosin, dofetilide, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, rifampin, cisapride, St. John's Wort, echinaccea, simvastatin, lovastatin, ergot derivatives, amiodarone, dronedarone, lurasidone, pinozide, sildenafil, midazolam (po), triazolam, bepridil, ranolazine, or any antiretroviral drug that is not part of the study regimen.

The trials differed in that Trial 1489 excluded subjects with chronic hepatitis B, and in Trial 1490, subjects with chronic hepatitis B coinfection were permitted to enter the study.

Statistical Analysis Plan

Analysis Windows:

- **Study Day 1** was defined as the day when the first dose of study drug was taken, as recorded on the Study Drug Administration eCRF form.

- **Study Days** were calculated relative to Study Day 1. For events that occurred on or after the Study Day 1 date, study days were calculated as (visit date minus Study Day 1 plus 1). For events that occurred prior to Study Day 1, study days were calculated as (visit date minus Study Day 1).

- **Last Dose Date** is the latest of the blinded study drug end dates recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked for subjects who prematurely discontinued or completed study drug in the "Blinded Treatment" study phase per the Study Drug Completion eCRF.

Subject visits might not have occurred on protocol-specified days. Therefore, for the analysis, observations were assigned to analysis windows. The analysis windows for HIV-1 RNA, CD4+ cell count, and CD4 % are presented in Table 25.

Table 25: Analysis Windows for HIV-1 RNA, CD4+ cell count and CD4 %*

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week 108	756	715	798
Week 120	840	799	882
Week K (K is every 12 weeks after previous visit)	K*7	(K-6)*7+1	(K+6)*7

*: Source: from trial GS-US-380-1489 SAP.

Analysis Populations:

- **Full Analysis Set (FAS):** all subjects who were randomized and received at least 1 dose of study drug. This population was used for the primary efficacy analyses. Subjects were grouped per the treatment to which they were randomized.

- **Per-Protocol (PP) Analysis Set**: all subjects who were randomized, received at least 1 dose of study drug, and did not commit any major protocol violation, including violation of key entry criteria. Subjects were grouped per the treatment received.

- **Safety Analysis Set:** all randomized subjects who received at least 1 dose of study drug. All the data collected up to 30 days after subjects permanently discontinue their study drug was included in the safety summaries, unless specified in SAP. Subjects were grouped per the treatment received.

Efficacy Analyses:

Non-inferiority was assessed using the conventional confidence interval approach. The point estimate of the treatment difference (B/F/TAF – active-control) and the associated 2-sided 95% confidence interval was constructed using a normal approximation method based on stratified Mantel-Haenszel proportions. Stratification factors included baseline HIV-1 RNA level (≤ 100,000 copies/mL vs. > 100,000 copies/mL) and region (US vs. Ex-US). CD4+ cell count was not used as a stratum in the analysis since HIV-1 RNA and CD4+ cell count are generally highly correlated. In addition, the exclusion of the stratum was proposed to avoid small or missing cells in the analysis.

The non-inferiority of B/F/TAF to the active-control was demonstrated if the lower bound of the 2-sided 95.002% CI of the difference (B/F/TAF – active-control) in the response rate was greater than -12%. If non-inferiority of B/F/TAF to active-control was established, the lower bound of the 95.002% CI was to then be compared to 0. Superiority would be demonstrated if the lower bound of the 95.002% CI was greater than 0. The 95.002% CI was used due to the interim analyses described below.

For the secondary efficacy endpoint, the change from baseline in CD4 count at Week 48, the applicant conducted completer analysis and last observation carry forward (LOCF) analysis to impute missing values. However, LOCF is not the recommended approach to imputing missing values due to its potential bias and it can underestimate the variability of the CD4 counts. Baseline observation carry forward (BOCF) analysis was conducted by the reviewer to impute missing values and the consistency of findings among these analyses were compared. The results based on these three approaches were similar and the completer analysis results were included in the label.

Interim analysis

An external Independent Data Monitoring Committee (IDMC) reviewed the progress, efficacy, and safety data of this study while the study was ongoing. No formal stopping rules were used by the IDMC.

The Independent Data Monitoring Committee (IDMC) analysis at Week 12 was conducted after approximately the first 50% of subjects enrolled completed their Week 12 visit or prematurely discontinued the study drug. The Week 24 IDMC analysis was conducted after all subjects enrolled completed their Week 24 visit or prematurely discontinued the study drug. The purpose of these interim analyses was to provide the IDMC with a statistical report for review.

For each interim analysis performed for the IDMC at Weeks 12 and 24, an alpha of 0.00001 was spent. Therefore, the significance level for the 2-sided test in the primary analysis at Week 48 was 0.04998 (corresponding to 95.002% CI).

Protocol Amendments

Amendment 1 on February 19, 2016 and Amendment 2 on October 19, 2016 were received for Trials 1489 and 1490 and are described below. For clarity in this section, the two amendments are bolded and the trials are underlined.

Amendment 1 for Trial 1489 included minor editorial changes, updated information, and the following:

1. Clinical Trials.gov identifier is NCT02607930 (EudraCT number is 2015-004024-54) for 1489
2. Subjects in UK and Sweden were given the option to continue B/F/TAF for an open label 48-week extension. Prior to this amendment, they were to stop taking study drug after 48 weeks and complete a 30 day follow up visit and return to standard of care.
3. Management of potential hepatobiliary toxicity was updated to specify a work up and prompt communication with the Gilead Medical Monitor because of biliary hyperplasia and hepatocyte hypertrophy on histopathologic examination in monkeys given high doses of B/F/TAF.

Amendment 1 for Trial 1490 included #2 and #3 above and the following:

- Clinical Trials.gov Identifier: NCT02607956 (EudraCT Number: 2015-003988-10)

Amendment 2 for Trials 1489 and 1490 included minor editorial changes and the following:

- Extended duration of the blinded phase of the study from 96 weeks of treatment to 144 weeks
- Added the open-label rollover extension and treatment assessments for subjects to receive open-label extension (OLE) B/F/TAF FDC
- Clarification of procedures throughout the study and OLE period
- Added HBV and HCV serology testing every 48 weeks

7.2.2 Trials 1844 and 1878 in Virologically-Suppressed HIV-1 Subjects

The efficacy of B/F/TAF for the treatment of HIV-1 infection in virologically suppressed adult patients was evaluated in Trials 1844 and 1878. These are two ongoing Phase 3, randomized, active-controlled trials differing by the antiretroviral drugs in the comparator arms, some inclusion/exclusion criteria, and whether the trials were blinded or open-label. The trials are described individually and aggregated, when feasible, in the section below.

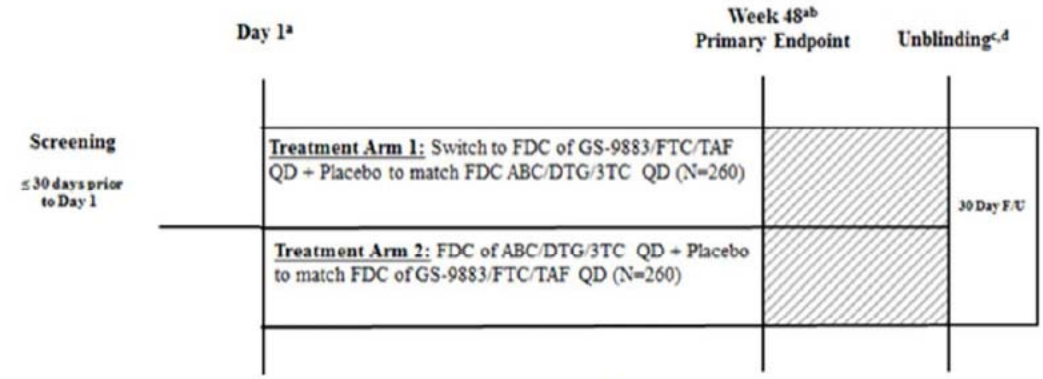
Trial Design and Endpoints

Trial 1844 is a phase 3, randomized, **double blind** active comparator trial that compared switching HIV-1 infected adults who were virologically suppressed on a regimen consisting of DTG and ABC/3TC, or on a regimen of fixed dose combination (FDC) of ABC/DTG/3TC, to either

B/F/TAF FDC or ABC/DTG/3TC FDC once daily. Subjects had to be virologically suppressed for ≥ 3 months prior to screening. Five hundred sixty-three subjects were randomized in a 1:1 ratio to one of the two treatment groups as described below:

- **Treatment Group 1**: FDC of B/F/TAF (50/200/25 mg) administered orally, once daily, without regard to food + Placebo to match FDC of ABC/DTG/3TC (600/50/300 mg) administered orally, once daily, without regard to food (n=260)

- **Treatment Group 2**: FDC of ABC/DTG/3TC (600/50/300 mg) + Placebo to match FDC of B/F/TAF (50/200/25 mg) administered orally, once daily, without regard to food (n=260)



a. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 48.
b. After Week 48, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded. Subjects' treatments will be unblinded after the last subject completes the Week 48 visit and Gilead completes the Week 48 analysis. After Week 48 Visit, subjects in the United Kingdom and Sweden will stop taking study drug and complete a 30 day follow up visit and return to the standard of care.
c. Once Gilead Sciences provides unblinded treatment assignments to the Investigators, all subjects will return to the clinic (preferably within 30 days) for an Unblinding Visit. At the Unblinding Visit, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC in an open label extension for 48 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.
d. Subjects who complete the study through the Unblinding Visit and do not continue on the open-label GS-9883/F/TAF FDC extension phase will be required to return to the clinic 30 days after the completion of study drugs for a 30-Day Follow-Up Visit.

Figure 6: Study Schema for Trial 1844

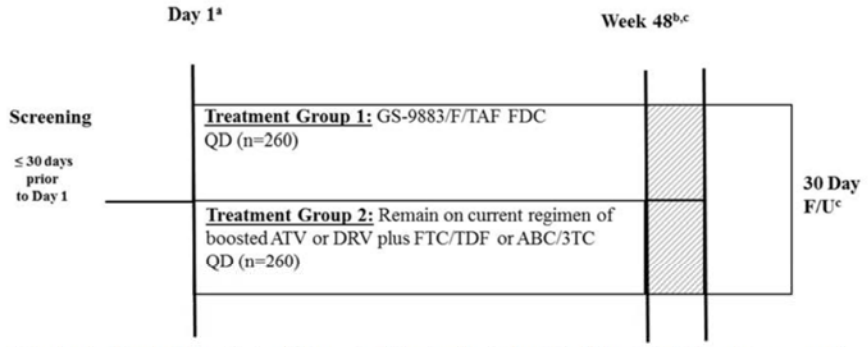
Source: Original protocol submission

Trial 1878 is a phase 3, randomized, **open label** trial that compared switching HIV-1 infected adults who were virologically suppressed on a regimen consisting of ritonavir (RTV) or cobicistat (COBI) boosted ATV or DRV plus either FTC/TDF or ABC/3TC, to either B/F/TAF FDC once daily or remaining on their current regimen. Subjects had to be virologically suppressed for ≥ 6 months prior to screening. Five hundred sixty-three subjects were randomized in a 1:1 ratio to one of the two treatment groups as described below:

- **Treatment Group 1:** Switch to a FDC of bictegravir 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) administered orally, once daily without regard to food (n=260)
- **Treatment Group 2:** Remain on current antiretroviral regimen consisting of ritonavir (RTV) or cobicistat (CO) boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally, once daily with food (n=260).

SBR (i.e., Stay on Baseline Regimen) is used throughout this review as an abbreviation to refer to Treatment Group 2.

Randomization was stratified by the prior treatment regimen group (i.e., TDF containing regimens and non-TDF containing regimens) at screening.



a. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Week 48.
b. After Week 48, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC for additional 48 weeks and attend study visits every 12 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first.
c. Subjects who complete the study through the Week 48 Visit and do not wish to receive GS-9883/F/TAF FDC will be required to return to the clinic 30 days after the completion of study drugs for a 30-Day Follow-Up Visit.

Figure 7: Study Schema for Trial 1878

Source: Original protocol submission

Trial Hypotheses:

- **Null hypothesis:** The B/F/TAF group (Treatment Group 1) is at least 4% higher than the active-control group (Treatment Group 2, FDC of ABC/DTG/3TC in trial 1844 or SBR for trial 1878) with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL as determined by the US FDA-defined snapshot algorithm) at Week 48.

- **Alternative hypothesis:** The B/F/TAF group (Treatment Group 1) is less than 4% higher than the active-control group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48.

Primary Efficacy Endpoint: Proportion of subjects who achieved HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the US FDA snapshot algorithm.

Selected Secondary Endpoints:

- The proportion of subjects who achieve HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA snapshot algorithm
- The change from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count at Week 48

Sample Size Calculation:

Assuming that both groups have 2% of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 (based on the historical Gilead Genvoya (GEN; E/C/F/TAF) and Stribild [STB] studies), 4% of non-inferiority (NI) margin, and a one-sided 0.025 significance level, approximately 520 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups was expected to achieve at least 90% power to detect a non-inferiority margin of 4% difference in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 between the 2 treatment groups. For the virologically suppressed population, a 4% NI margin is considered clinically acceptable.

Key Inclusion in Trials 1878 and 1844:

1. Age ≥ 18 years old
2. HIV RNA < 50 copies/mL at the screening visit
3. Estimated glomerular filtration rate ≥ 50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft-Gault formula
4. Subjects were to be on the first or second antiretroviral regimen with HIV RNA < 50 copies/mL with documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 3 months preceding the Screening Visit. Prior changes in antiretroviral regimen were only allowed due to tolerability issues or for regimen simplification. Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening were acceptable.
5. Life expectancy ≥ 1 year
6. Have no documented or suspected resistance to FTC, TFV, DTG, ABC, or 3TC including, but not limited to, the reverse transcriptase resistance mutations K65R and M184V/I
7. Normal ECG (or, if abnormal not clinically significant)
8. AST and ALT ≤ 5X ULN and Total bilirubin ≤ 1.5X ULN or normal direct bilirubin
9. Serum amylase ≤ 5X ULN or, if greater than 5X ULN, lipase must be ≤ 5X ULN
10. Adequate hematologic function (absolute neutrophil count ≥ 750/mm3; platelets ≥ 50,000/mm3; hemoglobin ≥ 8.5 g/dL
11. Females of childbearing potential must agree to utilize protocol recommended contraceptive methods or be non-heterosexually active or practice sexual abstinence from screening, throughout the duration of the study period, and for 30 days following the last dose of study drug.

12. Male subjects who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception throughout the study period and for 90 days following the last dose of study drug.

The trials differed in inclusion criteria regarding the regimen on which they were virologically suppressed with an HIV RNA < 50 copies/mL. In 1844, subjects were to currently be virologically suppressed and receiving a once daily antiretroviral regimen consisting of DTG + ABC/3TC, or ABC/DTG/3TC FDC for ≥ 3 months prior to the screening visit. In Trial 1878, subjects had to be virologically suppressed on a stable regimen of ritonavir (RTV)- or cobicistat (COBI)-boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 consecutive months prior to screening. In Trial 1878, they must not have previous use of any approved or experimental INSTI.

Key Exclusion Criteria in <u>Trials 1878 and 1844</u>:

- Any opportunistic infection indicative of Stage 3 HIV within 30 days prior to screening
- Any serious infection requiring parenteral antibiotic or antifungal within 30 days of Day 1
- Acute hepatitis within 30 days
- Decompensated cirrhosis
- Active tuberculosis infection
- Malignancy except some skin cancers and cutaneous KS not anticipated to require systemic therapy
- Women who are pregnant or breastfeeding
- Subjects taking any of the following disallowed medications:
  alfuzosin, dofetilide, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, rifampin, cisapride, St. John's Wort, echinaccea, simvastatin, lovastatin, ergot derivatives, amiodarone, dronedarone, lurasidone, pinozide, sildenafil, midazolam (po), triazolam, bepridil, ranolazine, or any antiretroviral drug that is not part of the study regimen.

These trials differed in that Trial 1844 excluded subjects with chronic hepatitis B, and Trial 1878, allowed subjects with chronic hepatitis B coinfection to enter the study, providing they were receiving a TDF-containing regimen at screening.

<u>Study procedures</u>

Standard hematology, clinical chemistry monitoring and urine tests were performed and metabolic assessments were analyzed at weeks 12, 24, and 48. Hepatitis B and C serologies were done at screening. For subjects who had HBV infection, plasma HBV DNA were drawn along with HBsAb, HBsAg, and HBeAg (if negative, reflex HBeAb) at Weeks 12, 24 and 48. Subjects in treatment group 1 had a single anytime pre- or post-dose PK blood at Weeks 8, 24 and 36. Subjects in this group also had an observed dosing in clinic with a trough PK blood sample collected between 20-28 hours following their last dose at Weeks 4 and 12.

In Trial 1844, a Bone Densitometry test (DXA scan) was done at baseline, Week 24, and Week 48. For subjects in Germany DXA scans were not performed.

Subjects had a 30-day follow-up visit after the Week 48 visit or after early discontinuation of study.

Statistical Analysis Plan

The definitions of study days, analysis windows, analysis populations and interim analyses in these two virologically suppressed trials were identical to the two TN trials, as detailed above.

Efficacy Analyses:

Non-inferiority was assessed using the conventional confidence interval approach. The point estimate of the treatment difference (B/F/TAF group – active-control group) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL and the associated 2-sided 95.002% CI was constructed based on an unconditional exact method using 2 inverted 1-sided tests.

The non-inferiority of B/F/TAF to the active-control (ABC/DTG/3TC for trial 1844 or SBR for trial 1878) was demonstrated if the upper bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF group – active-control group) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL was less than 4%.

If noninferiority of B/F/TAF to the active-control was established, the evidence of efficacy at Week 48 was also then be evaluated for superiority. Superiority would be demonstrated if the upper bound of the 95.002% CI is less than 0.

Reviewer Comment: 95.002% CI was used in the primary efficacy analysis due to the two interim analyses, each of which has spent an alpha of 0.00001. In the final analyses, the 95% CIs were very close to 95.002% CIs.

Protocol Amendments

The Applicant submitted two protocol amendments. Amendment 1 was submitted on February 19, 2016 and Amendment 2 on October 19, 2016 for Trials 1844 and 1878.

Amendment 1 for Trial 1844 included minor editorial changes, updated information, and the following changes:

1. Clinical Trials.gov identifier is NCT02603120 (EudraCT number is 2015-004025-14) for 1844
2. Subjects in UK and Sweden were given the option to continue B/F/TAF for an open label 48-week extension. Prior to this amendment, they were to stop taking study

drug after 48 weeks and complete a 30 day follow up visit and return to standard of care.

3. Inclusion criteria #4 above was revised to "Currently on a stable regimen for ≥ 3 months preceding the screening visit with documented plasma HIV-1 RNA < 50 copies/mL for ≥ 3 months preceding the screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL)." *This update removed the limit on the number of prior regimens at screening.*
4. Management of potential hepatobiliary toxicity was updated to specify a work up and prompt communication with the Gilead Medical Monitor because of biliary hyperplasia and hepatocyte hypertrophy on histopathologic examination in monkeys given high dose of B/F/TAF.

Amendment 1 for Trial 1878 included changes #2 and #4 as stated above and that Clinical Trials.gov Identifier is NCT02603107(EudraCT Number: 2015-004011-20)

Amendment 2 for Trials 1844 and 1878 included minor changes including :

- Open Label Extension (OLE) extended up to 96 weeks
- Clarification of procedures throughout the study and OLE period
- Subjects with HCV were to have HCV RNA test performed every 48 weeks

7.3 Study Results

7.3.1 Compliance with Good Clinical Practices

The Applicant states that clinical trials were conducted following Good Clinical Practice standards and considerations for the ethical treatment of human subjects and conducted under an IND application according to ICH standards and 21CFR 312.20. The Applicant specifies that clinical trials not conducted under U.S. IND were conducted in compliance with the European Community Directive 2001/20/EC, as well as other local legislation.

7.3.2 Financial Disclosure

Site-specific metrics provided by the Sponsor identified 41 sites with investigators and sub-investigators with disclosable financial interests/arrangements. The majority of the sites with investigators and sub-investigators with disclosable financial interests enrolled 2% or less of the subjects in the individual trials. The disclosed financial interests and/or arrangements did not appear to affect the approvability of this application (see Section 15.2 Financial Disclosure).

7.3.3. Patient Disposition, Demographics and Baseline Disease Characteristics

In three trials 1489, 1844, and 1878, the number of records in the ADSL datasets exceeded the number of subjects who were screened. This was a result of the re-screening of subjects who failed the initial screening. The number of subjects who were randomized or dosed in the trials was not impacted. Details were provided in the applicant's explanation of the discrepancy submitted on Oct. 2, 2017.

For **Trial 1489**, 739 subjects were screened (ADSL had 740 records) and 631 subjects were randomized. Two randomized subjects, both in the B/F/TAF group, were not dosed. As a result, the FAS included 629 subjects, 314 in the B/F/TAF group and 315 in the ABC/DTG/3TC group. Of these 629 subjects, 94% in the B/F/TAF group and 95% in the ABC/DTG/3TC group completed 48 weeks of drug treatment, and 6% of subjects prematurely discontinued study drug (see Table 26). The reasons for discontinuation of study drugs were comparable between the two groups.

Table 26: Subjects Disposition for Trial 1489 (Treated Subjects)

Category	B/F/TAF	ABC/DTG/3TC	Total
Completed Week 48 Study Drug			
N	314	315	629
YES	295(93.9%)	299(94.9%)	594(94.4%)
NO	**19(6.1%)**	**16(5.1%)**	**35(5.6%)**
Reasons of NOT completed treatment			
Adverse Event	0	4	4
Investigator's Discretion	3	0	3
Lost to Follow-Up	9	6	15
Non-Compliance with Study Drug	1	1	2
Pregnancy	1	0	1
Protocol Violation	1	0	1
Subject Decision	4	5	9
Completed Week 48 Study			
NO	18	14	32

Source: statistical reviewer's analysis

For **Trial 1490**, 742 subjects were screened (ADSL had 742 records) and 657 subjects were randomized. Twelve randomized subjects (three in the B/F/TAF group and nine in the TDG/F/TAF group) were not dosed. Thus, the FAS included 645 subjects, 320 in the B/F/TAF group and 325 in the DTG/F/TAF group. Of these 645 subjects, 91% in the B/F/TAF group and 94% in the DTG/F/TAF group completed 48 weeks of drug treatment, and 7% of subjects prematurely discontinued study drug (see Table 27). The reasons for discontinuation of study drugs were comparable between the two groups. Five subjects in the B/F/TAF group discontinued due to an Adverse Event (AE), and two subjects in the DTG/F/TAF group

discontinued due to death. Also, one subject in the B/F/TAF group discontinued from the trial due to death.

Table 27: Subjects Disposition for Trial 1490 (Treated Subjects)

Category	B/F/TAF	DTG/F/TAF	Total
Completed Week 48 Study Drug			
N	320	325	645
Yes	292(91.3%)	305(93.8%)	597(92.6%)
No	**28(8.8%)**	**20(6.2%)**	**48(7.4%)**
Reasons of NOT completed treatment			
Adverse Event	**5**	1	6
Death	0	**2**	2
Investigator's Discretion	4	0	4
Lost to Follow-Up	8	5	13
Non-Compliance with Study Drug	0	2	2
Pregnancy	2	2	4
Protocol Violation	2	1	3
Subject Decision	7	7	14
Completed Week 48 Study			
No	24	18	42

Source: statistical reviewer's analysis

For **Trial 1844**, 646 subjects were screened (ADSL had 651 records) and 567 subjects were randomized. Four randomized subjects, two in each group were not dosed. Thus, the FAS had 563 subjects, 282 in the B/F/TAF group and 281 in the ABC/DTG/3TC group. Of these 563 subjects, 95% in the B/F/TAF group and 95% in the ABC/DTG/3TC group completed 48 weeks of drug treatment, and 5% of subjects prematurely discontinued study drug (see Table 28). The reasons for discontinuation of study drugs were comparable between two groups. Two subjects in the B/F/TAF group discontinued due to death.

Table 28: Subjects Disposition for Trial 1844 (Treated Subjects)

Category	B/F/TAF	ABC/DTG/3TC	Total
Completed Week 48 Study Drug			
N	282	281	563
Yes	267(94.7%)	268(95.4%)	535(95.0%)
No	15(5.3%)	13(4.6%)	28(5.0%)
Reasons of NOT completed treatment			

Adverse Event	6	2	8
Death	2	0	2
Lost to Follow-Up	2	2	4
Pregnancy	1	1	2
Subject Decision	4	8	12
Completed Week 48 Study			
No	10	12	22

Source: statistical reviewer's analysis

For **Trial 1878**, 707 subjects were screened (ADSL had 710 records) and 578 subjects were randomized. One randomized subject in the SBR group was not dosed. Thus, the FAS had 577 subjects, 290 in the B/F/TAF group and 287 in the SBR group. Of these 577 subjects, 95% in the B/F/TAF group and 91% in the SBR group completed 48 weeks of drug treatment and 7% of subjects prematurely discontinued study drug (see Table 29). The reasons for discontinuation of study drugs were comparable between the two groups. Two subjects, one in each group, discontinued due to death.

Table 29: Subjects Disposition for Trial 1878 (Treated Subjects)

Category	B/F/TAF	SBR	Total
Completed Week 48 Study Drug			
N	290	287	577
Yes	274(94.5%)	261(90.9%)	535(92.7%)
No	16(5.5%)	26(9.1%)	42(7.3%)
Reasons of NOT completed treatment			
Adverse Event	2	1	3
Death	1	1	2
Investigator's Discretion	1	1	2
Lack of Efficacy	1	0	1
Lost to Follow-Up	0	3	3
Non-Compliance with Study D	1	1	2
Protocol Violation	1	5	6
Subject Decision	9	14	23
Completed Week 48 Study			
No	13	21	34

Source: statistical reviewer's analysis

Randomization

In the two treatment-naive trials, 1489 and 1490, randomization was stratified by three factors:

- HIV-1 RNA level: ≤ 100,000 copies/mL,
  > 100,000 to ≤ 400,000 copies/mL, or

- CD4+ cell count: > 400,000 copies/mL at screening
  < 50 cells/µL,
  50 – <200 cells/µL, or
  ≥ 200 cells/µL at screening
- Region: US or Ex-US at randomization.

Trial 1489:

The numbers of subjects randomized to two groups in each stratum were comparable with the maximum difference of 4 (Table 30); indicating that the randomization worked well. As shown in the Table 30, most subjects had a CD4 cell counts ≥ 200 cells/µL and an HIV-1 RNA viral load at the screening visit of ≤ 100,000 copies/mL. Thus, stratification factors only included baseline HIV-1 RNA level (≤ 100,000 copies/mL vs. > 100,000 copies/mL) and region (US vs. Ex-US) for the stratified efficacy analyses to avoid small or missing cells in analysis strata, as stated in the SAP (Table 31).

Table 30: Randomization Stratification for Trial 1489 (Randomized Subjects)

HIV-1 RNA Viral Load at Screening visit	CD4 Count at Screening visit (# in B/F/TAF : # in ABC/DTG/3TC)		
	[0, <50]	[≥ 50 , < 200]	[≥ 200]
[0, ≤ 100 K]	US: 3 : 3	US: 11 : 11	US: 176 (2*) : 178
	EX-US: 0 : 0	EX-US: 3 : 3	EX-US: 66 : 62
[> 100 K , ≤ 400 K]	US: 2 : 1	US: 8 : 7	US: 22 : 21
	EX-US: 0 : 0	EX-US: 2 : 0	EX-US: 9 : 13
[> 400 K,]	US: 2 : 3	US: 0 : 1	US: 6 : 7
	EX-US: 0 : 0	EX-US: 1 : 1	EX-US: 4 : 3

* two subjects were randomized but not dosed in the trial.
Source: statistical reviewer's analysis

Table 31: Stratification Used for Efficacy Analyses Adjustment for Trial 1489 (Treated Subjects)

HIV-1 RNA Viral Load at Baseline (not at Screening visit) for the analysis	Region (# in B/F/TAF : # in ABC/DTG/3TC)	
	US	EX-US
≤ 100 K, copies/mL	190 : 196	69 : 71
>100 K, copies/mL	38 : 37	15 : 13

Source: statistical reviewer's analysis

Trial 1490:

Like Trial 1489, the numbers of subjects randomized to two groups in each stratum were comparable with the maximum difference of 3 (Table 32). This indicated that the randomization worked well. As shown in the Table 32, most subjects had CD4 cell counts ≥ 200 cells/µL and an HIV-1 RNA viral load at the screening visit of ≤ 100,000 copies/mL. Thus, stratification factors

only included baseline HIV-1 RNA level (≤ 100,000 copies/mL vs. > 100,000 copies/mL) and region (US vs. Ex-US) for the stratified efficacy analyses to avoid small or missing cells in analysis strata as stated in the SAP (Table 33).

Table 32: Randomization Stratification for Trial 1490 (Randomized Subjects)

HIV RNA Viral Load at Screening visit	CD4 Count at Screening visit (# in B/F/TAF : # in DTG/F/TAF)		
	[0, <50]	[≥ 50 , < 200]	[≥ 200]
[0, ≤ 100 K]	US: 5 : 4	US: 12 : 11	US: 135 (2*) : 136 (3*)
	EX-US: 0 : 0	EX-US: 5 : 3	EX-US: 108 (3*) : 111 (2*)
[> 100 K , ≤ 400 K]	US: 5 : 5	US: 8 : 10	US: 22 : 22
	EX-US: 0 : 0	EX-US: 3 : 4	EX-US: 10 (2*) : 11
[> 400 K,]	US: 1 : 1	US: 3 : 2	US: 3 : 4
	EX-US: 0 : 0	EX-US: 1 : 1	EX-US: 5 : 4

*: Twelve subjects were randomized but not dosed in the trial.
Source: statistical reviewer's analysis

Table 33: Stratification Used for Efficacy Analyses Adjustment for Trial 1490 (Treated Subjects)

HIV-1 RNA Viral Load at Baseline (not at Screening visit) for the analysis	Region (# in B/F/TAF : # in DTG/F/TAF)	
	US	EX-US
≤ 100 K, copies/mL	148 : 161	106 : 110
>100 K, copies/mL	45 : 32	21 : 22

Source: statistical reviewer's analysis

Trial 1844:

There were no stratification factors used at randomization for this trial. Two hundred eighty-four subjects were randomized to the B/F/TAF group and 283 subjects were randomized to the ABC/DTG/3TC active-control group. The number of subjects between the two groups is balanced. There were 2 subjects in each group who were not dosed. Thus, the number of subjects in the FAS is 282 for the B/F/TAF group and 281 for the ABC/DTG/3TC group.

Trial 1878:

The numbers of subjects randomized to the two groups in each stratum were comparable with the maximum difference of 2 (Table 34). This indicated that the randomization worked well.

After reviewing all information of previous ARV treatment, two subjects were changed from previous ARV treatment containing non-TDF to containing TDF as shown in the Table 35. These were used for the final efficacy subgroup analyses.

Table 34: Randomization Stratification for Trial 1878 (Randomized Subjects)

Previous ARV regime from CRF at Screening Visit (Stratum)	Treatment Group	
	B/F/TAF	SBR
Containing TDF	244	242 (1*)
Containing Non-TDF	46	45

*One subject was randomized but not dosed in the trial.
Source: statistical reviewer's analysis

Table 35: Stratification Used for Efficacy Analyses Adjustment for Trial 1878 (Treated Subjects)

Previous ARV from All Available Information		Treatment Group			
		B/F/TAF		SBR	
Containing TDF	Boosted ATV + FTC/TDF	105	245	110	243
	Boosted DRV + FTC/TDF	140		133	
Containing Non-TDF	Boosted ATV + ABC/3TC	21	45	23	44
	Boosted DRV + ABC/3TC	24		21	

Source: statistical reviewer's analysis

Demographic and Baseline Disease Characteristics

Trial 1489:

Demographic and baseline characteristics were similar between the two groups (**Table 114** in the Appendix). Most subjects were male (90%), not Hispanic/Latino (78%), and white (57%) or black (36%). The mean age was 34 years (range 18-71). The mean baseline HIV-1 RNA viral load was 4.4 $\log_{10}$ copies/mL (range 1.3-6.5) and 84% of subjects had HIV-1 RNA ≤ 100,000 copies/mL at baseline. The mean baseline CD4+ cell count was 464 cells/µL (range 0-1424), 11% of subjects had CD4+ cell counts less than 200 cells/µL, and 41% of subjects had CD4+ cell counts equal to or greater than 500 cells/µL. Overall, 2.5% of subjects had a medical history of cardiovascular disease, 4.5% of subjects had a medical history of diabetes, 12.1% of subjects had a medical history of hypertension, and 12.4% of subjects had a medical history of hyperlipidemia. Most subjects (73%) were from the US.

Trial 1490:

Demographic and baseline characteristics were similar between the two groups (**Table 115** in the Appendix). Most subjects were male (88%), not Hispanic/Latino (75%), and white (59%) or black (31%). The mean age was 37 years (range 18-77). The mean baseline HIV-1 RNA viral load was 4.4 $\log_{10}$ copies/mL (range 2.3-6.6) and 81% of subjects had HIV-1 RNA ≤ 100,000 copies/mL at baseline. The mean baseline CD4+ cell count was 456 cells/µL (range 2-1636), 12% of subjects had CD4+ cell counts less than 200 cells/µL, and 37% of subjects had CD4+ cell counts equal to or greater than 500 cells/µL. Overall, 2.3% of subjects had a medical history of cardiovascular disease, 6.8% of subjects had a medical history of diabetes, 18.8% of subjects

had a medical history of hypertension, and 13.8% of subjects had a medical history of hyperlipidemia. Most subjects (60%) were from the US.

Trial 1844:

Demographic and baseline characteristics were similar between the two groups (Table 116 in the Appendix). Most subjects were male (89%), not Hispanic/Latino (82%), and white (73%) or black (22%). The mean age was 45 years (range 20-71). Even though 2.3% of subjects had baseline HIV-1 RNA viral load ≥ 50 copies/mL, their HIV-1 RNA viral load at screening visit was less than 50 copies/mL. The mean baseline CD4+ cell count was 723 cells/µL (range 124-2444), 2% of subjects had CD4+ cell counts less than 200 cells/µL, and 77% of subjects had CD4+ cell counts equal to or greater than 500 cells/µL. Overall, 2.7% of subjects had a medical history of cardiovascular disease, 7.6% of subjects had a medical history of diabetes, 27.2% of subjects had a medical history of hypertension, and 34.8% of subjects had a medical history of hyperlipidemia. Also, 26% of subjects were current smokers, 20% were former smokers, and 53% had never smoked. Most subjects (71%) were from the US.

Trial 1878:

Demographic and baseline characteristics were similar between the two groups (**Table 117** in the Appendix). Most subjects were male (83%), not Hispanic/Latino (82%), and white (66%) or black (26%). The mean age was 46 years (range 20-79). Even though 2.6% of subjects had baseline HIV-1 RNA viral load ≥ 50 copies/mL, their HIV-1 RNA viral load at screening visit was less than 50 copies/mL. The mean baseline CD4+ cell count was 663 cells/µL (range 62-2582), 2% of subjects had CD4+ cell counts less than 200 cells/µL, and 67% of subjects had CD4+ cell counts equal to or greater than 500 cells/µL. Overall, 5.7% of subjects had a medical history of cardiovascular disease, 8.3% of subjects had a medical history of diabetes, 26.3% of subjects had a medical history of hypertension, and 31.9% of subjects had a medical history of hyperlipidemia. Also, 31% of subjects were current smokers, 20% were former smokers, and 49% had never smoked. Slightly more than half of subjects (57%) were from the US. At screening, 37.3% of subjects were receiving boosted ATV + FTC/TDF, 47.3% of subjects were receiving boosted DRV + FTC/TDF, 7.6% of subjects were receiving boosted ATV + ABC/3TC, and 7.8% of subjects were receiving boosted DRV + ABC/3TC.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Per the CSRs, most subjects had adherence rates of ≥ 95% to blinded active study drugs up to the Week 48 in all four trials.

7.3.4. Results for the Primary Endpoint

Summary of Applicant's Results of the primary endpoint:

The reviewer reproduced the applicant's results for the primary endpoint in all four trials. Thus,

the applicant's results for the primary endpoint are not provided in this section.

Trial 1489:

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 were 92.4% in the B/F/TAF group and 93.0% in the ABC/DTG/3TC with a difference in percentages of −0.6%, 95.002% CI: (−4.8% to 3.6%). The non-inferiority of B/F/TAF to ABC/DTG/3TC was demonstrated since the lower bound of the 95.002% CI of the difference between treatment groups was greater than the prespecified −12% margin.

Trial 1490:

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 were 89.4% in the B/F/TAF group and 92.9% in the DTG+F/TAF group with a difference in percentages of −3.5%, 95.002% CI: −7.9% to 1.0%). Therefore, it can be concluded that B/F/TAF is non-inferior to DTG+F/TAF because the lower bound of the 95.002% CI of the difference between treatment groups (B/F/TAF – DTG+F/TAF) was greater than the pre-specified −12% margin.

Trial 1844:

The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48for each treatment group were: (B/F/TAF 1.1%; ABC/DTG/3TC 0.4%; difference in percentages: 0.7%, 95.002% CI: −1.0% to 2.8%). Therefore, it can be concluded that B/F/TAF is non-inferior to ABC/DTG/3TC because the upper bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF − ABC/DTG/3TC) was less than the pre-specified 4% margin.

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 were similar for each treatment group (B/F/TAF 93.6%; ABC/DTG/3TC 95.0%; difference in percentages: −1.4%, 95.002% CI: −5.5% to 2.6%).

Trial 1878:

The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 or each treatment group were 1.7% in the B/F/TAF group and 1.7% in the SBR group with a difference in percentages of −0.0%, 95.002% CI: (−2.5% to 2.5%). Therefore, it can be concluded that switching to B/F/TAF is non-inferior to SBR because the upper bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF − SBR) was less than the prespecified 4% margin.

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 were similar for each treatment group (B/F/TAF 92.1%; SBR 88.9%; difference in percentages: 3.2%, 95.002% CI: −1.6% to 8.2%).

Reviewer's Primary Efficacy Endpoint Analysis Results

The statistical reviewer was able to reproduce the applicant's primary efficacy endpoint results for the four trials. The following tables were created by the reviewer.

Trial 1489:

The rate difference between two groups was -0.6% with 95.0002% CI of [-4.8%, 3.6%], which was calculated based on the Mantel-Haenszel (MH) proportions adjusted by baseline HIV-1 RNA (≤100,000 copies/mL vs. >100,000 copies/mL) and region (US vs. Ex-US) (**Table 36**). These results are the same as the applicant's results.

The exact 95% CI of rate difference without any adjustment was [-4.7%, 3.6%]. These two results are almost the same, and the small difference is not clinically meaningful. The review team recommended the 95.002% CI values be displayed in Section 14 of the label, for simplicity, the table states that the 95% CI is used instead of 95.002%CI.

Table 36: Proportion of Subjects with HIV-1 RNA <50 copies/mL at Week 48 of Trial 1489 (FAS)

	B/F/TAF (N=314)	ABC/DTG/3TC (N=315)	Rate Difference & it CI (B/F/TAF – ABC/DTG/3TC)
HIV-1 RNA <50 copies/mL	290 (92.4%) (88.8%, 95.0%)[b]	293 (93.0%) (89.6%, 95.6%)[b]	**-0.6% (-4.8%, 3.6%)**[a] -0.7% (-4.7%, 3.6%)[c]
HIV-1 RNA ≥50 copies/mL	3 (1%)	8 (2.5%)	
HIV-1 RNA ≥50 copies/mL in Week 48 Window	2 (0.6%)	6 (1.9%)	
Discontinue Study Drug Due to Lack of Efficacy	0	0	
Discontinue Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 copies/mL	1 (0.3%)	2 (0.6%)	
No Virologic Data in Week 48 Window	21 (6.7%)	14 (4.4%)	
Discontinue Study Drug Due to AE/Death	0	4 (1.3%)	
Discontinue Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL	16 (5.1%)	9 (2.9%)	
Missing Data During Window but on Study Drug	5 (1.6%)	1 (0.3%)	

[a]: The confidence Interval (CI) is 95.002% CI with stratification adjustment as stated in the previous section.
[b]: The exact 95% CI for individual rates.
[c]: The 95% CI of rate difference with stratification adjustment as stated in the previous section.
Source: statistical reviewer's analysis

Trial 1490:

The rate difference between the two groups was -3.5% with 95.0002% CI of [-7.9%, 1.0%], which was calculated based on the MH proportions adjusted by baseline HIV-1 RNA (≤100,000 copies/mL vs. >100,000 copies/mL) and region (US vs. Ex-US) (Table 37). These results are the same as the applicant's results.

The exact 95% CI of rate difference without any adjustment was [-7.9%, 0.8%]. These two

results are almost the same, and the small difference is not clinically meaningful. The review team recommended the 95.002% CI values be displayed in Section 14 of the label, for simplicity, the table states that the 95% CI is used instead of 95.002%CI.

Table 37: Proportion of Subjects with HIV-1 RNA <50 copies/mL at Week 48 of Trial 1490 (FAS)

	B/F/TAF (N=320)	DTG/F/TAF (N=325)	Rate Difference & it CI (B/F/TAF - DTG/F/TAF)
HIV-1 RNA <50 copies/mL	286 (89.4%) (85.2%, 92.5%)[b]	302 (92.9%) (89.6%, 95.5%)[b]	**-3.5% (-7.9%, 1.0%)**[a] -3.5% (-7.9%, 1.0%)[c]
HIV-1 RNA ≥50 copies/mL	14 (4.4%)	4 (1.2%)	
HIV-1 RNA ≥50 copies/mL in Week 48 Window	3 (0.9%)	1 (0.3%)	
Discontinue Study Drug Due to Lack of Efficacy	0	0	
Discontinue Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 copies/mL	11 (3.4%)	3 (0.9%)	
No Virologic Data in Week 48 Window	20 (6.3%)	19 (5.8%)	
Discontinue Study Drug Due to AE/Death	3 (0.9%)	3 (0.9%)	
Discontinue Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL	11 (3.4%)	14 (4.3%)	
Missing Data During Window but on Study Drug	6 (1.9%)	2 (0.6%)	

[a]: The confidence Interval (CI) is 95.002% CI with stratification adjustment as stated in the previous section.
[b]: The exact 95% CI for individual rates.
[c]: The 95% CI of rate difference with stratification adjustment as stated in the previous section.
Source: statistical reviewer's analysis

The applicant proposed to (b) (4) (b) (4) (b) (4) the review team recommended that the efficacy results from Trials 1489 and 1490 be displayed separately in Table 10, in Section 14 of the label.

Trial 1844:

The rate difference of HIV-1 RNA ≥ 50 copies/mL at Week 48 between two groups was 0.7% with 95.0002% CI of [-1.0%, 2.8%] (Table 38)**.** These results are the same as the applicant's.

The exact 95% CI of rate difference without any adjustment was [-1.0%, 2.8%]. These two

results are almost the same, and the small difference is not clinically meaningful. The review team recommended the 95.002% CI values be displayed in Section 14 of the label, for simplicity, the table states that the 95% CI is used instead of the 95.002% CI.

The rate difference of HIV-1 RNA < 50 copies/mL at Week 48 between two groups were -1.4% with 95.0002% CI of [-5.5%, 2.6%] (Table 38). These results are the same as the applicant's.

Table 38: Proportion of Subjects with HIV-1 RNA ≥50 and <50 copies/mL at Week 48 of Trial 1844 (FAS)

	B/F/TAF (N=282)	ABC/DTG/3TC (N=281)	Rate Difference & it CI (B/F/TAF – ABC/DTG/3TC)
HIV-1 RNA < 50 copies/mL	264 (93.6%) (90.1%, 96.2%)[b]	267 (95.0%) (91.8%, 97.3%)[b]	-1.4% (-5.5%, 2.6%)[a] **(-5.5%, 2.6%)[c]**
HIV-1 RNA ≥ 50 copies/mL	3 (1.1%) (0%, 3.1%)[b]	1 (0.4%) (0%, 2.0%)[b]	**0.7% (-1.0%, 2.8%)[a]** (-1.0%, 2.8%)[c]
HIV-1 RNA ≥50 copies/mL in Week 48 Window	1 (0.4%)		
Discontinue Study Drug Due to Lack of Efficacy			
Discontinue Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥50 copies/mL	1 (0.4%)		
Discontinue Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 copies/mL	1 (0.4%)	1 (0.4%)	
No Virologic Data in Week 48 Window	15 (5.3%)	13 (4.6%)	
Discontinue Study Drug Due to AE/Death and Last Available HIV-1 RNA <50 copies/mL	5 (1.8%)	2 (0.7%)	
Discontinue Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL	5 (1.8%)	9 (3.2%)	
Missing Data During Window but on Study Drug	5 (1.8%)	2 (0.7%)	

[a] The confidence Interval (CI) is 95.002% CI without any adjustment using invert two one-sided test in StatXact.
[b] The exact 95% CI for individual rate.
[c] The exact 95% CI of rate difference using invert two one-sided test in StatXact.
Source: statistical reviewer's analysis

Trial 1878:

The rate difference of HIV-1 RNA ≥ 50 copies/mL at Week 48 between two groups was 0.0% with 95.0002% CI of [-2.5%, 2.5%] (Table 39). These results are the same as the applicant's.

The exact 95% CI of rate difference without any adjustment was [-2.5%, 2.5%]. These two results are almost the same, and the small difference is not clinically meaningful. The review team recommended the 95.002% CI values be displayed in Section 14 of the label, for simplicity, the table states that the 95% CI is used instead of 95.002%CI.

The rate difference of HIV-1 RNA < 50 copies/mL at Week 48 between two groups were 3.2% with 95.0002% CI of [-1.6%, 8.2%] (Table 39). These results are the same as the applicant's. The

proportion of subjects on B/F/TAF with <50 copies/mL was slightly lower (92.1%) than what was observed in the Trial 1844 (93.6%).

Table 39: Proportion of Subjects with HIV-1 RNA ≥50 and <50 copies/mL at Week 48 of Trial 1878 (FAS)

	B_F_TAF (N=290)	SBR (N=287)	Rate Difference & it CI (B/F/TAF - SBR)
HIV-1 RNA <50 copies/mL	267 (92.1%) (88.3%, 94.9%)[b]	255 (88.9%) (84.6%, 92.2%)[b]	3.2% (-1.6%, 8.2%)[a] (-1.6%, 8.2%)[c]
HIV-1 RNA ≥50 copies/mL	5 (1.7%) (0.6%, 4.0%)[b]	5 (1.7%) (0.6%, 4.0%)[b]	**0.0% (-2.5%, 2.5%)[a]** (-2.5%, 2.5%)[c]
HIV-1 RNA ≥50 copies/mL in Week 48 Window	2 (0.7%)	2 (0.7%)	
Discontinue Study Drug Due to Lack of Efficacy	1 (0.3%)		
Discontinue Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥50 copies/mL			
Discontinue Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 copies/mL	2 (0.7%)	3 (1.0%)	
No Virologic Data in Week 48 Window	18 (6.2%)	27 (9.4%)	
Discontinue Study Drug Due to AE/Death and Last Available HIV-1 RNA <50 copies/mL	3 (1.0%)	2 (0.7%)	
Discontinue Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL	10 (3.4%)	19 (6.6%)	
Missing Data During Window but on Study Drug	5 (1.7%)	6 (2.1%)	

[a] The confidence Interval (CI) is 95.002% CI without any adjustment using invert two one-sided test in StatXact.
[b] The exact 95% CI for individual rate.
[c] The exact 95% CI of rate difference using invert two one-sided test in StatXact.
Source: statistical reviewer's analysis

7.3.5. Results for Secondary Endpoints

The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 was a secondary efficacy endpoint for Trials 1844 and 1878. The results have been presented in the previous section along with the primary efficacy endpoint for these two trials.

Summary of Applicant's results of the change of CD4 cell count from baseline at Week 48:

Trial 1489:

CD4 cell count increased in each treatment group following initiation of study drugs (**Table 40**). Mean (SD) baseline CD4 cell counts were as follows: B/F/TAF 453 (220.8) cells/µL; ABC/DTG/3TC 476 (231.4) cells/µL. Mean (SD) changes from baseline at Week 48 for the FAS were as follows: B/F/TAF 233 (185.2) cells/µL; ABC/DTG/3TC 229 (188.8) cells/µL.

Using LOCF to impute missing values, the change from baseline in CD4 cell counts in each treatment group was consistent with the observed data (**Table 40**). However, LOCF is not the recommended approach in imputing missing values due to its potential bias and it can underestimate the variability of the CD4 counts. The reviewer conducted analysis using Baseline observation carry forward (BOCF) for imputation and evaluated the influence of the missing values by comparing the consistency of the findings based on these approaches. Because the results from these three approaches were similar, the completer analysis results were included in the label.

Table 40: Applicant's Results of CD4 Cell Count Change at Week 48 from Baseline for Trial 1489 (FAS)

Trial 1489	B/F/TAF (N=314)	ABC/DTG/3TC (N=315)	B/F/TAF vs. ABC/DTG/3TC	
			p-value	Diff in LSM (95% CI)
Change at Week 48 from Baseline (Completer Analysis)				
N	290	299	0.81	4 (-27, 34)
Mean (SD)	233 (185.2)	229 (188.8)		
95% CI	(211, 254)	(207, 250)		
Median	214	210		
Q1, Q3	105, 317	99, 345		
Min, Max	-170, 1036	-510, 796		
Change at Week 48 from Baseline (LOCF Analysis)				
N	314	315	0.85	3 (-26, 32)
Mean (SD)	229 (185.0)	225 (187.2)		
95% CI	(208, 249)	(205, 246)		
Median	207	210		
Q1, Q3	106, 315	100, 331		
Min, Max	-222, 1036	-510, 796		

Source: Trial 1489 CSR, Table 15.9.2.5.1. and Table 9.2.5.3

Trial 1490:

CD4 cell count increased in each treatment group following initiation of study drugs (**Table 41**). Mean (SD) baseline CD4 cell counts were as follows: B/F/TAF 457 (255.3) cells/µL; DTG+F/TAF 454 (231.5) cells/µL. Mean (SD) changes from baseline at Week 48 for the FAS were as follows: B/F/TAF 180 (166.6) cells/µL; DTG+F/TAF 201 (166.4) cells/µL.

Using LOCF to impute missing values, the change from baseline in CD4 cell counts in each treatment group was consistent with the observed data (**Table 41**).

Table 41: Applicant's Results of CD4 Cell Count Change at Week 48 from Baseline for Trial 1490 (FAS)

Trial 1490	B/F/TAF (N=320)	DTG+F/TAF (N=325)	B/F/TAF vs. DTG+F/TAF	
			p-value	Diff in LSM (95% CI)
Change at Week 48 from Baseline (Completer Analysis)				
N	287	301	0.10	-22 (-49, 5)
Mean (SD)	180 (166.6)	201 (166.4)		
95% CI	(161, 199)	(182, 220)		
Median	174	176		
Q1, Q3	97, 271	98, 296		
Min, Max	-626, 782	-214, 1006		
Change at Week 48 from Baseline (LOCF Analysis)				
N	320	325	0.11	-21 (-47, 5)
Mean (SD)	172 (167.9)	191 (167.5)		
95% CI	(154, 191)	(173, 209)		
Median	166	171		
Q1, Q3	77, 261	88, 291		
Min, Max	-626, 782	-214, 1006		

Source: Trial 1490 CSR, Table 15.9.2.5.1. and Table 15.9.2.3

Trial 1844:

Mean (SD) baseline CD4 cell counts were statistically significantly higher in the B/F/TAF group than the ABC/DTG/3TC group (B/F/TAF 752 [302.2] cells/µL; ABC/DTG/3TC 694 [291.6] cells/µL; difference in LSM: 58 cells/uL, 95% CI: 9 to 107 cells/uL, p = 0.021). Mean (SD) changes from baseline at Week 48 for the FAS were statistically significantly different between treatment groups (B/F/TAF −31 [181.3] cells/µL; ABC/DTG/3TC 4 [191.0] cells/µL (**Table 42**).

Using LOCF to impute missing values, the change from baseline in CD4 cell counts in each treatment group was consistent with the observed data (**Table 42**).

Table 42: **Applicant's Results of CD4 Cell Count Change at Week 48 from Baseline for Trial 1844 (FAS)**

Trial 1844	B/F/TAF (N=282)	ABC/DTG/3TC (N=281)	B/F/TAF vs. ABC/DTG/3TC	
			p-value	Diff in LSM (95% CI)
Change at Week 48 from Baseline (Completer Analysis)				
N	265	267	0.031	-35 (-67, -3)
Mean (SD)	-31 (181.3)	4 (191.0)		

95% CI	(-53, -9)	(-19, 27)		
Median	-14	3		
Q1, Q3	-125, 73	-93, 88		
Min, Max	-989, 494	-541, 962		
Change at Week 48 from Baseline (LOCF Analysis)				
N	282	281	0.051	-31 (-62, 0)
Mean (SD)	-25 (182.1)	6 (194.8)		
95% CI	(-46, -3)	(-16, 29)		
Median	-7	4		
Q1, Q3	-119, 79	-93, 100		
Min, Max	-989, 506	-541, 962		

Source: Trial 1844 CSR, Table 15.9.2.4.1. and Table 15.2.4.3

Trial 1878:

Mean (SD) baseline CD4 cells counts were similar between treatment groups (B/F/TAF 669 [303.4] cells/µL; SBR 657 [285.0] cells/µL) (**Table 43**). CD4 cell counts were maintained in both groups. Mean (SD) changes from baseline at Week 48 for the FAS were as follows: B/F/TAF 25 (151.2) cells/µL; SBR 0 (159.4) cells/µL.

Using LOCF to impute missing values, the change from baseline in CD4 cell counts in each treatment group was consistent with the observed data (**Table 43**).

Table 43: Applicant's Results of CD4 Cell Count Change at Week 48 from Baseline for Trial 1878 (FAS)

Trial 1878	B/F/TAF (N=290)	SBR (N=287)	B/F/TAF vs. SBR	
			p-value	Diff in LSM (95% CI)
Change at Week 48 from Baseline (Completer Analysis)				
N	265	256	0.068	25 (-2, 52)
Mean (SD)	25 (151.2)	0 (159.4)		
95% CI	(6, 43)	(-20, 20)		
Median	19	12		
Q1, Q3	-61, 115	-73, 82		
Min, Max	-191, 686	-841, 427		
Change at Week 48 from Baseline (LOCF Analysis)				
N	290	287	0.078	23 (-3, 48)
Mean (SD)	23 (153.5)	0 (155.6)		
95% CI	(5, 41)	(-18, 18)		
Median	19	9		

Q1, Q3	-61, 114	-73, 78		
Min, Max	-407, 686	-841, 427		

Source: Trial 1878 CSR, Table 15.9.2.4.1. and Table 15.9.2.4.3

Reviewer's Secondary Efficacy Endpoint Analysis Results

The statistical reviewer analyzed the change of CD4 cell count from baseline at Week 48 for the Phase 3 trials and the results are slightly different from the applicant's results. Because the differences were minimal and not clinically relevant, the Applicant's results were used in Section 14 of the label.

Trial 1489:

The baseline CD4 count was comparable between the two treatment groups. The reviewer's results of mean change (SD) from baseline at Week 48 for CD4 count are slightly different from the applicant's using both a completer analysis (233 (185.2) cells/µL in the B/F/TAF group and 227 (190.2) in the ABC/DTG/3TC group) and a Last-observation-carry-forward (LOCF) analysis (229 (185.0) cells/µL in the B/F/TAF group and 224 (188.9) in the ABC/DTG/3TC group). The results from the three approaches, completer analysis, LOCF and baseline-observation-carry-forward (BOCF) (215 (188.4) cells/µL in the B/F/TAF group and 217 (191.8) in the ABC/DTG/3TC group), for the mean change from baseline at Week 48 for CD4 count are similar; regardless of the method, the mean of CD4 count increased from baseline by about 215 to 233 cells/µL at Week 48 (Table 118 in Appendix Section 15.4).

Trial 1490:

The baseline CD4 count was comparable between the two treatment groups. The reviewer's results of the mean change (SD) from baseline at Week 48 for CD4 count are slightly different from the applicant's using both a completer analysis (179 (166.0) cells/µL in the B/F/TAF group and 202 (165.9) in the DTG/F/TAF group) and a LOCF analysis (172 (167.7) cells/µL in the B/F/TAF group and 192.5 (167.5) in the DTG/F/TAF group). The results from the three approaches, completer analysis, LOCF and BOCF (162 (166.5) cells/µL in the B/F/TAF group and 188 (167.9) in the DTG/F/TAF group), for the mean change from baseline at Week 48 for CD4 count are similar; regardless of the method of the analysis, the mean of CD4 count increased from baseline by about 160 to 200 cell/µL at Week 48 (Table 119 in appendix Section 15.4).

Trial 1844:

The mean (SD) CD4 count at baseline in the B/F/TAF group (752(302.2)) was higher than that in the ABC/DTG/3TC group (694(291.6)). The reviewer's results of the mean change (SD) from baseline at Week 48 for CD4 count are slightly different from the applicant's using both completer analysis (-30 (180.2) cells/µL in the B/F/TAF group and 4 (190.6) in the ABC/DTG/3TC

group) and LOCF analysis (-24 (182.2) cells/µL in the B/F/TAF group and 6 (194.7) in the ABC/DTG/3TC group). The results of the mean change (SD) from baseline at Week 48 for CD4 count from the three approaches, completer analysis, LOCF and BOCF (-29(176.1) cells/µL in the B/F/TAF group and 4 (186.1) in the ABC/DTG/3TC group) were similar (Table 120). Subjects in the B/F/TAF group had an approximate 30 cells/µL decrease from baseline in mean CD4 cell count at Week 48 compared to a 4 cells/µL increase in the ABC/DTG/3TC group. Clinically, these differences are small.

Trial 1878:

The baseline CD4 count was comparable between the two treatment groups. The reviewer's results of CD4 count mean change (SD) from baseline at Week 48 are slightly different from the applicant's using both a completer analysis (26 (151.0) cells/µL in the B/F/TAF group and -3 (159.3) in the SBR group) and a LOCF analysis (23 (151.8) cells/µL in the B/F/TAF group and -3 (157.0) in the SBR group). The results the mean change (SD) from baseline at Week 48 for CD4 count from the three approaches, completer analysis, LOCF and BOCF (24 (145.3) cells/µL in the B/F/TAF group and -2 (152.4) in the SBR group), are similar (Table 121 in appendix). Subjects in the B/F/TAF group had an approximate 26 cells/µL increase from baseline in mean CD4 cell count at Week 48 compared to a 3 cells/µL decrease in the SBR group. These differences are small and unlikely to have clinical impact.

7.3.6. Results of Subgroup Analyses

These are subgroup analyses with no multiplicity adjustments applied and are also based on small sample sizes with inherent uncertainties. The subgroup analyses of some baseline covariates (age, sex, race, ethnicity, baseline HIV-1 RNA, baseline CD4 cell count, region, Baseline BMI Category, etc.) on the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm based on the FAS were conducted.

Trial 1489:

Overall, the subgroup analyses of some baseline covariates on the proportions of subjects with <50 copies/mL at Week 48 were similar between the two treatment groups even though some numeric differences were observed (**Table 122** in appendix). For example, the younger age (≤32 years old) group (91.1%) appears had slightly lower proportion of subjects with <50 copies/mL at Week 48 than that in older age (>32 years old) group (95.3%), subjects with baseline CD4 count ≥ 200 cell/µL (527/561, 93.9%) appears had higher proportion of subjects with <50 copies/mL at Week 48 than that among subjects with baseline CD4 count < 200 cell/µL (56/68, 82.4%).

The subgroup analyses of the four strata used for the stratification justification were also conducted (Table 44). Subjects with the baseline HIV-1 RNA viral load ≤100,000 copies/mL appears to have slightly higher rate than that in subjects with baseline HIV-1 RNA viral load > 100,000 copies/mL, while region (US vs. Ex-US) had no impact on the rate.

Table 44: Subgroup Analysis of Strata for the Proportion of Subjects with <50 copies/mL at Week 48 in Trial 1489 (FAS)

1489 Stratum	B/F/TAF	ABC/DTG/3TC	Rate difference
Overall:	290/314 (92.4%)	293/315 (93.0%)	**-0.6% (-4.8%, 3.6%)**
1: US, ≤ 100 K	178/190 (93.7%)	182/196 (92.7%)	0.8% (-4.2%, 5.8%)[a]
2: EX-US, ≤ 100 K	66/71 (93.0%)	66/69 (95.6%)	-2.7% (-10.4%, 5.0%) [a]
3: US, >100 K	34/38 (89.5%)	34/37 (91.9%)	-2.4% (-15.5%, 10.7%)[a]
4: EX-US, >100 K	12/15 (80.0%)	11/13 (84.6%)	-4.6% (-32.8%, 23.6%) [a]

[a]: It is the asymptotic 95% CI
Source: statistical reviewer's analysis

Trial 1490:

Overall, the subgroup analyses of some baseline covariates on the proportions of subjects with <50 copies/mL at Week 48 were similar between the 2 treatment groups even though some numeric difference were observed (Table 123 in appendix). Like Trial 1489, younger age (≤32 years old) group (88.8%) appears had slightly lower proportion of subjects with <50 copies/mL at Week 48 than that in older age (>32 years old) group (94.0%), while opposite to what observed in Trial 1489 subjects with baseline CD4 count ≥ 200 cell/µL (512/567, 90.3%) appears to have had a slightly lower proportion of subjects with <50 copies/mL at Week 48 than that among subjects with baseline CD4 count < 200 cell/µL (76/78, 97.4%). Subjects from US sites (89.6%) appear to have a slightly lower proportion of subjects with <50 copies/mL at Week 48 that what was observed in subjects from Ex-US (93.4%).

The subgroup analyses of the four strata used for the stratification justification were also conducted (Table 45). With small sample sizes, subjects in the B/F/TAF group from US sites with the baseline HIV-1 RNA viral load >100,000 copies/mL appear to have slightly lower rates than subjects in DTG/F/TAF group from US sites with baseline HIV-1 RNA viral load > 100,000 copies/mL. This finding is likely due to chance because this is a two-factor subgroup analyses and the sample sizes are very small.

Table 45: Subgroup Analysis of Strata for the Proportion of Subjects with <50 copies/mL at Week 48 in Trial 1490 (FAS)

1490 Stratum	B/F/TAF	DTG/F/TAF	Rate difference
Overall:	286/320 (89.4%)	302/325 (92.9%)	**-3.5% (-7.9%, 1.0%)**
1: US, ≤ 100 K	131/148 (88.5%)	147/161 (91.3%)	-2.3% (-9.5%, 3.9%)[a]
2: EX-US, ≤ 100 K	98/106 (92.5%)	104/110 (94.6%)	-2.1% (-8.7%, 4.5%)[a]
3: US, >100 K	37/45 (82.2%)	31/32 (96.9%)	**-14.7% (-27.4%, -2.0%)[a]**
4: EX-US, >100 K	20/21 (95.2%)	20/22 (90.9%)	4.3% (-10.7%, 19.4%)[a]

[a] It is the asymptotic 95% CI
Source: statistical reviewer's analysis

Trial 1844:

Overall, the subgroup analyses of some baseline covariates on the proportions of subjects with <50 copies/mL at Week 48 were similar between the 2 treatment groups as the 95% CI of rate differences included zero, even though some numeric difference were observed (**Table 46**).

Table 46: Baseline Covariates Subgroup Analysis of the Proportion of Subjects with <50 copies/mL at Week 48 in Trial 1844 (FAS)

Covariates	Levels	B_F_TAF	ABC_DTG_3TC	Rate difference and its CI[a]
Age	<=46	130/137 (94.9%) (89.8%, 97.9%)	137/147 (93.2%) (87.8%, 96.7%)	1.7% (-3.8%, 7.2%)
	>46	134/145 (92.4%) 86.8%, 96.1%)	130/134 (97.0%) (92.5%, 99.2%)	-4.6% (-9.8%, 0.6%)
Age	<65	251/268 (93.7%) (90.0%, 96.3%)	257/271 (94.8%) (91.5%, 97.1%)	-1.2% (-5.1%, 2.8%)
	>=65	13/14 (92.9%) (66.1%, 99.8%)	10/10 (100%) (69.1%, 100%)	-7.1% (-20.6%, 6.3%)
Gender	Male	230/247 (93.1%) (89.2%, 95.9%)	242/252 (96.0%) (92.8%, 98.1%)	-2.9% (-6.9%, 1.1%)
	Female	34/35 (97.1%) (85.1%, 99.9%)	25/29 (86.2%) (68.3%, 96.1%)	10.9% (-2.8%, 24.6%)
Region	US	193/203 (95.1%) (91.1%, 97.6%)	189/198 (95.4%) (91.5%, 97.9%)	-0.4% (-4.5%, 3.8%)
	Ex-US	71/79 (89.9%) (81.0%, 95.5%)	78/83 (94.0%) (86.5%, 98.0%)	-4.1% (-12.5%, 4.3%)
CD4 cell Count at Baseline	<200	5/6 (83.3%) (35.9%, 99.6%)	4/4 (100%) (39.8%, 100%)	-16.7% (-46.5%, 13.1%)
	>=200	259/276 (93.8%) (90.3%, 96.4%)	263/277 (94.9%) (91.7%, 97.2%)	-1.1% (-4.9%, 2.7%)
HIV-1 RNA viral load at Screen	<50	261/278 (93.9%) (90.4%, 96.4%)	258/272 (94.8%) (91.5%, 97.2%)	-1.0% (-4.8%, 2.9%)
	>=50[b]	3/4 (75.0%) (19.4%, 99.4%)	9/9 (100%) (66.4%, 100%)	-25% (-67.4%, 17.4%)

[a] It is the asymptotic 95% CI
[b] These subjects had HIV-1 RNA viral load <50 at baseline
Source: statistical reviewer's analysis

Trial 1878:

Overall, the subgroup analyses of some baseline covariates on the proportions of subjects with <50 copies/mL at Week 48 were similar between the two treatment groups as the 95% CI of rate differences included zero, even though some numeric difference were observed (**Table 47**).

Table 47: Baseline Covariates Subgroup Analysis of the Proportion of Subjects with <50

copies/mL at Week 48 in Trial 1878 (FAS)

Factor	Levels	B F TAF	SBR	Rate difference and its CI[a]
Age	<=48	136/148 (91.9%) (86.3%, 95.7%)	141/161 (87.6%) (81.5%, 92.2%)	4.3% (-2.4%, 11.0%)
	>48	131/142 (92.2%) (86.6%, 96.1%)	114/126 (90.5%) (84.0%, 95.0%)	1.8% (-5.0%, 8.5%)
Age	<65	257/279 (92.1%) (88.3%, 95.0%)	245/276 (88.8%) (84.4%, 92.2%)	3.4% (-1.5%, 8.2%)
	>=65	10/11 (90.9%) (58.7%, 100%)	10/11 (90.9%) (58.7%, 100%)	0% (-24.0%, 24.0%)
Gender	Male	226/243 (93.0%) (89.0%, 95.9%)	208/234 (88.9%) (84.1%, 92.6%)	4.1% (-1.0, 9.3%)
	Female	41/47 (87.2%) (74.3%, 95.2%)	47/53 (88.7%) (77.0%, 95.7%)	-1.5% (-14.2%, 11.4%)
Region	US	153/166 (92.2%) (87.0%, 95.8%)	145/164 (88.4%) (82.5%, 92.9%)	3.8% (-2.6%, 10.1%)
	Ex-US	114/124 (91.9%) (85.7%, 96.1%)	110/123 (89.4%) (82.6%, 94.3%)	2.5% (-4.7%, 9.8%)
CD4 cell Count at Baseline	<200	4/4 (100%)	8/8 (100%)	0%
	>=200	263/286 (92.0%) (88.2%, 94.8%)	247/279 (88.5%) (84.2%, 92.0%)	3.4% (-1.5%, 8.3%)
HIV RNA at Screen	<50	263/285 (92.3%) (88.6%, 95.1%)	250/277 (90.3%) (86.1%, 93.5%)	2.0% (-2.6%, 6.7%)
	>=50[b]	4/5 (80.0%) (28.4%, 99.5%)	5/10 (50.0%) (18.7%, 81.3%)	30.0% (-16.8%, 76.8%)
Stratum	TDF	225/244 (92.2%) (88.1%, 95.3%)	216/242 (89.3%) (84.7%, 92.9%)	3.0% (-2.2%, 8.1%)
	Non-TDF	42/46 (91.3%) (79.2%, 97.6%)	39/45 (86.7%) (73.2%, 95.0%)	4.6% (-8.2%, 17.5%)
Previous regimen	Boosted ATV+ABC/3TC	21/21 (100%) (83.9%, 100%)	21/23 (91.3%) (72.0%, 98.9%)	8.7% (-2.8%, 20.2%)
	Boosted ATV+FTC/TDF	98/105 (93.3%) (86.8%, 97.3%)	99/110 (90.0%) (82.8%, 94.9%)	3.3% (-4.0%, 10.7%)
	Boosted DRV+ABC/3TC	20/24 (83.3%) (62.6%, 95.3%)	17/21 (81.0%) (58.1%, 94.6%)	2.4% (-20.1%, 24.8%)
	Boosted DRV+FTC/TDF	128/140 (91.4%) (85.5%, 95.5%)	118/133 (88.7%) (82.1%, 93.6%)	2.7% (-4.4%, 9.8%)

[a]: It is the asymptotic 95% CI
[b]: These subjects had HIV-1 RNA viral load <50 at baseline
Source: statistical reviewer's analysis

7.4 Conclusions and Recommendations

Evidence for efficacy in this submission as provided is based on four Phase 3 trials, GS-US-380-1489 and GS-US-380-1490 in the treatment-naive population, and GS-US-380-1844 and GS-US-380-1878 in the virologically suppressed population.

The primary efficacy endpoint for the TN trials was the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. In Trial 1489, the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 between the two groups was comparable, 92.4% in the B/F/TAF group and 93.0% in the ABC/DTG/3TC group; and, in Trial 1490, 89.4% in the B/F/TAF group and 92.9% in the DTG/F/TAF group. The lower bound of 2-sided 95.002% CI of the rate difference (B/F/TAF – active-control) was -4.8% in Trial 1489 and -7.9% in Trial 1490, which is greater than -12%, the pre-specified non-inferiority (NI) margin. Therefore, B/F/TAF demonstrated non-inferiority to the active-control regimens, ABC/DTG/3TC in Trial 1489 and DTG/F/TAF in Trial 1490. The rates were similar across subgroup by age group, gender, race, baseline HIV-1 RNA viral load, baseline CD4+ cell count, and regions within the trials.

In trials with virologically suppressed patients, the primary efficacy endpoint was the proportion of subjects with HIV-1 RNA ≥50 copies/mL at Week 48. In Trials 1844 and 1878 which enrolled virologically suppressed patients, the upper bounds of 2-sided 95.002% CI of the rate difference (B/F/TAF – active-control) based on HIV-1 RNA ≥50 copies/mL at Week 48 were 2.8% and 2.5%, respectively, which is less than 4%, the pre-specified NI margin. Therefore, B/F/TAF is non-inferior to the active-control regimens, ABC/DTG/3TC in Trial 1844 and boosted ATV- or boosted DRV- based regimens in Trial 1878. The proportions of subjects who maintained HIV-1 viral suppression at Week 48 were comparable between the treatment groups; 94% in the B/F/TAF group and 95% in the ABC/DTG/3TC group in Trial 1844, and 92% in the B/F/TAF group and 89% in the SBR group in Trial 1878. The proportions of subjects who maintained HIV-1 viral suppression were similar across subgroup by age group, gender, race, baseline CD4+ cell count, and regions within the trials.

In conclusion, these four trials demonstrate the efficacy of B/F/TAF for treatment of HIV-1 in both the treatment-naïve and virologically suppressed adult population. It is recommended to approve the FDC of B/F/TAF with the indication of once daily use as a complete regimen for the treatment of HIV-1 infection in adult patients, aged 18 years and older, who have no ARV treatment history or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of B/F/TAF.

8 Virology

8.1 Nonclinical Virology

Numerous nonclinical virology study results were submitted in support of the NDA for B/F/TAF FDC tablets. As the bictegravir component of the FDC tablet is a new chemical entity, the applicant included full nonclinical virology data on bictegravir in the submission, which are summarized in this section. Importantly, the applicant published key findings from those

studies of BIC in the Journal of Antimicrobial Agents and Chemotherapy in 2016 (Tsiang et al., 2016). Emtricitabine (F or FTC) and tenofovir alafenamide (TAF) are FDA-approved antiretroviral agents of the NRTI class that inhibit the activity of HIV-1 reverse transcriptase. See the Clinical Virology reviews of NDAs 21500 and 207561 by Nara Battula, Ph.D. and by Lisa K. Naeger, Ph.D. for detailed descriptions of FTC and TAF, respectively. (b) (4)

8.1.1 Mechanism of Action

Bictegravir inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase (IN) prevents the integration of linear HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the virus.

In the Nonclinical Study Report PC-141-2036 (Tsiang et al., 2016), the applicant evaluated the inhibitory activity of BIC on HIV-1 integrase in biochemical assays, as described previously (Tsiang et al., 2012; Wang et al., 2005), designed to measure the strand transfer and 3'-processing (removal of dinucleotides from the 3'-ends of linear viral DNA occurring prior to the strand transfer step) activities of purified recombinant HIV-1 integrase (expressed in BL21 cells). BIC inhibited the enzymatic strand transfer activity of HIV-1 IN with a mean IC_{50} value of 7.5±0.3 nM, comparable to those determined for dolutegravir (DTG; 7.4±0.6 nM) and elvitegravir (EVG; 8.4±0.7 nM). In contrast, BIC was a substantially weaker inhibitor of the 3'-processing activity of HIV-1 IN with a mean IC_{50} value of 241±51 nM; similar potency in this assay was observed for DTG (232±33 nM) and EVG (556±40 nM).

Nonclinical Study Report PC-141-2037 (Tsiang et al., 2016) describes the effect of BIC on viral DNA integration into the host chromosomal DNA in MT-2 cells infected with HIV-1_{IIIB} at a multiplicity of infection (MOI) of 10 by measuring the accumulation of 2-long terminal repeat (LTR) circles, Alu-LTR products, and Late-RT products using quantitative PCR. In the presence of BIC 28 nM (approximately 20 times the antiviral EC_{50} value in MT2 cells), the level of 2-LTR circles increased 3.3-fold, indicative of increased viral DNA integration failure (Butler et al., 2001), relative to infected, mock-treated MT-2 cells. This level of 2-LTR circle accumulation was comparable to the 4.5-fold increase observed with DTG (31 nM = 20xEC_{50} value). In addition, the level of Alu-LTR products (direct measurement of virus integration into host DNA; Butler et al., 2001) decreased by 99% in the presence of 28 nM BIC, as compared to a 98% decrease in the presence of 31 nM DTG. However, the accumulation of Late-RT products representing the completion of reverse transcription of the viral RNA genome was unaffected by treatment with BIC or DTG (0.9- and 0.8-fold relative to the DMSO-treated controls, respectively). As expected, the NNRTI efavirenz decreased the Late-RT products with subsequent downstream effects on both 2-LTR circles and integration products, consistent with the inhibition of the reverse transcription step, whereas the PI darunavir had no effect on these products, consistent with its acting after the integration step.

These nonclinical (biochemical and cell-culture) studies collectively demonstrated that BIC is an HIV-1 INSTI that serves to block the integration of viral DNA into host cell genomic DNA during HIV infection after the completion of the RT-catalyzed viral DNA synthesis. Characterization of BIC resistant isolates provides *in vivo* validation of the mechanism of action.

8.1.2 Antiviral Activity and Cytotoxicity

The antiviral activity of BIC was evaluated using a 5-day cytopathic assay in MT-2 and MT-4 lymphoblastoid T-cell lines acutely infected with HIV-1_{IIIB} (Nonclinical Study Report PC-141-2032; Tsiang et al., 2016). In parallel, the cytotoxicity of BIC was assessed in corresponding uninfected cells. BIC displayed antiviral activity with a mean EC_{50} value of 1.5±0.2 nM and a selectivity index (CC_{50} value/EC_{50} value) of 6,867 in MT-2 cells, and of 2.4±0.4 nM and a selectivity index of 1,541in MT-4 cells. The concentrations that resulted in 50% cell death (CC_{50} values) of BIC were 10.3 µM and 3.7 µM in MT-2 and MT-4 cells, respectively. In both tested cell lines, the antiviral activity of BIC was comparable to that of DTG (mean EC_{50} value of 1.5±0.2 nM in MT-2 cells and of 1.5±0.3 nM in MT-4 cells). In addition, an EC_{95} value of 8.3 nM was calculated for BIC in MT-4 cells using a dose response with high density concentration points. This EC_{95} value was used in conjunction with the human serum shift determined by competitive equilibrium dialysis to obtain a protein binding-adjusted EC_{95} value of 361 nM. This protein binding-adjusted EC_{95} value was subsequently used for the estimation of clinical inhibitory quotient from the projected trough concentration of BIC in human. Of note, in Nonclinical Study Report AD-141-2287, BIC was shown to be highly bound to human plasma proteins (99.75% by equilibrium dialysis), and using competitive equilibrium dialysis between cell culture medium containing 10% fetal bovine serum and 100% human plasma, the relative protein binding of BIC was 43.6±7.7-fold higher in human plasma (human serum shift). It should be noted that these antiviral assays were done in MT-2 and MT-4 cells infected with HIV-1_{IIIB} at an MOI of 0.01. The applicant reported in Nonclinical Study Report PC-141-2054 that the EC_{50} values increased in infected MT-2 cells as MOI increased for all tested drugs including BIC, DTG, EVG, raltegravir (RAL), and tenofovir (TFV). BIC and DTG had similar antiviral potencies at all MOIs tested (0.009, 0.03, 0.09, and 0.3) with mean EC_{50} values ranging from 0.44 to 2.86 nM versus 0.30 to 2.33 nM. Thus, the EC_{50} values of BIC and DTG increased approximately 6.5- and 7.8-fold across the 30-fold range in virus MOI, respectively. Similar relative changes in EC_{50} values were observed with the other tested ARVs: 8.3-fold (0.46 to 3.83 nM) for EVG, 10.5-fold (1.47 to 15.4 nM) for RAL, and 8.0-fold (1.92 to 15.4 µM) for TFV.

In Nonclinical Study Report PC-141-2034 (Tsiang et al., 2016), the applicant evaluated the antiviral activity and cytotoxicity of BIC in freshly isolated primary human $CD4^+$ T lymphocytes and monocyte-derived macrophages from healthy donors' PBMCs, as these are the major target cells for HIV-1 replication in patients. In PHA/IL-2-activated primary $CD4^+$ T lymphocytes infected with HIV-1_{BaL} (at an MOI of 15 ng p24 equivalent/million cells), BIC exhibited an antiviral potency in a 5-day virus production assay (p24 ELISA), comparable to that determined in T-cell lines, with a mean EC_{50} value of 1.5±0.3 nM and a selectivity index of approximately

8,700 (mean CC_{50} value of 13±4 µM). In monocyte-derived macrophages infected with HIV-1_{BaL}, BIC also displayed similar antiviral activity and selectivity as DTG with mean EC_{50} values of 6.6±4.1 nM versus 3.1±2.5 nM, and selectivity indices of approximately 4,500 versus approximately 8,000 (mean CC_{50} values of 29.8±7.7 µM versus 24.9±1.2 µM). The cytotoxicity of BIC was also low with a mean CC_{50} value of 8.4±1.9 µM in total PBMCs in the resting state, which did not significantly change upon the mitogenic activation with PHA/IL-2 (mean CC_{50} values of 5.7±2.2 µM).

When evaluated against clinical isolates (MOI of approximately 0.1) in activated PBMCs, BIC displayed similar antiviral activity across all tested 18 clinical isolates (14 group M isolates covering subtypes A-G, 3 group O isolates, and one group N isolate) with median and mean EC_{50} values of 0.55 and 0.60 nM, respectively, and a range of EC_{50} values between <0.05 and 1.71 nM (Nonclinical Study Reports PC-141-2035 and PC-141-2057; Tsiang et al., 2016). Four subtype B isolates included in this assay were susceptible to BIC with EC_{50} values of 0.35-0.88 nM. In addition, BIC showed similar potency against one clinical isolate of HIV-2 tested with an EC_{50} value of 1.11 nM.

Using the 5-day cytopathic assay in MT-2 cells infected with HIV-1 xxLAI (a chimeric laboratory strain containing an HIV-1 HXB2 RT sequence spanning amino acids 14 to 491 cloned into a RT-defective HIV-1 proviral vector xxLAI-Δ [Shi and Mellors, 1997]) at an MOI of 0.005, the antiviral activity of BIC was evaluated in combination with FTC and TAF (Nonclinical Study Report PC-380-2001). The combination effect of the three-drug combination was analyzed using the combination index method of the CalcuSyn software as previously described by Kulkarni et al. (2014). The triple drug combination of BIC+FTC+TAF displayed no antagonism (mean combination index [CI] score of 0.60 ± 0.11, comparable to a mean CI score of 0.61 ± 0.23 obtained with the DTG+FTC+TAF triple combination) with no evidence of cytotoxicity observed at tested drug concentrations in the absence of HIV-1 infection. In addition, Nonclinical Study Report PC-141-2038 (Tsiang et al., 2016) also describes no antagonistic anti-HIV activity in pair-wise combinations of BIC with different-class ARVs DRV (PI), FTC (NRTI), or TAF (NRTI) in MT-2 cells acutely infected with HIV-1_{IIIB} at an MOI of approximately 0.01 using the 5-day cytopathic assay. The combination effect of each tested pair of inhibitors was analyzed by the Prichard and Shipman method using MacSynergy™ II program (Prichard and Shipman, 1990). As expected, BIC exhibited additive activity when combined with itself or same-class INSTIs RAL or EVG. In contrast, the antiviral activity of BIC was not affected (up to 1.1-fold change in the BIC EC_{50} value) in the presence of clinically relevant concentrations of sofosbuvir an HCV nucleotide inhibitor (up to 2 times the C_{max} value observed at the clinical dose) in the 2-drug combination study conducted in HIV-1_{IIIB}-infected MT-4 cells using the 5-day cytopathic assay (Nonclinical Study Report PC-120-2032). Similarly, the anti-HIV activities of FTC and TAF, individually, were not significantly affected by sofosbuvir (up to 1.5-fold and 1.2-fold changes in the EC_{50} value for FTC and TAF, respectively).

BIC demonstrated no specific antiviral activity at up to the highest concentration tested (44 µM) against non-retroviruses in cell-based assays, such as HBV in HBV genotype D-expressing AD38

cells, HCV in Huh-7-derived cells containing HCV1b or HCV2a replicons, influenza A and B viruses (A/Port Chalmers/1/73 and B/LEE/40, respectively) in NHBE cells, human rhinovirus (mixture of 3 serotypes, HRV1A, HRV14, and HRV16) in H1-HeLa cells, and respiratory syncytial virus (RSV type A) in HEp-2 cells (Study Report PC-141-2043; Tsiang et al., 2016). CC_{50} values for BIC in these tested cells ranged from 31.7 to >50 μM.

BIC showed low to undetectable cytotoxicity against several non-target human cell lines of different tissue origin when cultured for 5 days (Nonclinical Study Report PC-141-2042; Tsiang et al., 2016); CC_{50} values ranged from 34.6 to >44 μM in hepatoma-derived Huh-7 and HepG2 cells, prostate carcinoma-derived PC-3 cells, and normal fetal lung-derived MRC-5 cells. BIC also did not display in the 5-day cytotoxicity assay any significant cytotoxicity in human primary hepatocytes with a CC_{50} value of >100 μM. Furthermore, no marked off-target activities (≥50% inhibition or stimulation in biochemical assays; LeadProfilingScreen, Eurofins Panlabs, Inc.) of BIC at 10 μM were observed against a panel of 68 targets consisting of neuroreceptors, ion channels, and nuclear receptors (Nonclinical Study Report PC-141-2029).

8.1.3 Resistance Development in Cell Culture

Cell-based resistance selection experiments were conducted in MT2 cells infected with HIV-1_{IIIB} at an MOI of approximately 0.01 (Selection 1; Nonclinical Study Report PC-141-2052; Tsiang et al., 2016) or with HIV-1 xxLAI at an MOI of approximately 0.1 (Selection 2; Nonclinical Study Report PC-141-2056) by serial passage of culture supernatants containing virus in the presence of increasing concentrations of BIC. Virus replication was measured by monitoring of virus-induced cytopathic effects (CPEs). When extensive CPE was observed, the supernatant was collected and was used to infect fresh cultures in the presence of a 2-fold higher concentration of BIC than the previous culture. Successive viral passages were obtained by repeating this. In MT-2 cells infected with HIV-1, CPE manifests itself predominantly as syncytia formed by the fusion of infected cells, and CPE was observed in the no-drug culture approximately one week after initiation of infection. For comparison, parallel resistance selection experiments were performed under the same conditions with the other FDA-approved INSTIs DTG, EVG, and/or RAL. Genotypic changes that emerged in HIV-1 IN under the selective pressure of tested inhibitors were assessed by population-based sequencing and/or next-generation sequencing (performed (b) (4) using the deepTypeHIV assay) of the entire IN coding region of virus collected from various passages.

In Selection 1 (Nonclinical Study Report PC-141-2052; Tsiang et al., 2016), resistance selection using BIC progressed at a rate considerably slower than that of EVG, indicating that BIC has a higher barrier to resistance emergence than EVG. Stepwise selection with BIC required 234 days to reach a drug concentration equivalent to 256 times its EC_{50} value, while selection with EVG progressed to a drug concentration equivalent to 1024 times its EC_{50} value in 119 days. The kinetics of DTG resistance development was similar to that of BIC, requiring 202 days to break through a drug concentration equivalent to 68 times its EC_{50} value.

Population-based sequencing of BIC-selected viruses at various passages revealed the emergence of R263K at passages 3 (mixture with wild-type R263), 5, and 6 followed by the emergence of a R263K/M50I variant at passage 8. These 2 substitutions were persistently observed in the virus population at passages 9 and 10 (end of the selection at a drug concentration equivalent to 256 times the EC_{50} value). The virus pools from passage 3 to passage 10 displayed slowly increasing phenotypic resistance to BIC; the EC_{50} value increased 1.7-, 2.6-, and 3.5-fold for viruses at passages 3, 5, and 6, and 5.0-, 7.9-, and 6.1-fold for those at passages 8, 9, and 10, compared to that of the wild-type virus (HIV-1_{IIIB}). When R263K and M50I were introduced, individually or in combination, into the infectious wild-type HIV-1 DNA clone HXB2 by site-directed mutagenesis, R263K+M50I double substitutions conferred low-level resistance to BIC (2.9-fold reduction in BIC susceptibility, compared to the wild-type virus), while the single R263K or M50I substitutions resulted in a 2.2-fold and 1.3-fold change, respectively, in BIC susceptibility. The clinical cutoff by the PhenoSense® Integrase assay (Monogram Biosciences) for BIC has not been determined; the applicant utilized a biological cutoff of 2.5-fold for BIC as a cutoff for reduced susceptibility in phenotypic resistance analysis.

Emergence of R263K or M50I was not observed in post-baseline isolates from B/F/TAF-treatment virologic failure subjects in 2 ART-naïve trials 1489 and 1490 and 2 switch trials 1844 and 1878 (see below Section 8.2.3 and Table 52 for details). The R263K substitution is a rare non-polymorphic substitution (Stanford HIV Drug Resistance Database) that was reported in cell-culture selection with EVG (Margot et al., 2012) and DTG (Quashie et al., 2012). This substitution infrequently emerged in EVG-treated patients (0.8% [2/266] of evaluated virologic failures; FDA Virology review for VITEKTA [NDA 203093]) and in DTG-treated patients (Cahn et al., 2013). The R263K substitution by itself conferred 6.3-fold reduced susceptibility to EVG (Margot et al., 2012) and 11.2-fold reduced susceptibility to DTG (Quashie et al., 2012). R263K prevalence within the treatment-naïve HIV-infected patients is extremely low (Lataillade et al., 2007); the substitution was not detected in pre-treatment isolates from subjects with evaluable data in 2 ART-naïve trials 1489 and 1490 (n=1,262). The M50I substitution is a polymorphism that has been found in 10-25% of INSTI-naïve patients (Ceccherini-Silberstein et al., 2009), and emerged after R263K in previous resistance selection with DTG (Quashie et al., 2012). Emergence of M50I was infrequently observed in EVG-treated subjects' virologic failure isolates (8 of the 266 examined subjects [3%]). The M50I substitution by itself conferred no significant reduction in susceptibility to DTG and EVG (1.2- and 1.4-fold higher in EC_{50} values, respectively). M50I was present in 21.4% (231/1078) of pre-treatment isolates from subjects with evaluable data in the 2 ART-naïve trials, and all subjects (n=124) with baseline M50I-containing virus achieved a viral load of <50 copies/mL at Week 48 (or early discontinuation) on B/F/TAF and 99.1% (106/107) on the DTG-containing regimens.

Additionally, the applicant conducted a resistance breakthrough study in MT-2 cells infected with HIV-1_{IIIB} (MOI of 0.05) and in primary human $CD4^+$ T lymphocytes (pooled from 4 healthy donors) infected with HIV-1_{BaL} (MOI of 50 ng p24 equivalent/million cells) using a fixed concentration of drug (Nonclinical Study Report PC-141-2052; Tsiang et al., 2016). In infected MT-2 cells, while HIV-1 started breaking through at Days 7 and 22 post-infection, respectively,

when cells were cultured in the presence of FTC (25 µM, 4 times the EC_{95} value) and of EVG (48 nM, 5 times the EC_{95} value), no virus breakthrough was observed at Day 32 post-infection with either BIC (21 and 42 nM) or DTG (16 and 32 nM) at 2.5 and 5 times their EC_{95} values. Emergence of the RT M184I and IN T66I+D232N substitutions, previously known substitutions associated with resistance to FTC and EVG, respectively, emerged in FTC and EVG breakthrough selections. In HIV-1_{BaL}-infected primary human $CD4^+$ T lymphocytes cultured at a cell culture-equivalent clinical minimum drug concentration (C_{min}) of drug, BIC (138 nM) and DTG (73 nM) suppressed viral breakthrough over a period of 35 days, whereas EVG (48 nM) and RAL (60 nM) were associated with a higher incidence of viral breakthrough (54 and 58%, respectively). Substitutions T66I, L74M, E92G, F121Y, Q148R, N155H, G163R, S230R, R263K, associated with resistance to EVG and/or RAL, were frequently detected in virus variants that emerged in the presence of EVG or RAL. Collectively, these cell-culture resistance breakthrough studies also indicated that BIC has a barrier to resistance emergence higher than EVG or RAL, but similar to DTG.

In the second resistance selection experiment in MT-2 cells infected with HIV-1 xxLAI (Nonclinical Study Report PC-141-2056), as observed in Selection 1 conducted in HIV-1_{IIIB}-infected MT-2 cells, the BIC and DTG selections progressed at a slower rate than that of EVG and RAL, also indicating BIC and DTG have higher genetic barriers to resistance emergence than EVG and RAL. At the end of the experiment (passage 13), the selections with BIC and DTG had progressed to drug concentrations equivalent to 4,096 times their EC_{50} values in 207 and 229 days, respectively, while the selections with EVG and RAL required 138 and 166 days.

Following 6 passages in the presence of increasing concentration of BIC over the course of 79 days, a viral pool expressing INSTI resistance-associated substitutions T66I and S153F emerged at frequencies of 8.0% and 2.4%, respectively, by next-generation sequencing. As the selection progressed to passage 9 (131 days), the frequency of T66I declined to 3.1%, while the S153F population was enriched to 37.9%. By passage 12 (191 days), the S153F substitution was present at 97.4% of the sequences, and the T66I substitution was not detected. Additionally, at passage 12, an S24G substitution emerged at a frequency of 31.9%. At the end of the selection at passage 13 after 207 days, the emergent viral pool predominantly contained the S153F substitution (present in >99.5% of the sequences), while the S24G substitution decreased to 11.3%. Additional IN substitutions E152K, M154I, and E157K were transiently present at low frequencies (up to 3.4%) at passages 9, 12, and 13. The E152K substitution was present at passages 9 (3.2%) and 13 (2.4%), but undetectable at passage 12, while the M154I and E157K substitutions were present at passages 9 (2.4 and 3.4%, respectively) and 12 (2.7 and 3.2%), but undetectable at the final passage of the selection.

Emergence of T66I or S153F was not observed in post-baseline isolates from B/F/TAF-treatment virologic failure subjects in 2 ART-naïve trials 1489 and 1490 and 2 switch trials 1844 and 1878 (see below Section 8.2.3 and Table 52 for details). T66I and S153F are non-polymorphic substitutions reported previously as primary and secondary substitutions associated with resistance to EVG and DTG, respectively (Stanford HIV Drug Resistance Database; Table 49).

The T66I primary EVG-resistance substitution was selected in cell culture and in patients receiving EVG (Goethals et al., 2008; Margot et al., 2012; FDA Virology review for VITEKTA [NDA 203093]; FDA Virology review for STRIBILD [NDA 203100]), and conferred in phenotypic analysis using recombinant site-directed HIV-1 mutant variants 9.2-fold reduced susceptibility to EVG. However, significant reductions (above the biological or lower clinical cutoffs by the PhenoSense® Integrase assay) were not observed in susceptibility to BIC (0.4-fold), DTG (0.4-fold), or RAL (1.3-fold). The S153F secondary DTG-resistance substitution was selected in cell culture by DTG (Kobayashi et al., 2011) and caused 1.9-, 1.6-, 2.1-, and 1.0-fold increases in the EC_{50} values of BIC, DTG, EVG, and RAL, respectively (all below the biological or lower clinical cutoffs for those tested drugs). It should be noted that, since the S153F substitution was selected in the presence of BIC in cell culture, a 1.9-fold reduction in BIC susceptibility may be relevant. A recombinant site-directed mutant HIV-1 harboring T66I/S153F double substitutions showed increased resistance to EVG (33-fold) but remained susceptible to BIC, DTG, and RAL (EC_{50} value changes of 0.5- to 1.0-fold). These 2 substitutions were not detectable in pre-treatment isolates from subjects in 2 ART-naïve trials 1489 and 1490 (n=1,267).

In summary, cell-culture emergence of resistance to BIC appeared to involve at least 2 distinct pathways: R263K/M50I (Selection 1) and S153F with a transient T66I (Selection 2). In addition, S24G, E152K, M154I, and/or E157K substitutions emerged at low frequency or transiently during the selection process. BIC appeared to have a higher barrier to resistance emergence than EVG and RAL but similar to DTG, based on the duration until a virus breakthrough that can grow in the presence of BIC was observed in HIV-1-infected cells. In the recombinant site-directed HIV-1 mutant variants, R263K+M50I double substitutions conferred low-level resistance to BIC (2.9-fold reduction in BIC susceptibility, compared to the wild-type virus), while M50I, T66I, S153F, or R263K single and T66I/S153F double substitutions resulted in, respectively, 1.3-, 0.4-, 1.9-, 2.2-, and 0.5-fold increases in the EC_{50} value of BIC (below the biological cutoff of 2.5-fold for BIC by the Monogram Biosciences PhenoSense® Integrase assay).

8.1.4 Cross-Resistance with Other FDA-Approved Antiretrovirals

BIC was tested for its antiviral activity against a panel of HIV-1_{HXB2} variants (n=9) expressing key clinically relevant IN substitutions, generated by site-directed mutagenesis, associated with resistance to other INSTIs DTG, EVG, and RAL in MT-2 cells (Nonclinical Study Report PC-141-2040; Tsiang et al., 2016): E92Q, Y143R, Q148R, N155H, R263K, Q148K/E138K, Q148R/G140S, E92Q/N155H, and Q148R/N155H. Overall, BIC displayed a level of resistance that was either comparable to or slightly lower than that determined with DTG against the same tested viruses; 9 tested mutant viruses displayed 0.7- to 8.8-fold and 0.8- to 10.1-fold reduced susceptibility to BIC and DTG, respectively, compared to control wild-type virus. This degree of resistance to BIC and DTG is substantially less compared to that observed with EVG (4.4- to 1,520-fold) and RAL (1.1- to 262-fold), when tested against the same set of mutant viruses. BIC showed no significant changes in its antiviral potency (<2-fold loss of activity) against variants with single substitutions tested. BIC was 2.0- to 8.8-fold less active against viruses expressing

Q148K/E138K, Q148R/G140S, or Q148R/N155H double substitutions, while it appeared to retain its activity against viruses with E92Q/N155H with a 1.3-fold change in drug susceptibility.

In addition, in Nonclinical Study Report PC-141-2055, the applicant investigates cross-resistance of site-direct mutant variants expressing T97A in the absence of other known primary INSTI resistance-associated substitutions (listed in Table 49 in Section 8.2.1). The 97A substitution is a polymorphism that occurs in 1% to 4% of viruses from untreated persons depending on subtype (Stanford HIV Drug Resistance Database; Varghese et al., 2010), and considered a primary substitution associated with resistance to EVG (U.S. Prescribing Information for VITEKTA®). It was selected in patients experiencing virologic failure on EVG or RAL (review article by Abram et al., 2017). T97 by itself did not confer significantly reduced susceptibility to EVG (2.1-fold) or RAL (2.4-fold; FDA Virology review for STRIBILD [NDA 203100]), however, in a recent analysis of clinical isolates from the U.S., it was associated with 5- to 10-fold reduced susceptibility to RAL and EVG, possibly because many of these isolates had other secondary INSTI resistance substitutions or minority variant primary resistance mutations (White et al., 2016). Nonclinical Study Report PC-141-2055 describes the antiviral activity of 4 INSTIs (BIC, DTG, EVG, and RAL) against site-direct mutants containing the T97A substitution, alone or in combination with one to 3 additional selected secondary INSTI-resistance substitutions: T97A alone (n=1), T97A+one secondary substitution (n=9; M50I, V72I, L74M, G118R, S119G, S119P, S119R, S119T, or G163R), T97A+2 secondary substitutions (n=6; L72I/L74M, L74M/G119G or P or R or T, and G118R/S119R), and T97A+3 secondary substitutions (n=1; V72I/L74M/S119R). Both BIC and DTG retained their activity against all but one T97A variant tested with <1.1- and ≤1.2-fold reductions in drug susceptibility, respectively; the one T97 variant having reduced susceptibility to BIC and DTG (2.8-fold and 11-fold, respectively) harbored T97A and G118R double substitutions. As expected, all tested T97A variants showed 2.9- to 26-fold and 1.6- to 20-fold reduced susceptibility to EVG and RAL, respectively, all above the biological cutoffs of 2.5-fold for EVG and 1.5-fold for RAL. G118R is a rare non-polymorphic substitution (Stanford HIV Drug Resistance Database) that has been selected rarely in patients treated with DTG (Brenner et al., 2016) and RAL (Malet et al., 2011 and 2014). Highly variable effects of the G118R substitution on drug susceptibility were previously reported, from ≤1-fold changes in susceptibility to DTG, EVG, and RAL (Brenner et al., 2016) to 3.1- to 20-fold reductions (Malet et al., 2014; Munir et al., 2015). In this nonclinical study report (PC-141-2055), the applicant reported cross-resistance of site-directed mutant viruses expressing G118R and G118R+T97A among 4 INSTIs; the 2 variants had reduced susceptibility (above the biological or lower clinical cutoffs for each tested INSTI), respectively, of 3.4- and 2.8-fold to BIC, 6.1- and 11-fold to DTG, 4.9- and 8.6-fold to EVG, and 6.2- and 20-fold to RAL.

Reviewer's Comment: With observed fold-reductions being above the biological or lower clinical cutoffs for each tested INSTI, in the FDA reviewer's resistance analysis the G118R substitution was considered as a primary INSTI resistance substitution (the applicant considered this substitution as a secondary INSTI-resistance substitution in Table 49 in Section 8.2.1).

In order to further characterize the cross-resistance profile of BIC, BIC potency was assessed,

compared to those of DTG, EVG, and RAL, against 47 clinical isolates (polyclonal) harboring INSTI resistance-associated IN substitutions (n=1 to 3) and exhibiting phenotypic resistance to at least one FDA-approved INSTI (Nonclinical Study Report PC-141-2051; Tsiang et al., 2016; White et al., 2016). In this study, T66I/A/K, E92Q/G, T97A, Y143C/H/R, S147G, Q148H/K/R, N155H were considered as primary INSTI-resistance substitutions, and H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K were considered as secondary INSTI-resistance substitutions. The Monogram Biosciences PhenoSense® Integrase assay was utilized to obtain phenotypic data (EC_{50} values) of recombinant viruses containing the patient-derived IN coding region. The EC_{50} values for the wild-type control virus (HIV-1_{NL4-3}) were 1.94 nM for BIC, and 2.79 nM for DTG, 2.34 nM for EVG, and 7.06 nM for RAL.

Reviewer's Comment: Previously reported substitutions in HIV-1 IN, F121C/Y, P145S, and Q146I/K/L/P/R, were considered in this FDA reviewer's cross-resistance analysis as primary INSTI resistance substitutions (U.S. Prescribing Information for ISENTRESS®; U.S. Prescribing Information for VITEKTA®; Stanford HIV Drug Resistance Database; FDA Virology review for VITEKTA [NDA 203093]).

Of the 47 INSTI-resistance substitution-containing isolates tested, compared to the wild-type control virus, 33 (70.2%) had <2.5-fold reduced susceptibility to BIC (below the biological cutoff by the Monogram Biosciences PhenoSense® Integrase assay), 7 had 2.5- to <5-fold reduced susceptibility, 6 had 5- to <10-fold reduced susceptibility, and one had ≥10-fold reduced susceptibility. The one isolate with ≥10-fold reduced susceptibility to BIC had a 19-fold change, compared to 63-, >150-, and >143-fold reductions in susceptibility to DTG, EVG, and RAL, respectively, and had a complex INSTI resistance pattern of Q148K+E138K+G140S. All isolates (n=14) with >2.5-fold reduced susceptibility to BIC contained both Q148H/K/R and G140A/C/S substitutions. Of note, there were 23 isolates included in this study that expressed both Q148H/K/R and G140A/C/S substitutions and 60.9% (14/23) of those had >2.5-fold reduced susceptibility to BIC (41.7% [5/12] and 81.8% [9/11] of those without and with additional INSTI-resistance substitutions, respectively). In susceptibility to DTG, 28 (59.6%) of the 47 tested isolates had <4-fold reductions (below the lower clinical cutoff), 11 had 4- to <10-fold reduction, and 8 had ≥10-fold reductions. As observed with BIC, the majority (78.3%, n=18) of the 23 isolates expressing Q148H/K/R and G140A/C/S substitutions had >4-fold reduced susceptibility to DTG (66.7% [8/12] and 90.9% [10/11] of those without and with additional INSTI-resistance substitutions, respectively). To EVG and RAL, 2.1% (3/47) and none of the 47 tested isolates had <2.5-fold and <1.5-fold reduced susceptibility (below the biological cutoffs), respectively, and 91.5% (43/47) and 89.4% (42/47) had ≥10-fold reduced susceptibility. All 23 isolates expressing Q148H/K/R and G140A/C/S substitutions were resistant to EVG (>141-fold reduced susceptibility) and RAL (88- to >143-fold reduced susceptibility).

As summarized in Table 48, the observed fold-reductions in BIC susceptibility of all 22 isolates expressing one or 2 primary INSTI-resistance substitutions other than Q148H/K/R with or without detectable secondary substitutions remained below the biological cutoff of <2.5-fold

for BIC (cell color-coding in this Table; green if all observed fold-changes in drug susceptibility remained below the biological or lower clinical cutoffs for the tested drug). Similarly, the observed fold-changes in DTG susceptibility of all but one (95.5%) of those 22 isolates evaluated were also below the lower clinical cutoff of <4-fold: all 15 isolates with single primary substitutions (-Q148H/K/R) having <4.0-fold reduced susceptibility (colored green) and 7 isolates with 2 primary substitutions (-Q148H/K/R) having mixed phenotypic susceptibility (colored yellow; 6 having fold-changes below the lower clinical cutoff and one having a fold-change [4.1-fold] above the lower clinical cutoff). In contrast, all those 22 isolates had >1.5-fold reduced susceptibility to RAL (above the biological cutoff; colored red), and 80% (12/15) of isolates with single primary substitutions (-Q148H/K/R; mixed phenotypic susceptibility, colored yellow) and all 7 isolates with 2 primary substitutions (-Q148H/K/R; red) had >2.5-fold reduced susceptibility to EVG (above the biological cutoff; colored red).

When 25 clinical isolates were evaluated expressing the Q148H/K/R substitutions, all were resistant to EVG (>141-fold reductions in EVG susceptibility; colored red in Table 48) and RAL (43- to >143-fold reductions in RAL susceptibility; colored red). However, these Q148H/K/R variants were observed to have mixed phenotypic susceptibility to BIC and DTG. Of the 14 evaluated Q148H/R variants harboring one additional secondary INSTI-resistance substitution, E138A/K (n=2) or G140A/S (n=12), approximately half of those isolates, 9 (64.3%) and 6 (42.9%), showed <2.5-fold and <4-fold reductions in BIC and DTG susceptibility (below the biological or lower clinical cutoffs), respectively. However, when variants (n=9) had Q148H/K/R with 2 additional secondary INSTI-resistance substitutions (G140A/C/S plus L74M, E138A/K, or G163K), the majority, 77.8% (7/9) and 88.9% (8/9), showed >2.5-fold and >4-fold reduced susceptibility BIC and DTG, respectively. There were 2 isolates expressing Q148H plus G140S with one additional primary INSTI-resistance substitution T97A, and both isolates showed reduced susceptibility to BIC (4.4- to 7.6-fold) and DTG (14- to 15-fold). Thus, phenotypic analysis of viruses expressing Q148H/K/R substitutions may be useful when BIC is considered for INSTI experienced patients.

Table 48: Cross-Resistance between BIC and FDA-Approved Drugs in the INSTI Class (FDA analysis)

	Drug susceptibility (fold-reduction[a])			
	BIC	DTG	EVG	RAL
Isolates expressing primary INSTI-resistance substitutions (other than Q148H/K/R)				
single detectable primary substitution[b] (n=15)	0.5 - 1.7	0.5 - 2.1	1.9 - >150	1.8 - >143
2 detectable primary substitutions[c] (n=7)	0.8 - 2.0	1.1 - 4.1	20 - >150	53 - >143
Isolates expressing primary INSTI-resistance Q148H/K/R substitutions				
with a single detectable secondary substitution (E138A/K or G140A/S; n=14)	1.7 - 7.1	2.1 - 17	>150	43 - >143
with 2 detectable secondary substitutions (G140A/C/S + L74M or E138A/K or G163K ; n=9)	2.4 - 19	3.6 - 63	>141	>114
one additional detectable primary substitution[d] (n=2)	4.4 - 7.6	14 - 15	>150	>143

Source: Reviewer's summary, based on the drug susceptibility data (fold-reduction) of clinical isolates with IN substitutions associated with INSTI resistance summarized in Table 1 in Nonclinical Study Report PC-141-2051.

a. Fold-reduction in drug susceptibility of tested isolates, compared to the reference infectious molecular clone HIV-1_{NL4-3} in the Monogram Biosciences PhenoSense® Integrase assay.
b. Primary INSTI-resistance substitutions detectable are E92Q (n=3), T97A (n=2), F121Y (n=1), Y143C (n=2), Y143R (n=3), and N155H (n=4). Of 15 isolates with single primary substitutions, 7 isolates also had one or 2 detectable secondary substitutions L68V (n=2), L74M (n=3), E157Q (n=2), G163R (n=1).
c. Primary INSTI-resistance substitutions detectable are E92Q (n=2), T97A (n=5), F121Y (n=1), Y143C (n=2), Y143R (n=1), and N155H (n=3).
d. In both, 2 primary substitutions T97A and Q148H and one secondary substitution G140S were detected.

In addition, 17 HIV-1 clonal variants derived from clinical isolates containing IN sequences obtained from 11 STRIBILD-treated subjects who experienced virologic failure and had failure isolates with emergent INSTI-resistance substitutions were isolated and utilized to further define the cross-resistance profile of BIC (Nonclinical Study Report PC-141-2050; Tsiang et al., 2016). Those tested clones expressed E92Q only (n=8), Q148R only (n=1), Q148R+G140C (n=1), N155H only (n=4), N155H+G163R (n=1), T66I+E157Q (n=1), and T66I+T97A+E157Q (n=1). BIC was active against all tested clonal variants expressing INSTI-resistance substitutions with 0.18- to 1.52-fold changes in BIC susceptibility (below the biological cutoff of 2.5-fold for BIC), compared to the wild-type virus. Median and mean fold-change values were 1.17 and 1.06±0.37, respectively. Similarly, DTG also retained its antiviral potency against the tested clonal viruses with observed 0.25- to 1.97-fold changes in DTG susceptibility (below the lower clinical cutoff of 4-fold for DTG). In contrast, these tested clones were resistant to EVG with 22- to 208-fold decreased susceptibility (above the biological cutoff of 2.5-fold for EVG) and RAL with 1.6- to 32-fold decreased susceptibility (above the biological cutoff of 1.5-fold for RAL). Of note, one additional clone (from one virologic failure subject) with no detectable INSTI-resistance substitutions that was included in this study retained full susceptibility to BIC, DTG, EVG, and RAL (0.79- to 0.87-fold changes in drug susceptibility).

In summary, BIC displayed a cell culture cross-resistance profile significantly improved compared to EVG and RAL but comparable to that of DTG when evaluated against site-direct HIV-1 mutants and clinical isolates (polyclonal and clonal) expressing previously known IN substitutions associated with resistance to FDA-approved INSTIs DTG, EVG, and/or RAL. The apparent dissociation half-life of DTG from HIV-1 integrase (IN)-DNA complexes was previously shown to be longer than EVG and RAL, and was predicted to correlate with potent antiretroviral activity and a higher genetic barrier to resistance (Hightower et al., 2011). In Nonclinical Study Report PC-141-2058, the applicant reported the dissociation half-life of BIC from HIV-1 IN-DNA complexes in a biochemical assay, as described previously in Hightower et al. (2011), with purified recombinant HIV-1 integrase expressed in BL21 cells. BIC formed a stable complex with the HIV-1 IN bound to HIV-1 long terminal repeat DNA. The dissociation half-life for BIC (38±19 hours by the equilibrium binding model) from HIV-1 IN-DNA complexes was longer than that of DTG (16±9 hours), EVG (1.5±0.2 hours), and RAL (5.2±0.6 hours). Furthermore, BIC was shown to be dissociated more slowly than DTG from the Q148H+G140 IN-DNA complex: the dissociation half-life of 2.5±0.07 for BIC versus 0.65±0.2 for DTG. The dissociation half-life for EVG and RAL could not be determined due to low binding. Thus, the significantly slow dissociation of BIC from both wild-type and mutant IN-DNA complexes may contribute to its

improved antiviral activity against wild-type HIV-1 and clinically relevant INSTI-resistant viruses, thus providing improved resistance profile, compared to EVG and RAL, as observed with DTG.

No cross-resistance was observed to BIC with <2-fold reductions in drug susceptibility, compared to the wild-type virus, against individual HIV-1 variants (n=12) expressing substitutions associated with resistance to NNRTIs, NRTIs, and PIs (Nonclinical Study Report PC-141-2039; Tsiang et al., 2016): NNRTI-resistance RT substitutions K103N, Y181C, Y188L, L100I/K103N, or K103N/Y181C, and NRTI-resistance RT substitutions K65R, M184V, or 6 thymidine analog mutation substitutions (TAMs: M41L, D67N, K70R, L210W, T215Y, and K219Q), and PI-resistance PR substitutions L10F/M46I/I50V, I84V/L90M, G48V/I54V/V82S, or G48V/V82A/L90M. This phenotypic cross-resistance testing was performed using the 5-day cytopathic assay in MT-2 cells infected with wild-type and site-directed mutant variants at an MOI of 0.01.

8.2 Clinical Virology

8.2.1 Assay Descriptions and Methodologies

Quantification of Plasma HIV-1 RNA Levels

Plasma HIV-1 RNA levels were quantified by (b) (4) (b) (4) using the U.S. FDA-approved, Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2.0 (PMA # BP050069; original marketing approval [version 1.0] on May 11, 2007; Schumacher et al., 2007). The test is a nucleic acid amplification test for the quantification of HIV-1 RNA in human plasma using the COBAS® AmpliPrep Instrument for automated specimen processing and the COBAS® TaqMan® Analyzer or COBAS® TaqMan® 48 Analyzer for automated amplification and detection. The test version 2.0, developed based on the original version (version 1.0), targets two highly conserved regions of the HIV-1 genome (*gag* and long terminal repeat), and can quantify HIV-1 RNA from samples of HIV-1 groups M, N, and O over the range of 20 to 10,000,000 copies/mL (Pas et al., 2010; Wojewoda et al., 2012).

Drug Resistance Analyses

Drug resistance analyses consist of genotypic and phenotypic analyses of IN, PR, and RT domains of the HIV-1 *pol* gene as defined in the virology analysis plan for the B/F/TAF Phase 3 clinical trials (Report PC-141-2053). (b) (4) is the designated reference laboratory for primary drug resistance analyses consisting of HIV-1 population genotyping and phenotyping at Screening/Baseline and virologic failure.

- Pretreatment Genotypic Resistance Analyses at Screening/Baseline

For Trials 1489 and 1490 in ART-naïve subjects, as required by the enrollment criteria, the PR/RT genotype was assessed for all subjects at Screening using the GenoSure® MG assay

(Monogram Biosciences). The assay covers the entire PR-coding region (amino acids 1-99) and a portion of the RT-coding region (amino acids 1-400), encompassing all clinically relevant NNRTI, NRTI, and PI resistance-associated substitutions. A retrospective genotypic analysis of the IN-coding region was conducted using next-generation sequencing (NGS) data of baseline samples from all randomized and treated subjects. NGS data were generated using the deepTypeHIV assay (SeqIT GmbH & Co. KG), and any amino acid variations at each position were reported if they were present in ≥15% of the total population.

For Trials 1844 and 1878 in virologically suppressed subjects, when available, historical genotype reports that were previously generated by commercial or local assays are reported in the virology listings.

- Treatment-Emergent Genotypic and Phenotypic Resistance Analyses

For treatment-emergent resistance analysis, subjects who experienced virologic failure with HIV-1 RNA ≥200 copies/mL as defined below were identified as the resistance analysis population:

- In Trials 1489 and 1490 in ART-naïve subjects, virologic failure with HIV-1 RNA ≥200 copies/mL is defined as having HIV-1 RNA ≥200 copies/mL at Week 48 (or early study drug discontinuation) or having confirmed virologic rebound with HIV-1 RNA ≥200 copies/mL. Confirmed virologic rebound with HIV-1 RNA ≥200 copies/mL is defined as HIV-1 RNA ≥200 copies/mL at any study visit after achieving HIV-1 RNA <50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; OR a >1 $\log_{10}$ copies/mL increase in HIV-1 RNA at any visit from the nadir, which is subsequently confirmed at the following scheduled or unscheduled visit. Of note, HIV-1 RNA ≥200 copies/mL at early study drug discontinuation or Week 48 did not require confirmation of virologic failure.

- In Trials 1844 and 1878 in virologically suppressed subjects, virologic failure with HIV-1 RNA ≥200 copies/mL is defined as having confirmed virologic rebound with HIV-1 RNA ≥200 copies/mL at any study visit, which is subsequently confirmed at the following scheduled or unscheduled visit. Of note, HIV-1 RNA ≥200 copies/mL at early study drug discontinuation or Week 48 did not require confirmation of virologic failure.

Treatment-emergent resistance analyses consisted of genotypic and phenotypic analyses of the IN, PR, and RT domains of the HIV-1 *pol* gene of paired baseline and virologic failure samples (preferably sample from the confirmation visit). The PhenoSense® GT assay (Monogram Biosciences) was used to determine the HIV-1 PR and RT genotypes and phenotypes relevant to all currently approved NNRTIs, NRTIs, and PIs. This assay also determines HIV-1 subtype. The HIV-1 IN genotypes and phenotypes relevant to currently approved INSTIs as well as BIC were determined using the GeneSeq® Integrase and PhenoSense® Integrase assays (Monogram Biosciences), respectively. In Trials 1844 and 1878 in virologically suppressed subjects,

GenoSure Archive® test (Monogram Biosciences) was used for retrospective analyses of baseline samples. The GenoSure Archive test analyzes archived HIV-1 proviral DNA integrated into the host cell genome using NGS methods to provide genotypic resistance information for INSTIs, NNRTIs, NRTIs, and PIs.

- Previously Identified Substitutions Associated with Drug Resistance

The applicant provided a reference list of previously identified substitutions associated with drug resistance by ARV drug class (Table 49).

Reviewer's Comment: Previously reported substitutions in HIV-1 IN, E92A, G118R, F121C, P145S, and Q146I/K/L/P/R, were considered in the FDA reviewer's resistance analysis as primary INSTI resistance substitutions (U.S. Prescribing Information for ISENTRESS®; U.S. Prescribing Information for VITEKTA®; Stanford HIV Drug Resistance Database; FDA Virology review for VITEKTA [NDA 203093]). Additional IN substitutions G70R, I73V, L74I, T112I/M/S, E138T, V151I, K160N, G163E/Q/S, H183P, G193E/R, Y226C/D/F/H, S230R, and D232N previously reported were considered in the FDA reviewer's resistance analysis as secondary INSTI resistance substitutions (U.S. Prescribing Information for ISENTRESS®; U.S. Prescribing Information for TIVICAY®; U.S. Prescribing Information for VITEKTA®; Stanford HIV Drug Resistance Database; FDA Virology review for TIVICAY by Lisa K. Naeger, Ph.D.; Malet et al., 2015).

Table 49: Applicant-Provided List of Previously Identified Substitutions Associated with Drug Resistance by ARV Class

Resistance Associated Substitutions[a]	
Mutation Groups	**Codon Mutations**
Primary Integrase Strand Transfer Inhibitor (INSTI) Resistance (-R) substitutions	T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI-R substitutions	M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A
Primary Nucleoside and Nucleotide Reverse Transcriptase Inhibitor (N(t)RTI)-R substitutions	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R
Thymidine Analogue Mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F, K219Q/N/E/R
Tenofovir (TFV) resistance associated substitutions	K65R/E/N, K70E
Emtricitabine (FTC) and lamivudine (3TC) resistance associated substitutions	M184V/I
Abacavir (ABC) resistance associated substitutions	K65R/E/N, K70E, L74V, Y115F, M184V/I
Secondary NRTI-R substitutions	E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, T215A/C/D/E/G/H/I/L/N/S/V[b]
Primary Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-R substitutions	L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230L/I
Secondary NNRTI-R substitutions	V90I, A98G, K101H, V106I, V179D/F/T
Primary Protease Inhibitor (PI)-R substitutions	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
Atazanavir (ATV) or Darunavir (DRV) resistance associated substitutions	I47V, I50L/V, I54M/L, L76V, I84V, N88S
Secondary PI-R substitutions	L10I/F/R/V/C, V11I, I13V, G16E, K20I/M/R/T/V, L24I, L33F/I/V, E34Q, M36I/L/V, K43T, F53L/Y, I54A/S/T/V, D60E, I62V, L63P, I64L/M/V, H69K, A71V/T/I/L, G73A/C/S/T, V77I, V82I, I85V, N88D, L89M/I/V, I93L/M

Source: Virology Report PC-380-2005 Table 2.

a. Adapted from the current IAS-USA list with some modifications (Wensing et al., 2017).
b. Reversion mutations at RT codon T215 including T215A/C/D/E/G/H/I/L/N/S/V have not been definitively shown to be associated with reduced response to either FTC or TFV.

8.2.2 Clinical Virology Analyses of Efficacy (Virology-Censored Population)

The antiviral efficacy analyses of 4 pivotal Phase 3 trials (ART-naïve trials 1489 [NCT02607930] and 1490 [NCT02607956] in treatment-naïve subjects and switch trials 1844 [NCT02603120] and 1878 [NCT02603107] in virologically suppressed subjects) were conducted using the as-treated virology-censored subject population to determine whether B/F/TAF had potent and

durable antiretroviral activity, compared to control treatments. The virology-censored subject population includes all randomized subjects who received at least one dose of study medication, but excludes subjects who had no reported on-treatment viral load data or who discontinued their assigned treatment with a last evaluable on-treatment viral load of <50 copies/mL before the primary efficacy assessment at Week 48. In addition, subjects who had HIV-1 RNA <50 copies/mL at their Week-36 visit with missing Week-48 viral load data were not included in the Week-48 antiviral efficacy analysis. Overall, 4.1 to 9.1% of subjects who were included in the primary efficacy analysis population for overall efficacy analysis of each treatment group of the individual trial were excluded from the Week-48 virology analysis population (Table 50).

The Week-48 antiviral efficacy of B/F/TAF (percentage of subjects with HIV-1 RNA <50 copies/mL during the Week-48 evaluation window [Study Days between 295 and 378, inclusive]) was comparable to that of the respective comparator group in all 4 trials (Table 50). The observed differences (-1.4% to 2.3%) in the rate of Week-48 virologic response (HIV-1 RNA <50 copies/mL) between the 2 treatment groups (B/F/TAF - its respective comparator) in each trial were not statistically significant with p values of >0.05 (based on Fisher's exact test). In ART-naïve subjects in the virology-censored population, the majority achieved early virologic response (Table 50); 78.8% and 75.8% of subjects in the B/F/TAF and ABC/DTG/3TC groups in Trial 1489, and 74.6% and 78.4% of those in the B/F/TAF and DTG+F/TAF groups in Trial 1490 had HIV-1 RNA <50 copies/mL at Week 4 (during the Week-4 evaluation window, Study Days between 2 and 42, inclusive), respectively. Furthermore, all 3 study regimens demonstrated durable antiviral activity over 48 weeks of treatment with 97.7% to 99.6% of early virologic responders maintaining HIV-1 RNA levels of <50 copies/mL at Week 48.

Reviewer's Comment: Results from independent FDA antiviral efficacy analyses using the virology-censored population are supportive of the applicant's conclusions, derived from the primary efficacy analysis (missing=failure approach) of each trial including all subjects who received at least one dose of study medication, that (1) B/F/TAF has potent antiviral efficacy, comparable to ABC/DTG/3TC in Trial 1489 and to DTG+F/TAF in Trial 1490, in ART-naïve subjects, and (2) with high rates of maintained virologic suppression in virologically suppressed subjects, switching to B/F/TAF is noninferior to remaining on a DTG+ABC/LAM regimen (as the ABC/DTG/3TC FDC) in Trial 1844 and to remaining on an ATV- or DRV-based regimen in Trial 1878.

Table 50: Week-48 Antiviral Efficacy in Virology-Censored Population (FDA analysis)

	Trial 1489		Trial 1490	
	B/F/TAF	ABC/DTG/3TC	B/F/TAF	DTG+F/TAF
Virology-censored	6.7% (21/314)	4.1% (13/315)	7.8% (25/320)	5.8% (19/325)
Discontinued study drug with HIV-1 RNA <50 copies/mL	76.2% (16/21)	76.9% (10/13)	48.0% (12/25)	84.2% (16/19)
Missing data at Week 48 but still on study drug[a]	23.8% (5/21)	7.7% (1/13)	24.0% (6/25)	15.8% (3/19)
No on-treatment viral load data evaluable	0	7.7% (1/13)	28.0 % (7/25)	0
Other reasons[b]	0	7.7% (1/13)	0	0
HIV-1 RNA <50 copies/mL	99.0% (290/293)	96.7% (292/302)	97.3% (287/295)	98.7% (302/306)
HIV-1 subtype B	99.2% (262/264)	96.7% (265/274)	96.9% (252/260)	98.9% (269/272)
HIV-1 subtype non-B	96.6% (28/29)	96.4% (27/28)	100% (35/35)	97.1% (33/34)
Early virologic response[c]	78.8% (231/293)	75.8% (229/302)	74.6% (220/295)	78.4% (240/306)
Durability of response[c]	99.6% (230/231)	98.7% (226/229)	97.7% (215/220)	99.6% (239/240)
	Trial 1844		**Trial 1878**	
	B/F/TAF	ABC/DTG/3TC	B/F/TAF	SBR
Virology-censored	5.0% (14/282)	4.6% (13/281)	6.6% (19/290)	9.1% (26/287)
Discontinued study drug with HIV-1 RNA <50 copies/mL	71.4% (10/14)	84.6% (11/13)	68.4% (13/19)	65.4% (17/26)
Missing data at Week 48 but still on study drug[a]	28.6% (4/14)	15.4% (2/13)	31.6% (6/19)	26.9% (7/26)
No on-treatment viral load data evaluable	0	0	0	7.7% (2/26)
HIV-1 RNA <50 copies/mL	98.5% (264/268)	99.3% (266/268)	98.5% (267/271)	97.3% (254/261)
HIV-1 subtype B	95.9% (94/98)	99.0% (95/96)	99.0% (97/98)	94.4% (68/72)
HIV-1 subtype non-B	100% (6/6)	100% (5/5)	91.7% (11/12)	92.3% (12/13)
HIV-1 subtype unknown	100% (164/164)	99.4% (166/167)	98.8% (159/161)	98.9% (174/176)

SBR, stay on baseline regimen

Source: Reviewer's analysis, based on analysis datasets adeff.xpt and advr.xpt

a. Subjects were excluded from the virology analysis population who had HIV-1 RNA <50 copies/mL at their Week-36 visit but missing Week-48 viral load data. These subjects were still on study drug during the Week-48 evaluation window.
b. One subject (Subject 01208-1505) was excluded from the virology analysis population because the subject had HIV-1 RNA <20 copies/mL at Baseline and remained suppressed through Week 48. The subject had HIV-1 RNA 7,540 copies/mL at Screening.
c. Early virologic response was defined as achieving suppression of HIV-1 RNA <50 copies/mL at Week 4. The durability of virologic response to study treatment was analyzed by determining the proportion of subjects, among early virologic responders, who maintained HIV-1 RNA levels of <50 copies/mL at Week 48.

8.2.3 Resistance Analyses

Treatment-Emergent Resistance

For treatment-emergent resistance analysis, virologic failure subjects who are eligible for resistance testing per protocol (resistance analysis population; see Section 8.2.1) were identified; a total of 34 subjects from those 4 pivotal Phase 3 trials (1.4% of subjects in the primary efficacy analysis population) were included in the Week-48 resistance analysis population (Table 51). Evaluable resistance data (genotypic and/or phenotypic) were obtained from 10/15 subjects in the resistance analysis population in the combined B/F/TAF groups, 10/12 subjects in the combined DTG groups (receiving DTG-containing regimens), and 5/7 subjects in the stay on baseline regimen (SBR) group (receiving PI-containing regimens).

Reviewer's Comment: In addition to 29 subjects who the applicant identified as eligible for resistance testing for Week-48 resistance analysis, independent FDA analysis of viral load data identified 5 additional subjects who experienced protocol-defined virologic failure with HIV-1 RNA ≥200 copies/mL by Week 48: 3 ART-naïve subjects and 2 virologically suppressed subjects. Resistance data were not obtained from these 5 subjects: (1) Subject 02434-1436 (B/F/TAF treatment in Trial 1489) who had HIV-1 RNA 275,000 copies/mL at Baseline and discontinued study drug treatment early with a last evaluable on-treatment viral load of 220,000 copies/mL at Treatment Day 32 without experiencing virologic rebound (thus, not responding to study treatment), (2) Subject 00310-2436 (DTG+F/TAF treatment in Trial 1490) who had HIV-1 RNA 73,500 copies/mL at Baseline and discontinued study drug treatment early with a viral load of 213 copies/mL at Treatment Day 11 (one day after the last dose of study drug) without experiencing virologic rebound (this subject had HIV-1 RNA <20 copies/mL [target RNA detected] at 22 days after the last dose of study drug), (3) Subject 01534-2415 (B/F/TAF treatment in Trial 1490) who achieved virologic suppression with HIV-1 RNA <20 copies/mL (target RNA detected) but experienced virologic rebound with a viral load of 1,690 copies/mL at Week 48; (4) Subject 02856-4632 (ATV/r+FTC/TDF treatment in Trial 1878) who experienced virologic rebound with HIV-1 RNA 16,800 copies/mL at 2 days after the last dose of study drug, and (5) Subject 05126-4753 (DRV/r+FTC/TDF treatment in Trial 1878) who had a last evaluable on-treatment viral load of 307 copies/mL at Week 48 but had HIV-1 RNA <20 copies/mL (target RNA not detected) at 6 days after the last dose of study drug.

Table 51: Summary Table of Week-48 Resistance Analysis (FDA analysis)

	Number of Subjects			
	Trial 1489		Trial 1490	
	B/F/TAF	ABC/DTG/3TC	B/F/TAF	DTG+F/TAF
RAP (% of primary efficacy analysis population[a])	2 (0.6%)	4 (1.3%)	8 (2.5%)	6 (1.8%)
IN genotypic data	1	2	7	3
Treatment-emergent substitutions	1	1	4	3
Any INSTI-R substitutions	0	1	3	0
Primary INSTI-R substitutions	**0**	**0**	**0**	**0**
RT genotypic data	1	3	7	5
Treatment-emergent substitutions	1	2	3	2
Any NRTI-R substitutions	0	0	0	0
Primary NRTI-R substitutions	**0**	**0**	**0**	**0**

	Number of Subjects			
	Trial 1844		Trial 1878	
	B/F/TAF	ABC/DTG/3TC	B/F/TAF	SBR
RAP (% of primary efficacy analysis population[a])	3 (0.8%)	2 (0.7%)	2 (0.7%)	7 (2.5%)
IN genotypic data	0	2[b]	1	-
Treatment-emergent substitutions	-	1[b]	0	-
Any INSTI-R substitutions	-	1[b]	0	-
Primary INSTI-R substitutions	**-**	**0**	**0**	**-**
RT genotypic data	1	2[b]	1	5
Treatment-emergent substitutions	1	1	1	2
Any NRTI-R substitutions	0	0	0	1
Primary NRTI-R substitutions	**0**	**0**	**0**	**1**
PR genotypic data	-	-	-	5
Treatment-emergent substitutions	-	-	-	1
Any PI-R substitutions	-	-	-	0
Primary PI-R substitutions	**-**	**-**	**-**	**0**

RAP, resistance analysis population; -, not applicable
Source: Reviewer's analysis, based on analysis datasets adeff.xpt and advr.xpt, and on the information in Table 52.
a. Primary efficacy analysis population includes all subjects who were randomized and had received at least one dose of study medication. This subject population was used for primary efficacy analysis.
b. Including one subject (Subject 02191-3182) who had genotypic resistance data only from a virologic failure isolate (collected one day after the last dose). Any detectable substitutions that are associated with drug resistance (Table 49 and Reviewer's comment in Section 8.2.1) were considered as treatment-emergent.

In the pooled resistance analysis (FDA analysis), treatment-emergent IN substitutions were observed in virologic failure isolates from 10 (62.5%) of the 16 subjects with evaluable IN genotypic data who were treated with B/F/TAF (55.6% [5/9]) or DTG-containing regimens (71.4% [5/7]; Table 51). IN substitutions I72T (one subject), A91T (n=1), T112I (n=2), I122T (n=1), K188R (n=1), and I201V (n=1) emerged in those from B/F/TAF subjects, and L/I63M (one subject), L68R (n=1), T112I (n=2), F181L (n=1), E212D (n=1), and D253E (n=1) emerged in those from DTG subjects (Table 52). Emergence of T112I occurred in 2 B/F/TAF subjects and in 2 DTG subjects, while the remaining substitutions occurred once. Among the emerging substitutions, I72T and T112I were previously reported as secondary substitutions associated with INSTI resistance without directly reducing drug susceptibility. I72T is a non-polymorphic substitution

observed in EVG-treated subjects (Virology review I072177.119&125 for IND 72177 SDN 125), while T112I is a polymorphic substitution observed in DTG-treated subjects (FDA Virology review for TIVICAY [NDA 204790] by Lisa K. Naeger, Ph.D.). All isolates with evaluable IN genotypic data (including those with emerging IN substitutions I72T and T112I) remained sensitive to BIC or to FDA-approved INSTIs with fold-change susceptibility being below the biological or clinical cutoffs for BIC (≤1-fold change), DTG (≤1.1-fold change), EVG (≤2-fold change), and RAL (≤1-fold change). Thus, genotypic resistance pathways for BIC may involve I72T and T112I substitutions that could serve as secondary substitutions, as observed with other INSTIs, without directly conferring reduced susceptibility to BIC. No significant impact of these 2 substitutions was observed on virological response to B/F/TAF therapy or to DTG-based therapy. In the 2 ART-naïve trials of B/F/TAF (1489 and 1490), HIV-1 variants with a threonine residue at IN amino acid position 72 (T72) were detectable in 0.5% (6/1,192) of baseline isolates with evaluable data in the virology-censored subject population (2 B/F/TAF and 4 DTG subjects), and all 6 subjects achieved virologic response with HIV-1 RNA <50 copies/mL at Week 48. T112I-expressing HIV-1 variants were found in 9.7% (116/1,192) of baseline isolates with evaluable data (53 B/F/TAF and 53 DTG subjects), and virologic response with HIV-1 RNA <50 copies/mL at Week 48 was achieved by 97.4% (113/116) of those having T112I baseline variants.

In summary, during the first year of B/F/TAF treatment, no subjects developed treatment-emergent phenotypic resistance to BIC, and no subjects developed known primary substitutions associated with resistance to DTG, EVG, and RAL. In addition, no specific amino acid substitutions in the HIV-1 IN protein emerged commonly in the B/F/TAF-treatment virologic failure isolates to establish an association with primary genotypic BIC resistance. Of note, IN substitutions, M50I, T66I, S153F, and R263K, detected in virus pools emerged during the cell-based BIC-resistance selection experiments (see Section 8.1.3) were previously identified as primary or secondary INSTI-resistance substitutions (Table 49). Emergence of these substitutions was not observed in B/F/TAF-failure isolates in the 4 trials (Table 51 and Table 52). M50I, a known secondary INSTI-resistance substitution, is a polymorphic substitution (detectable in 21.4% [231/1078] of baseline isolates with evaluable data in the 2 ART-naïve trials), and all subjects (n=124) with baseline M50I-containing virus achieved a viral load of <50 copies/mL at Week 48 (or early discontinuation) while on B/F/TAF and 99.1% (106/107) on the DTG-containing regimens. A HIV-1 variant with a M50I IN substitution introduced by site-directed mutagenesis showed a 1.3-fold reduction in BIC susceptibility, compared to wild-type virus (see Section 8.1.3). The remaining cell-selected BIC-resistance substitutions T66I, S153F, and R263K were undetectable in those evaluated baseline isolates.

All subjects in the 4 Phase 3 trials received one of the following 2 NRTIs, ABC/3TC, F/TAF, or FTC/TDF. Treatment-emergent RT substitutions were detectable in virologic failure isolates from 13 (52%) of the 25 subjects with evaluable RT genotypic data (Table 51), and RT substitutions associated with NRTI resistance (listed in Table 49) emerged in only one subject's failure isolate. As summarized in Table 52, emergence of L74V that is known to primarily associate with ABC and ddI resistance (Wensing et al., 2017) and also reduces susceptibility to

TFV was observed in a virologic rebound sample from Subject 00554-4695 in the stay on baseline regimen group of Trial 1878 (Table 52). The subject was eligible for participation in this switch trial with a screening viral load of <20 copies/mL (target RNA not detected), but had HIV-1 RNA 6,980 copies/mL at Baseline (before the study drug DVR/r+ABC/3TC was administered) and 874 copies/mL at Day 40 (Week 4; one day after the last dose of study drug). The Day-40 sample contained a mixture of wild-type and mutant viruses with emerging L74V, and remained sensitive to ABC and other FDA-approved NRTIs with fold-change susceptibility being below the biological or clinical cutoffs for 3TC, ABC, AZT, ddI, d4T, FTC, and TFV (Table 52, Footnote b). Among the failure isolates with NRTI susceptibility data (from 24/25 subjects with RT genotypic data), isolates from 2 subjects (Subjects 01236-4680 and 06748-4201 in Trial 1878) showed reduced susceptibility (above the biological or clinical cutoffs) to FTC (>94-fold), 3TC (>127-fold) and ddI (1.40- to 1.45-fold), while the remaining 22 subjects' isolates evaluated remained sensitive to all FDA-approved NRTIs. Those 2 subjects who had on-treatment HIV-1 variants with reduced susceptibility to FTC, 3TC, and ddI had been on boosted DRV+FTC/TDF and then were randomized to receive open-label FTC-containing regimens (DRV/c+FTC/TDF or B/F/TAF) in this switch trial. At pre-dose Day 1 (Baseline) both subjects had HIV-1 variants expressing M184I or M184V, both known to be primarily associated with resistance to many NRTIs including FTC (Wensing et al., 2017), which were persistently detected in samples collected during study treatment (Table 52). Thus, it was confirmed FTC-resistant virus in these 2 subjects did not emerge while on study treatment in this switch trial. Subject 01236-4680 had a baseline viral load of 99,900 copies/mL, received DRV/c+FTC/TDF to re-suppress HIV-1 RNA levels to <50 copies/mL at Week 12, but subsequently experienced a virologic rebound to >50 copies/mL at Weeks 24 and 36 (early discontinuation). Subject 06748-4201 had a rebound on B/F/TAF at Week 8 and remained viremic through Week 12 (one day after the last dose). In summary, during the first year of B/F/TAF treatment, no subjects developed treatment-emergent genotypic and phenotypic resistance to F/TAF.

Subjects in the stay on baseline regimen group of Trial 1878 remained on PI-based regimens (boosted ATV or DRV). Treatment-emergent PR substitutions were detectable in virologic failure isolates from one (20%) of the 5 subjects with evaluable PR genotypic data (Table 51), but emergence of known PR substitutions associated with PI resistance (listed in Table 49) was not observed (Table 52). All failure isolates with evaluable PR genotypic data remained sensitive to all FDA-approved PIs with fold-change susceptibility being below the biological or clinical cutoffs for AMP, ATV, DRV, IDV, LPV, NFV, RTV, SQV, and TPV (Table 52, Footnote b).

Reviewer's Comment: Results from independent FDA treatment-emergent drug resistance analyses agree with the applicant's conclusions that (1) no subjects who experienced virologic failure during the first year of B/F/TAF treatment or of DTG-based therapy developed treatment-emergent resistance to study drugs; and (2) one subject receiving DVR/r+ABC/3TC in the stay on baseline regimen group of Trial 1878 developed genotypic resistance to ABC with emergence of a primary ABC resistance L74V RT substitution.

Table 52: Individual Subjects' Resistance Data in the Resistance Analysis Population by Trial (FDA analysis)

Treatment	Subject ID	Resistance testing						
		Sample isolation	Treatment-emergent substitutions[a] in IN	Susceptibility to INSTIs[b]	Treatment-emergent substitutions[a] in RT	Susceptibility to NRTIs[b]	Treatment-emergent substitutions[a] in PR	Susceptibility To PIs[b]
Trial 1489								
B/F/TAF	00729-1609	Week 36	(**I201V**)	**sensitive**	(**D123D/E**), (**I178I/M**), (**T200T/A**), **R211R/K**	**sensitive**	-	-
		Week 48	no changes detectable	sensitive	**R211R/K**	**sensitive**	-	-
ABC/DTG/3TC	01598-1106	Week 24	no changes detectable	sensitive	no changes detectable	sensitive	-	-
ABC/DTG/3TC	02825-1085[c]	Week 48	**T112T/I**	**sensitive**	**K126K/E**	**sensitive**	-	-
ABC/DTG/3TC	02838-1390	Week 48	nd	nd	**E194E/K**, **P243H**	**sensitive**	-	-
Trial 1490								
B/F/TAF	00031-2093	Week 8	**A91A/T**, **T112T/I**, **I122I/T**	**sensitive**	no changes detectable	sensitive	-	-
B/F/TAF	01543-2111	Week 36	no changes detectable	sensitive	**K249K/R**	**sensitive**	-	-
B/F/TAF	01624-2140	Week 24	**K188K/R**	**sensitive**	no changes detectable	sensitive	-	-
B/F/TAF	01624-2534	Week 8	**T112T/I**	**sensitive**	no changes detectable	sensitive	-	-
B/F/TAF	02035-2333	Week 24	no changes detectable	sensitive	**R101R/K**	**sensitive**	-	-
B/F/TAF	02511-2326	Week 48	**I72I/T**	**sensitive**	no changes detectable	sensitive	-	-
B/F/TAF	11678-2182	Week 24	no changes detectable	sensitive	(**P243P/S**)	**sensitive**	-	-
		Week 48	no changes detectable	sensitive	**K277K/N**	**sensitive**		
DTG+F/TAF	00031-2272[c]	Week 48	nd	nd	no changes detectable	nd	-	-
DTG+F/TAF	00310-2435[c]	Week 24	**L/I63M**	**sensitive**	**D69D/A**, **R72R/G**, **S98S/A**	**sensitive**	-	-
DTG+F/TAF	00310-2556[c]	Week 36	**L68L/R**, **E212E/D**	**sensitive**	no changes detectable	sensitive	-	-
DTG+F/TAF	01942-2507	Week 12	no changes detectable	sensitive	no changes detectable	sensitive	-	-
		Week 36	**F181F/L**, **D253D/E**	**sensitive**	**I/V135I/V/A/T**, **T243T/P**, **L283L/I**	**sensitive**		
DTG+F/TAF	02106-2037	Week 8	nd	nd	no changes detectable	sensitive	-	-
Trial 1844								
B/F/TAF	01808-3475[c]	Week 4	nd	nd	**G45E**	**sensitive**	-	-
		Week 8	nd	nd	**G45E**	**sensitive**		
ABC/DTG/3TC	02191-3182	Week 8	**I112**[d]	**sensitive**	None[d]	sensitive	-	-

ABC/DTG/3TC	02728-3121[c]	Week 12	no changes detectable	sensitive	**M178M/I**	**sensitive**	-	-
Trial 1878								
B/F/TAF	06748-4201	Week 12	no changes detectable	sensitive	**R211R/G**, M/V184V	**FTC-R**, **3TC-R, partial ddI-R**	-	-
DRV/c+FTC/TDF	00433-4598[c]	Week 8	-	-	no changes detectable	sensitive	no changes detectable	sensitive
DRV/r+ABC/3TC	00554-4695	Week 4	-	-	**K11K/T**, **L74L/V**, **A272A/P**	**sensitive**	no changes detectable	sensitive
ATV/r+FTC/TDF	00608-4660	Week 36	-	-	**E138E/K**	**sensitive**	no changes detectable	sensitive
		Week 48			**V8V/A**, **E138E/K**	**sensitive**	no changes detectable	sensitive
DRV/c+FTC/TDF	01236-4680	Week 8	-	-	no changes detectable, I184I	**FTC-R**, **3TC-R, partial ddI-R**	no changes detectable	sensitive
DRV/c+FTC/TDF	02825-4606[c]	Week 12	-	-	no changes detectable	sensitive	**N37D**	**sensitive**

nd, not determined; -, not applicable; -R, resistance; /c, COBI-boosted; /r, RTV-boosted
Source: Reviewer's analysis, based on analysis datasets adeff.xpt and advr.xpt
Note 1: Amino acid substitutions in parenthesis indicate that the substitution was found in samples isolated at earlier on-treatment time points but became undetectable at later time points, possibly due to the outgrowth of or reversion to wild-type virus.
Note 2: Amino acid substitutions underlined indicate that the substitution is associated with drug resistance (listed in Table 49), and was present at Baseline and persistently detectable in on-treatment samples.

a. Amino acid substitutions emerged during study drug treatment in paired genotypic analyses of the baseline and on-treatment isolates (virus samples collected one day after the last dose were considered as on-treatment samples). Any substitutions that are associated with drug resistance listed in Table 49 and Reviewer's comment in Section 8.2.1 are written in red.
b. Drug susceptibility of the subject virus to each ARV was assessed by comparing the fold-change value of the subject virus (calculated by dividing the EC_{50} value of the subject virus by that of a reference infectious molecular clone HIV-1_{NL4-3}) to the clinical or biological cutoff for the tested ARV (cutoff values listed in the Monogram Bioscience PhenoSense® GT and PhenoSense® Integrase assays were used). In this Table, Drug-R (e.g., FTC-R; written in blue) means the fold-change value was above the cut-off for the tested drug; partial Drug-R (written in blue) means the fold-change value fell between the lower and upper cutoffs for the tested drug. When the fold-change value was below the cut-offs for all tested ARVs within the same class, the subject virus was denoted by sensitive. Tested ARVs are BIC, DTG, EVG, and RAL in the INSTI class; 3TC, ABC, AZT, ddI, d4T, FTC, and TFV in the NRTI class; and AMP, ATV, DRV, IDV, LPV, NFV, RTV, SQV, and TPV in the PI class.
c. The subject had HIV-1 RNA <50 copies/mL at Week 48 (based on the last value evaluable during the Week-48 evaluation window [Study Days between 295 and 378, inclusive]). Samples for resistance testing were collected at the time of confirmed but transient virologic rebound.
d. Genotypic resistance data were obtained only from a virologic failure isolate (collected one day after the last dose). Any detectable substitutions associated with drug resistance (Table 49 and Reviewer's comment in Section 8.2.1) were written in red; none means no resistance substitutions were detectable.

Impact of Pre-Existing Substitutions Associated with Drug Resistance on Treatment Response

Baseline genotypic data of the IN domain of the HIV-1 *pol* gene were obtained from 1267 of 1274 subjects in 2 ART-naïve trials 1489 and 1490 (628/629 and 639/645 subjects, respectively) by next-generation sequencing. Any amino acid variations at each amino acid position were reported if they were present in 15% of the total population. Pretreatment primary INSTI resistance-associated substitutions (listed in Table 49 and Reviewer's comment in Section 8.2.1) were present in 1.3% (n=17) of subjects (Table 53), and the T97A substitution that has been known to be associated with emergent INSTI resistance in patients experiencing virologic failure on EVG or RAL (review article by Abram et al., 2017) was the most frequently detected (15 [88.2%] of the 17 subjects having baseline HIV-1 variants with primary INSTI-resistance substitutions). Recently, in a cross-study pooled analysis involving INSTI-naïve patients who were enrolled in clinical studies on an INSTI-based regimen, Abram et al. (2017) observed pretreatment detection of T97A did not increase the risk of virologic failure on EVG or RAL-based therapies. In addition, in a cell-culture phenotypic study using the site-directed mutagenesis, the T97A substitution alone had no appreciable impact on virus susceptibility to BIC and DTG (both yielding a 0.6-fold shift in the EC_{50} value compared to that of wild-type control), whereas it conferred 3.8- and 1.6-fold reduced susceptibility to EVG and RAL, respectively (see Section 8.1.4). In agreement with these previous findings, all 15 subjects having T97A-containing baseline virus had HIV-1 RNA <50 copies/mL at Week 48 (n=14) or Week 4 (last evaluable on-treatment viral load data; n=1) on BIC- or DTG-based therapies in these ART-naïve trials (Table 53). Of the 17 subjects with baseline HIV-1 variants expressing primary INSTI-resistance substitutions, the remaining 2 subjects had baseline viruses expressing Q146R (associated primarily with EVG resistance; FDA Virology review for VITEKTA [NDA 203093]) or Q148H (associated primarily with EVG and RAL resistance; review article by Thierry et al., 2017). Both subjects received B/F/TAF in Trial 1489, and achieved HIV-1 RNA <20 copies/mL (target RNA detected) at Week 4 and remained <20 HIV-1 copies/mL through Week 48 (Table 53).

In addition, among IN substitutions selected by EVG, DTG, or RAL that have not been shown to directly reduce susceptibility (considered as secondary INSTI-resistance substitutions; listed in Table 49 and Reviewer's comment in Section 8.2.1), the following secondary substitutions were present in 837 (66.1%) of 1267 subjects with evaluable genotypic data in Trials 1489 and 1490: M50I, L74I, T112I, S119P/R/T, V151I, E157Q, K160N, G163E, and G193E/R polymorphic substitutions (present in 1.5% to 21.6% of baseline isolates from ART-naïve subjects with subtype B HIV-1 infection in Trials 1489+1490), and H51Y, L68I/V, G70R, I72T, I73V, L74M, Q95K, T112M/S, A128T, E138A/K, G140S, S153A, E157K, G163Q/S/R/K, S230R, and D232N non-polymorphic substitutions (present in <1.0% of evaluated baseline isolates).

Based on the Week-48 or last evaluable on-treatment viral load data, subjects with baseline HIV-1 expressing INSTI-resistance substitutions (primary and/or secondary) showed no significant differences in the rate of virologic success with HIV-1 RNA <50 copies/mL, compared to those with baseline HIV-1 with no detectable INSTI-resistance substitutions: in Trial 1489,

99.5% (204/205) versus 98.2% (107/109) for B/F/TAF subjects and 97.2% (208/214) versus 96.0% (95/99) for ABC/DTG/3TC subjects, and in Trial 1490, 97.2% (209/215) versus 97.9% (93/95) for B/F/TAF subjects and 99.5% (202/203) versus 98.3% (117/119) for DTG+F/TAF subjects. Thus, observed pre-existing INSTI-resistance substitutions appeared to have no impact on virologic response to study therapies in these 2 ART-naïve trials.

Genotyping of the RT domains of the HIV-1 *pol* gene was conducted at Screening by population-based nucleotide sequencing to assess for pre-existing genotypic resistance to NRTI components of 3-drug study regimens in Trials 1489 and 1490 as part of the enrollment criteria for all subjects in the primary efficacy analysis population. As summarized in Table 53, all but 2 subjects demonstrated no genotypic resistance specific to 3TC, ABC, FTC, and TFV (listed in Table 49); 2 subjects (Subjects 00959-2594 and 01016-1548) had RT substitutions (L74V and Y115F, respectively) associated with ABC resistance (Wensing et al., 2017). Subject 00959-2594 who had screening HIV-1 expressing L74V with one TAM K219N received B/F/TAF in Trial 1490 and achieved sustained virologic suppression from Week 12 through Week 36 (last evaluable on-treatment data). Subject 01016-1548 who had screening HIV-1 expressing Y115F with no detectable substitutions associated with multi-NRTI resistance including TAMs (Wensing et al., 2017) received ABC/DTG/3TC in Trial 1489 and achieved sustained virologic suppression with HIV-1 RNA <20 copies/mL from Week 4 through Week 48. Pre-treatment HIV-1 variants expressing one or 2 TAMs were detected in 25 subjects (16 B/F/TAF and 9 DTG-containing regimens; Table 53), and all had HIV-1 RNA <50 copies/mL at Week 48 (or at the last study visit prior to Week 48 with evaluable on-treatment viral load data); observed TAMs are M41L (n=7), D67N (n=4), K70R (n=3), L210W (n=1), and K219E/N/Q/R (n=12). In summary, 26 subjects had pre-treatment HIV-1 variants expressing RT substitutions primarily associated with NRTI resistance (2.5% [16/634] of B/F/TAF-treated subject and 1.6% [10/640] of those treated with DTG-containing regimens), and those pre-existing NRTI-resistance RT substitutions appeared to have no impact on virologic response, based on the Week-48 or last evaluable on-treatment viral load data, to study therapies in these 2 ART-naïve trials.

Table 53: Virologic Outcome of Subjects with Pre-Treatment Drug-Resistant HIV-1 Variants (FDA analysis)

	Trial 1489		Trial 1490	
	B/F/TAF	ABC/DTG/3TC	B/F/TAF	DTG+F/TAF
Number of subjects (% of primary efficacy analysis population[a])				
Any INSTI-R substitutions[b]	205 (65.3%)	214 (68.2%)	219 (69.1%)	203 (63.0%)
Primary INSTI-R substitutions[b]	4 (1.3%)	4 (1.3%)	3 (0.9%)	6 (1.9%)
Secondary INSTI-R substitutions[b]	205 (65.3%)	212 (67.5%)	219 (69.1%)	201 (62.4%)
Primary NRTI-R substitutions[b]	6 (1.9%)	5 (1.6%)	10 (3.1%)	5 (1.5%)
ABC-R substitutions[b]	0 (0%)	1 (0.3%)	1 (0.3%)	0 (0%)
TAMs[b]	6 (1.9%)	4 (1.3%)	10 (3.1%)	5 (1.5%)
Virologic response with HIV-1 RNA <50 copies/mL[c]				
Any INSTI-R substitutions[b]	99.5% (204/205)	97.2% (208/214)	97.2% (209/215)	99.5% (202/203)
Primary INSTI-R substitutions[b]	100% (4/4)	100% (4/4)	100% (3/3)	100% (6/6)
Primary NRTI-R substitutions[b]	100% (6/6)	100% (5/5)	100% (10/10)	100% (5/5)

Source: Reviewer's analysis, based on analysis datasets adeff.xpt and advr.xpt

a. Primary efficacy analysis population includes all subjects who were randomized and had received at least one dose of study medication. This subject population was used for primary efficacy analysis.
b. Known IN and RT substitutions associated with resistance to FDA approved INSTIs and NRTIs, respectively, are listed in Table 49 and Reviewer's comment in Section 8.2.1.
c. Virologic response with HIV-1 RNA <50 copies/mL to each study therapy was determined based on the Week-48 or last evaluable on-treatment viral load data using the primary efficacy analysis population.

8.2.4 Independent Analysis of NGS Data Obtained at Baseline for Trials 1489 and 1490

The sponsor performed next generation sequencing analyses using the deepType HIV assay by Seq-IT (Kaiserslautern, Germany), which utilized the Illumina MiSeq platform, to determine the baseline genotypes of the IN, PR, and RT (determine retrospectively) genes derived from the plasma viral RNA of HIV-1-infected subjects in clinical trials GS-US-380-1489 and GS-US-380-1490. The sponsor used a ≥15% frequency cutoff to define substitutions. Baseline IN, PR, and RT sequences were analyzed for the presence of previously identified resistance-associated substitutions to study drugs consisting of TAF, FTC, ABC, 3TC, BIC, and DTG depending on the study design.

Detection of resistance substitutions to TAF, FTC, 3TC, or ABC excluded subjects from enrollment. HIV-1 genotyping of the PR/RT genes was conducted at screening using the GenoSure® MG assay (Monogram Biosciences) to assess for preexisting resistance as part of the enrollment criteria for all 1274 subjects in the FAS from Studies GS-US-380-1489 and GS-US-380-1490. No IN genotyping was conducted at screening in the study, but baseline IN genotypic data was obtained retrospectively for 1267 of 1274 subjects. The baseline IN genotyping for 7 subjects was missing or failed primarily due to low viral load.

The sponsor reported that overall, the prevalence of baseline resistance-associated substitutions (RAS) was similar across all three treatment groups. These are the overall baseline results reported by the sponsor:

- Pretreatment primary INSTI resistance substitutions were infrequent and were present in 1.3% (16 of 1267) of subjects with IN data and consisted of T97A in 15 subjects and Q148H in 1 subject.
- Pretreatment primary NNRTI-associated resistance substitutions were observed in 13.2% (168 of 1274) of subjects with the most frequent substitutions consisting of K103N/S (n = 89) or E138A/G/K/Q (n = 53).
- Pretreatment primary NRTI-associated resistance substitutions were observed in 2.0% (26 of 1274) of subjects and consisted of M41L (n = 7), D67N (n = 4), K70R (n = 3), L74V (n = 1), Y115F (n = 1), L210W (n = 1), and K219E/N/Q/R (n = 12).
- Pretreatment primary PI-associated resistance substitutions were observed in 2.9% (37 of 1274) of subjects with the most frequent substitutions consisting of M46I/L (n = 14), Q58E (n = 11), or L90M (n=9).

For the independent analyses, Clinical Virology reviewer Eric Donaldson, Ph.D. used the High-performance Integrative Virtual Environment (HIVE) under maximum security provisions (Maxi-HIVE) to align all of the fastq sequences in Trials 1489 and 1490 to the appropriate IN, PR, or RT gene, using the NL3-4 HIV-1 reference genome, and to call variants and generate frequency tables (see Section 15.4 Clinical Virology NGS Data Analysis Appendix). For the independent analysis, Clinical Virology used the SUBS10 criteria, which used a ≥10% frequency cutoff to define substitutions.

Overall, there was general agreement between the results reported by the sponsor and those determined by Clinical Virology but there were several substitutions that were reported by one and not the other analyses. The variation that was observed was not completely explained by the differences in frequencies used to call substitutions.

A comparison of baseline resistance-associated substitutions identified by each method for subjects in the Clinical Virology resistance analysis population (see Table 52) was performed to see if the incongruence in the variant calls at baseline could determine potential baseline resistance-associated substitutions against B/F/TAF. The results of this comparison indicated that there were no major known resistance-associated substitutions missed by either method and that the resulting differences were not likely to impact overall resistance conclusions (Table 54).

Table 54: Comparison of NGS data results for the resistance analysis population from clinical trials 1489 and 1490 (FDA analysis).

Trial	Subject ID	Treatment	INSTI		NNRTI		NRTI		PI		Compare
			GS	HIVE	GS	HIVE	GS	HIVE	GS	HIVE	
1489	00729-1609	B/F/TAF									AGREE
	01598-1106	ABC/DTG/3TC	S119P	S119P							AGREE
	02825-1085	ABC/DTG/3TC	S119T	S119T							AGREE
	02838-1390	ABC/DTG/3TC									AGREE
1490	00031-2093	B/F/TAF									AGREE
	01543-2111	B/F/TAF	S119P	S119P	V179D	N/D					V179D not detected by HIVE
	01624-2140	B/F/TAF									AGREE
	01624-2534	B/F/TAF	N/D	S119P (99%)							S119P not detected by GS
	02035-2333	B/F/TAF	N/D N/D	S119P (100%) E157K (51%)							S119P and E157K not detected by GS
	02511-2326	B/F/TAF	V72T/I S119P	V72T/I S119P							AGREE
	11678-2182	B/F/TAF									AGREE
	00031-2272	DTG+F/TAF	M50I	M50I	K103N	K103N	N/D	T69S (100%)			T69S not detected by GS
	00310-2435	DTG+F/TAF	M50I E157K	M50I E157K			T69D	T69D			AGREE
	00310-2556	DTG+F/TAF									AGREE
	01942-2507	DTG+F/TAF									AGREE
	02106-2037	DTG+F/TAF									AGREE

GS, analyses results from Seq-IT reported by the sponsor; HIVE, analyses results reported by Clinical Virology; Blue, subjects treated with B/F/TAF; N/D, not detected; %, frequency by which a substitution was detected with HIVE.

8.3 Conclusions and Recommendations

Approval of this original NDA for BIKTARVY tablet is recommended with respect to Clinical Virology, based on Week-48 data from 2 Phase 3 trials in ART-naïve adult subjects and 2 Phase 3 trials in virologically suppressed adult subjects. The proposed indication for the BIKTARVY tablet is for once daily use as a complete regimen for the treatment of HIV-1 infection in adult patients, aged 18 years and older, who have no ARV treatment history or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY. BIKTARVY tablet is a fixed-dose combination (FDC) product containing 3 active ARVs, an HIV-1 integrase strand transfer inhibitor (INSTI) bictegravir (BIC, 50 mg; a new chemical entity), and 2 FDA-approved ARVs of the HIV-1 nucleos(t)ide reverse transcriptase inhibitor (NRTI) class emtricitabine (FTC, 200 mg; EMTRIV®) and tenofovir alafenamide (TAF, 25 mg).

BIC inhibits the strand transfer activity of HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication, with a mean IC_{50} value of 7.5±0.3 nM. Inhibition of integrase prevents the integration of linear HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the virus. In MT-4 lymphoblastoid T-cell lines acutely infected with HIV-1_{IIIB}, BIC displayed antiviral activity with a mean EC_{50} value of 2.4±0.4 nM and a selectivity index of 1,541; a protein binding-adjusted EC_{95} value was estimated to be 361 nM. In PHA/IL-2-activated primary $CD4^+$ T lymphocytes infected with HIV-1_{BaL}, BIC exhibited an antiviral potency, comparable to that determined in T-cell lines, with a mean EC_{50} value of 1.5±0.3 nM and a selectivity index of approximately 8,700. The cytotoxicity of BIC was low with a mean CC_{50} value of 8.4±1.9 µM in total PBMCs in the resting state, which did not significantly change upon the mitogenic activation with PHA/IL-2 (mean CC_{50} values of 5.7±2.2 µM). When evaluated against clinical isolates in activated PBMCs, BIC displayed similar antiviral activity across all tested 18 clinical isolates (14 group M isolates covering subtypes A-G, 3 group O isolates, and one group N isolate) with median and mean EC_{50} values of 0.55 and 0.60, respectively, and a range of EC_{50} values between <0.05 and 1.71 nM. Four subtype B isolates included in this assay were susceptible to BIC with EC_{50} values of 0.35-0.88 nM. In addition, BIC showed similar potency against one clinical isolate of HIV-2 tested with an EC_{50} value of 1.11 nM. No antagonistic anti-HIV activity was observed in pair-wise combinations of BIC with different-class ARVs DRV (PI), FTC (NRTI), or TAF (NRTI) in MT-2 cells acutely infected with HIV-1_{IIIB}.

Cell-culture emergence of resistance to BIC appeared to involve at least 2 distinct pathways: R263K/M50I and S153F with a transient T66I. BIC appeared to have a higher barrier to resistance emergence than EVG and RAL but similar to DTG, based on the duration until a virus breakthrough that can grow in the presence of BIC was observed in HIV-1-infected cells. In the recombinant site-directed HIV-1 mutant variants, R263K+M50I double substitutions conferred low-level resistance to BIC (2.9-fold reduction in BIC susceptibility, compared to the wild-type virus), while M50I, T66I, S153F, or R263K single and T66I/S153F double substitutions resulted

in, respectively, 1.3-, 0.4-, 1.9-, 2.2-, and 0.5-fold increases in the EC_{50} value of BIC. BIC displayed a cell culture cross-resistance profile significantly improved compared to EVG and RAL but comparable to that of DTG when evaluated against site-direct HIV-1 mutants and clinical isolates (polyclonal and clonal) expressing previously known IN substitutions associated with resistance to FDA-approved INSTIs, DTG, EVG, and/or RAL. The observed fold-reductions in BIC susceptibility of clinical isolates expressing one or 2 primary INSTI-resistance substitutions other than Q148H/K/R remained below the biological cutoff of <2.5-fold for BIC, while those expressing the Q148H/K/R substitutions showed mixed phenotypic susceptibility to BIC depending on the number of INSTI-resistance secondary substitutions. The majority (64.3%) of Q148H/R variants harboring one additional secondary INSTI-resistance substitution, E138A/K or G140A/S, still showed <2.5-fold reductions in BIC susceptibility, whereas the majority (77.8%) of Q148H/K/R variants with 2 additional secondary INSTI-resistance substitutions (G140A/C/S plus L74M, E138A/K, or G163K) had >2.5-fold reduced susceptibility to BIC (up to 19-fold). In a biochemical assay using purified recombinant HIV-1 integrase, BIC was shown to form a stable complex with the HIV-1 IN bound to HIV-1 long terminal repeat DNA, and dissociated more slowly from the complex (dissociation half-life of 38±19 hours) than DTG (16±9 hours), EVG (1.5±0.2 hours), and RAL (5.2±0.6 hours). Furthermore, BIC dissociated more slowly than DTG from the Q148H+G140 IN-DNA complex: the dissociation half-life of 2.5±0.07 for BIC versus 0.65±0.2 for DTG.

In virology-censored analysis, the Week-48 antiviral efficacy of B/F/TAF (percentage of subjects with HIV-1 RNA <50 copies/mL at Week-48) was comparable to that of the respective comparator group in all 4 pivotal Phase 3 trials. The observed differences (-1.4% to 2.3%) in the rate of Week-48 virologic response between the 2 treatment groups (B/F/TAF - its respective comparator) in each trial were not statistically significant with p values of >0.05 (based on Fisher's exact test). Overall, B/F/TAF was shown to have potent antiviral efficacy, comparable to ABC/DTG/3TC in Trial 1489 and to DTG+F/TAF in Trial 1490, in ART-naïve subjects. Furthermore, with high rates of maintained virologic suppression in virologically suppressed subjects, switching to B/F/TAF was noninferior to remaining on a DTG+ABC/LAM regimen (as the ABC/DTG/3TC FDC) in Trial 1844 and to remaining on an ATV- or DRV-based regimen in Trial 1878. In ART-naïve subjects, the majority achieved early virologic response; 78.8% and 75.8% of subjects in the B/F/TAF and ABC/DTG/3TC groups in Trial 1489, and 74.6% and 78.4% of those in the B/F/TAF and DTG+F/TAF groups in Trial 1490 had HIV-1 RNA <50 copies/mL at Week 4, respectively. Furthermore, all 3 study regimens demonstrated durable antiviral activity over 48 weeks of treatment with 97.7% to 99.6% of early virologic responders maintaining HIV-1 RNA levels of <50 copies/mL at Week 48.

During the first year of B/F/TAF treatment in 4 pivotal Phase 3 trials, no subjects developed treatment-emergent phenotypic resistance to BIC, and no subjects developed known primary substitutions associated with resistance to DTG, EVG, and RAL. In addition, no specific amino acid substitutions in the HIV-1 IN protein emerged commonly in the B/F/TAF-treatment virologic failure isolates to establish an association with primary genotypic BIC resistance. Emergence of IN substitutions, M50I, T66I, S153F, and R263K, detected in virus pools emerged

during the cell-based BIC-resistance selection experiments, was not observed in B/F/TAF-failure isolates from the 4 trials. In addition, during the first year of B/F/TAF treatment, no subjects developed treatment-emergent genotypic and phenotypic resistance to F/TAF.

9 Review of Safety

9.1 Safety Review Approach

Two pivotal Phase 3 trials in HIV-1 infected treatment naïve subjects, Trials 1489 and 1490, were analyzed both individually and pooled for the B/F/TAF arms for the safety analyses. Pooling of the trials for the B/F/TAF arms is appropriate because the trial designs were similar with generally similar inclusion and exclusion criteria, except for differences in baseline sensitivity to abacavir and exclusion of subjects with chronic hepatitis B. The two pivotal Phase 3 trials in HIV-1 infected virologically suppressed subjects, Trials 1844 and 1878, were analyzed individually because the trial designs were different, one was double-blinded while the other was open label, which could affect adverse events reporting, and the comparator regimens were in different antiviral classes. In addition to a complete independent analysis of safety for the Phase 3 trials, selected safety analyses from the Phase 2 Trial 1475 (see Table 24), are included in this review when applicable.

Clinical trial data were independently analyzed in JMP, JMP Clinical, MAED, and JReview. Any differences in findings by the FDA reviewer compared to the Applicant were relatively minor and attributable to variable methods of pooling and subgroup analyses. All the safety assessments and conclusions are those of the FDA reviewer unless otherwise specified.

A thorough hepatic safety review was conducted, as liver safety concerns are a key safety issue in review of antiretroviral medications. A review of skin AEs related to study drug and psychiatric AEs related to study drug were performed because these are safety events that have been identified with use of other integrase inhibitors and antiretroviral drugs.

Analyses of renal and bone events were performed, as these safety issues have been of concern for HIV infected patients, and in particular for those on tenofovir (TFV) containing products. It is theorized that renal tubular injury and bone mineral density (BMD) abnormalities associated with use of tenofovir disoproxil fumarate (TDF) are related to serum concentrations of tenofovir (TFV). TAF has been demonstrated to have better tissue penetration into target cells than TDF, which allows for a 90% lower dosage. Lowered TFV serum concentrations may therefore lower the incidence of renal and bone adverse events.

The Applicant submitted a Safety Update Report (SUR) two months after the original NDA submission. Deaths, SAEs, and discontinuations due to AEs reported in the SUR are included in

the relevant safety sections.

9.2 Review of the Safety Database

9.2.1 Overall Exposure

A total of 1511 subjects have received at least 1 dose of B/F/TAF in the Phase 2 and 3 trials (see Table 55). This includes 1206 subjects in the randomized phases of the Phase 3 trials and 65 subjects in the Phase 2 trials. Two hundred and forty subjects have received B/F/TAF as part of an open-label extension in the Phase 2 and 3 trials.

Table 55: Safety Population for B/F/TAF NDA

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication of HIV antiretroviral naïve and virologically suppressed adult subjects N=1511 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	**New Drug (n=1511)**	**Active Control (n=1241)**	**Placebo (n=0)**
Phase 2 or 3 Controlled trials conducted for this indication[2]	1271	1241	N/A
All other than controlled trials conducted for this indication[3]	240	N/A	N/A
Controlled trials conducted for other indications[4]	0	N/A	N/A

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

9.2.2 Relevant characteristics of the safety population:

The studied populations adequately reflect the types of patients that will be exposed to B/F/TAF post-marketing. Per treatment guidelines, INSTI and NRTI containing regimens are preferred treatment regimens for HIV treatment naïve subjects. Virologically suppressed subjects may want to simplify their regimen with desired characteristics of a complete ART

regimen in a FDC, particularly one without a pharmacokinetic booster that can increase the potential for drug-drug interactions.

Please refer to Table 114, Table 115, Table 116, and Table 117 describing the demographics of the subjects enrolled in the four Phase 3 clinical trials. Efficacy outcomes by race and gender were evaluated during this NDA review. Please refer to Table 122, and Table 123 for details. Caution should be exercised when interpreting the results, as the trials were not powered for subpopulation-specific analysis. Of note, 90% of the Phase 2 and 3 trials consisted of men. Similar to findings in many HIV development programs, recruitment of female subjects into the Phase 3 clinical trials can be challenging. The applicant is performing a dedicated women's trial that is anticipated to enroll at least 200 more women to B/F/TAF.

9.2.3 Adequacy of the safety database:

Overall, the safety database of over 1500 subjects is comprehensive and adequate to assess the safety of B/F/TAF for the proposed indication, dosage regimen, duration, and patient populations. Trials 1489 and 1490 provided sufficient safety data to support labeling of B/F/TAF for HIV-1 infected adult patients with no antiretroviral treatment history.

Trials 1844 and 1878 provided sufficient safety data to support labeling of B/F/TAF in HIV-1 infected adult patients who are currently on a suppressive (HIV RNA <50 copies/mL) ARV regimen for at least 3 months and have no history of virologic failure or resistance to the components of B/F/TAF.

9.3 Adequacy of Applicant's Clinical Safety Assessments

9.3.1 Issues Regarding Data Integrity and Submission Quality

There were no identified issues regarding data integrity. For Phase 3 trials, all narratives for deaths, SAEs, and treatment discontinuations were reviewed and compared to the Applicant's summary and assessment.

The quality of the submission was adequate to perform the safety review for B/F/TAF. The Jump Start service analyzed data fitness and found no major issues that would preclude performing a safety review.

9.3.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA), version 19.1 was used for AE coding. Adverse events were summarized by MedDRA System Organ Class and Preferred Term.

A serious adverse event (SAE) is any event that results in any one of the following outcomes: death; life-threatening AE; persistent or significant disability/incapacity; required in-patient

hospitalization or prolonged hospitalization; congenital anomaly or birth defect; other important medical events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

The Applicant provided guidelines for assessment of laboratory AEs. There were no identified issues with respect to recording, coding, and categorizing AEs. The Applicant categorized SAEs in accordance with standard, regulatory definitions. The applicant grouped by AEs in standard MedDRA hierarchy. AEs were graded using the Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, which is derived by Gilead Sciences from the Division of AIDS (DAIDS) toxicity grading criteria. The clinical reviewers verified the Applicant's translation of verbatim terms to preferred terms for events reported in Trials 1489, 1490, 1844, and 1878.

9.3.3 Routine Clinical Tests

Routine clinical evaluations for safety included medical history taking for assessment of symptoms of adverse events, vital sign measurements and physical examinations for assessment of signs of adverse events, laboratory evaluations, and ECGs. In phase 3 trials, key evaluations were performed at baseline, Weeks 4, 8, 12, and every 12 weeks thereafter (depending on the trial duration). Follow-up visits were scheduled for subjects who discontinued treatment prematurely due to adverse events.

9.4 Safety Results

9.4.1 Deaths

All deaths in the Phase 3 trials were reviewed both in the datasets and in the provided narratives. Seven deaths were reported in the NDA application in the four Phase 3 trials, of which four deaths occurred in the B/F/TAF arms (see Table 56). In the Safety Update Report, three additional deaths were reported, of which two deaths occurred in the B/F/TAF arms (See Table 56). None of the deaths were assessed as being related to study drug, and the clinical reviewer concurs with that assessment. No deaths were reported for Trial 1475, the Phase 2 trial, or for Trial 1489, the Phase 3 trial, in the NDA application or the Safety Update Report.

Table 56: Deaths in Trials 1490, 1844, and 1878

Subject ID	Age and Sex*	Treatment (Tx)	Cause of Death	Tx Day	Applicable comorbidities	Related (R) /Not Related (NR)
Reported in the NDA application						
1490-00031-2042	71 yo male	B/F/TAF	Cardiac Arrest	28	Appendicitis Septic Shock	NR

1844-00365-3221	71 yo male	B/F/TAF	Sudden death	96	Hypertensive and Atherosclerotic cardiovascular disease	NR
1844-01624-3360	46 yo female	B/F/TAF	Unknown	311	Spinal stenosis Alcohol abuse Suicidal Ideation D165-169	NR
1878-01236-4098	63 yo male	B/F/TAF	Complications from Lung cancer with brain metastasis	286	COPD Lung cancer with brain metastasis	NR
1878-06046-4597	54 yo male	SBR	Unknown; Information obtained that subject was murdered	106	Head injury	NR
1490-02856-2288	58 yo male	DTG + F/TAF	Unknown	174		NR
1490-03379-2511	47 yo male	DTG + F/TAF	Possible PE	266	COPD	NR
Reported in the Safety Update Report						
1490-00986-2440	57 yo male	B/F/TAF	Poorly differentiated Gastric adenocarcinoma	376		NR
1490-02843-2211	64 yo male	B/F/TAF	Hypertensive heart disease with Congestive heart failure	412	Diabetes mellitus	NR
1490-03379-2228	58 yo male	DTG + F/TAF	Unknown	422		NR

Source: ADAE and narratives for Trials 1490, 1844, and 1878
Note: COPD is chronic obstructive pulmonary disease

The following three deaths in subjects on B/F/TAF, have additional pertinent information below that clarifies the events leading to or contributing to the cause of death:

- Subject 1490-00031-2042 (SAE) was a 71-year-old (yo) male with a history of hypertension and high cholesterol who experienced abdominal pain on Day (D) 28 that worsened over 3 days. He went to the hospital and was found to have a ruptured appendix that was removed. The post-operative period was complicated by septic shock and cardiac arrest on D32. The event was considered not related to study drug.
- Subject 1844-01624-3360 was a 46 yo female with history of spinal stenosis with spinal fusion surgery, anxiety, and post-traumatic stress disorder (PTSD) (on venlafaxine and mirtazapine, both antidepressants) who had a Percocet overdose on unspecified date reported followed by a Percocet and alcohol overdose and an event of worsened spinal stenosis on D165. The subject was found by her mother deceased in bed on D311 and, therefore, was reported to have died of an unknown cause.
- Subject 1844-00365-3221 was a 71 yo male who experienced Grade 4 sudden cardiac death on D96. The event was assessed as serious and unrelated to study drug. This event occurred after a flight where he collapsed during dinner and was pronounced dead at the scene. The cause of death was hypertensive and atherosclerotic cardiovascular disease by autopsy report.

Review of the events of deaths in the clinical trials supporting B/F/TAF did not reveal any novel safety patterns and use of B/F/TAF did not appear to increase the risk of mortality.

9.4.2 Serious Adverse Events

As summarized in Table 57, in Trials 1489 and 1490, 58 (9%) subjects in the B/F/TAF arm, 25 (8%) subjects in the ABC/DTG/3TC arm, and 23 (7%) subjects in the DTG+F/TAF arm experienced SAEs. In Trial 1844, 15 (5%) subjects in the B/F/TAF arm and 22 (8%) subjects in the ABC/DTG/3TC arm experienced SAEs, respectively (see Table 58). Similarly, in Trial 1878, 19 (7%) of subjects in the B/F/TAF arm and 22 (8%) of subjects in the SBR arm experienced SAEs, respectively (see Table 57). The most frequently reported Body System or Organ Class (SOC) with SAEs was Infections and Infestations with 3-4% of subjects in any treatment arm. This is similar to other HIV development programs and is likely due to an HIV infected patient population susceptible to pathogens because of relative immunosuppression. The SAEs by SOC were generally balanced among treatment arms.

Table 57: SAEs by Body System Organ Class in Trials 1489 and 1490

Body System or Organ Class	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Infections and infestations	22 (3%)	12 (4%)	11 (3%)
Psychiatric disorders	12 (2%)	4 (1%)	3 (1%)

Metabolism and nutrition disorders	6 (1%)	2 (1%)	0
Gastrointestinal disorders	6 (1%)	4 (1%)	1 (<1%)
General disorders and administration site conditions	5 (1%)	2 (1%)	2 (1%)
Cardiac disorders	4 (1%)	2 (1%)	0
Injury, poisoning and procedural complications	3 (<1%)	5 (2%)	4 (1%)
Respiratory, thoracic and mediastinal disorders	3 (<1%)	3 (1%)	3 (1%)
Blood and lymphatic system disorders	3 (<1%)	0	0
Musculoskeletal and connective tissue disorders	3 (<1%)	1 (<1%)	1 (<1%)
Nervous system disorders	2 (<1%)	0	1 (<1%)
Renal and urinary disorders	2 (<1%)	1 (<1%)	1 (<1%)
Vascular disorders	2 (<1%)	1 (<1%)	2 (1%)
Neoplasms benign, malignant and unspecified	2 (<1%)	1 (<1%)	0
Eye disorders	1 (<1%)	1 (<1%)	1 (<1%)
Pregnancy, puerperium and perinatal conditions	1 (<1%)	0	0
Reproductive system and breast disorders	1 (<1%)	0	1 (<1%)
Investigations	0	2 (<1%)	0
Total Subjects	59 (9%)	25 (8%)	23 (7%)

Source: ISS ADAM ADAE Trials 1489 and 1490

Table 58: SAEs by Body System Organ Class in Trial 1844

Body System or Organ Class	B/F/TAF N=282	ABC/DTG/3TC N=281
Infections and infestations	4 (1%)	9 (3%)
Injury, poisoning and procedural complications	3 (1%)	1 (<1%)
Psychiatric disorders	3 (1%)	4 (1%)
Nervous system disorders	2 (1%)	0
Musculoskeletal and connective tissue disorders	2 (1%)	0
General disorders and administration site conditions	2 (1%)	1 (<1%)
Metabolism and nutrition disorders	1 (<1%)	0
Cardiac disorders	1 (<1%)	2 (1%)
Eye disorders	0	1 (<1%)
Hepatobiliary disorders	0	1 (<1%)

Renal and urinary disorders	0	2 (1%)
Gastrointestinal disorders	0	3 (1%)
Total Subjects with SAE	15 (5%)	22 (8%)

Source: ADAE Trial 1844

Table 59: SAEs by Body System Organ Class in Trial 1878

Body System or Organ Class	B/F/TAF N=290	SBR N=287
Infections and infestations	9 (3%)	6 (2%)
Nervous system disorders	2 (1%)	1 (<1%)
Psychiatric disorders	2 (1%)	2 (1%)
Cardiac disorders	2 (1%)	4 (1%)
Injury, poisoning and procedural complications	1 (<1%)	3 (1%)
Musculoskeletal and connective tissue disorders	1 (<1%)	0
Neoplasms benign, malignant and unspecified	1 (<1%)	2 (1%)
General disorders and administration site conditions	1 (<1%)	1 (<1%)
Eye disorders	1 (<1%)	0
Renal and urinary disorders	1 (<1%)	2 (1%)
Respiratory, thoracic and mediastinal disorders	1 (<1%)	0
Hepatobiliary disorders	0	1 (<1%)
Pregnancy, puerperium and perinatal conditions	0	1 (<1%)
Reproductive system and breast disorders	0	1 (<1%)
Vascular disorders	0	1 (<1%)
Gastrointestinal disorders	0	5 (2%)
Subjects(filtered)	19 (7%)	22 (8%)

Source: ADAE Trial 1878

Further analyses of SAEs were conducted by preferred term. Overall, the pattern and types of SAEs reported were similar across the treatment arms for both the treatment-naïve and virologically suppressed populations. There were no patterns or safety signals suggesting a novel safety issue related to B/F/TAF.

The following five SAEs were assessed as related to the B/F/TAF by the Investigator and are detailed as follows:

1. Subject 1489-11563-1530 is a 45 yo male with a history of seizure disorder who

experienced a Grade 3 grand mal seizure on D21 that resolved the same day. No change in study drug occurred.

2. Subject 1490-00573-2206 is a 60 yo male with history of coronary artery disease (CAD) and diabetes mellitus (DM) who had Grade 3 chest pain after D1. Drug was withdrawn and he was admitted to the hospital on D29. The subject was discharged with a diagnosis of atypical chest pain that resolved on D32.
3. Subject 1844-04140-3252 is a 51 yo male smoker who experienced a Grade 4 stroke 101 days after starting study drug and was assessed as being related to study drug by the investigator. This stroke was a right MCA stroke and the subject received TPA, ASA and Lipitor, and the event was resolved on D103. The investigator decided to unblind the subject on D107 and started an alternative therapy with Descovy and dolutegravir.
4. Subject 1490-02434-2389 is a 40 yo male without history of psychiatric illness who phoned clinic and stated on D293 that he had serious suicide attempt (Grade 4) and did not come back to clinic. Outcome was reported as ongoing. Although this subject had no history of psychiatric illness, he was reported to have fluctuating "mental health" since inclusion in the study. The SAEs of depression and suicide attempt were considered related to study mediation and led to discontinuation (details provided in the Safety Update Report).
5. Subject 1878-07880-4237 is a 24 yo male without history of psychiatric illness who was hospitalized on D233 for Grade 3 paranoid schizophrenia, and causality was related to study drug by the investigator. The subject discontinued study drug on D247 and the trial on D274 due to AE.

The first three SAEs above were temporally related to study drug initiation and observed at the frequency of only one case each. While these SAEs were considered related to B/F/TAF by the Investigator, it is difficult to associate these individual events to study drug other than to state that they occurred while on study drug. In the first three cases, the subjects had underlying risks that confound the assessment.

In the latter two cases, the fact that the events occurred later in the treatment course also confounds the causality assessment. Suicidal ideation, attempt and completion have been observed in the development programs of other INSTIs and other ARVs. This is likely partially attributable to an HIV infected patient population with relatively high baseline psychiatric co-morbidities, social stressors, and substance use which often confounds the ability to determine the causative role of the antiretrovirals.

In the Safety Update Report, in the treatment naïve trials, an additional 18 subjects had SAEs. The only SAE reported for greater than one subject was appendicitis (B/F/TAF 2 subjects and ABC/DTG/3TC 1 subject). An additional subject on B/F/TAF experienced a SAE of depression and suicide attempt considered related to B/F/TAF (Subject 1490-2434-2389) which led to discontinuation. No SAEs were reported in more than one subject in Trials 1848 or 1878. One SAE in Trial 1878 was considered related to study drug in a subject that was in the SBR group, but the event occurred after switching to the open-label extension of B/F/TAF. Fifty-five days

after starting B/F/TAF, he had a Grade 2 DVT; however, this event is confounded by the subject's comorbidities of obesity (baseline BMI 34.5 kg/m^2), tobacco use, and a medical history of thrombosis.

Overall, review of the SAEs in the Phase 3 trials did not reveal new or significant safety concerns as there were no concerning trends that have not been previously identified either in the HIV infected population or in other INSTIs. Suicidal ideation and attempt are important events that occurred and have been recommended to be added to the package insert. See Section 9.5.2 for further discussion and details.

9.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs were low across the Phase 3 trials; only 1-2% of subjects in each trial and on any treatment arm discontinued study drug due to AEs. In the treatment naïve trials, overall 10 subjects (1%) discontinued due to an AE, of which five subjects (1%) were in the B/F/TAF arms. In Trial 1844, eight subjects (1%) discontinued due to an AE, of which six subjects (2%) were in the B/F/TAF arms. In Trial 1878, overall three subjects (1%) discontinued due to an AE, of which two subjects (1%) were in the B/F/TAF arm. Discontinuations because of AEs are detailed as follows, first by AEs related to study drug and then by AEs not related to study drugs.

<u>AE considered related to study drug and leading to discontinuation:</u>

- Subject 1490-06259-2604 is a 30 yo male randomized to B/F/TAF who experienced insomnia, depression, and headache that began almost as soon as he started study drug, but worsened during his participation in the trial, and improved within a day or two of discontinuing the study drug. He stopped study drug and switched to Complera on D65.
- Subject 1490-00573-2206 is a 60 yo male with a history of CAD, hypercholesterolemia, HTN, and DM who experienced SAE of chest pain and is described in Section 9.4.2 above.
- Subject 1490-2434-2389 is a 40 yo male without history of psychiatric illness who 11 months after study initiation had SAEs of depression and suicide attempt considered related to study medication and leading to discontinuation of B/F/TAF (reported in the Safety Update Report). This subject is also described in Section 9.4.2.
- Subject 1490-04152-2515 is a 40 yo male who gradually developed abdominal distension. The fat distribution was described by the investigator as "typical HIV drug-related central lipohypertrophy." The AE of abdominal distension was considered severe and the drug was discontinued on D304.
- Subject 1844-01624-3344 is a 52 yo male who developed Grade 1 headache on D1 with subsequent malaise and fatigue and stopped study drug on D32. The event resolved on D34, two days after stopping study medication.

- Subject 1844-03027-3521 is a 51 yo male with history of insomnia and anxiety who developed Grade 1 (mild) abnormal dreams on D1. He elected to discontinue study drug on Week 48.
- Subject 1844-04140-3252 is a 51 yo male smoker who experienced a Grade 4 CVA (SAE) at D101 (see Section 9.4.2 for further details).
- Subject 1844-09416-3462 is a 52 yo male with depression, anxiety, and intermittent diarrhea. He had moderate (Grade 2) increased vomiting on D1. The subject stopped study drug on D3, after taking a single dose of study, when his amylase had also increased from Grade 1 (140 U/L). Approximately 6 weeks after stopping medication on his follow up visit he had reported occasional abdominal discomfort and epigastric pain but no further vomiting. He had Grade 2 amylase elevation (147 U/L) and Grade 3 lipase elevation (403 U/L). He went back to taking Triumeq.
- Subject 1844-3946-3305 is a 38 yo male on zolpidem for sleep (AE of sleep disorder) on B/F/TAF who developed Grade 1 headache on D14 for 10 days that resolved on D24 and then recurred on D28 (maximum toxicity Grade 2 headache on D59). The headaches led to discontinuation on D140 and the event was considered related to study drug. Headache resolved 7 days after discontinuation (D147).
- Subject 1878-01598-4501 is a 46 yo male on SBR initially, and then switched to B/F/TAF on D341. He had an AE of Grade 1 diarrhea consider related to study drug and on D345 had mild vomiting related to study drug. The subject stopped study drug on D346 due to these AEs and diarrhea was considered resolved on D349.
- Subject 1878-0059-4774 (reported in the Safety Update Report) is a 52 yo male with history of insomnia and depression who was on the SBR arm and 12 days after rolling over to B/F/TAF (Study D314) had moderate dizziness, headache, insomnia, and irritability that were considered related to study drug and led to study drug discontinuation. The AEs of dizziness, headache, insomnia, and irritability were considered resolved two days later (Study D316).

Reviewer comment: Abnormal dreams, as experienced by Subject 1844-03027-3521, and or sleep disorders were not proposed by the Applicant for inclusion in the product label. However, sleep disorders, including insomnia and abnormal dreams, have been associated with INSTIs including dolutegravir. Further discussion of sleep abnormalities is included in Section 9.4.5 Common Adverse Events and Adverse Reactions.

<u>AE considered not related to study drug and leading to discontinuation</u>

- Subject 1490-00062-2256 is a 38 yo male with no history of drug use or psychiatric illness who experienced paranoid symptoms on D302 probably due to crystal methamphetamine use. The investigator determined that this event was not related to study drug but thought it best to take subject off blinded study drug and start on a regimen of raltegravir and Truvada.
- Subject 1490-00031-2042 (SAE) is a 71 yo male with a history of HTN and high cholesterol who experienced abdominal pain that worsened over 3 days on D28 and went to the hospital and found to have a ruptured appendix that was removed. The

post-operative period was complicated by septic shock and cardiac arrest. The event was considered not related to study drug.

- Subject 1844-07881-3397 is a 29 yo male with history of depression (on quetiapine and escitalopram and mephedrone) who had Grade 4 suicidal ideation D8-18 resolved. This subject had a second episode of Grade 3 suicidal ideation on D206 which led to discontinuation of study drug on D258. Of note, detailed information of the second suicidal ideation was not provided with the original NDA application, and further information was obtained by information request (IR) response from the Applicant.
- Subject 1878-1221-4195 is a 49 yo male baseline CD4 809 who had moderate rash on both arms on D6 with pruritus not considered to be related (subject had mild influenza like illness not related on D4). "Allergist counselor" suggested it could be prurigo nodularis. Nevertheless, rash lead to drug discontinuation on D9. At D11 the rash was ongoing and his antiretroviral treatment was changed off B/F/TAF.

9.4.4 Significant Adverse Events

Evaluation of reported AEs according to CDER's list of Designated Medical Events (DME) was performed to identify subjects who experienced one of the following: acute pancreatitis, acute respiratory failure, agranulocytosis, anaphylaxis or anaphylactoid reaction, aplastic anemia, blindness, bone marrow depression, deafness, disseminated intravascular coagulation, hemolytic anemia, liver failure, liver necrosis, liver transplant, pancytopenia, renal failure, seizure, Stevens-Johnson syndrome, torsades de pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation. DMEs are events reflecting serious medical conditions that may be related to drugs.

All DMEs from the four trials were fully reviewed. There was no pattern to the reported DMEs and most cases were transient, had alternate risk factors or related medical conditions or other confounding issues. Acute kidney injury (AKI) is included as a DME. The subjects with AKI were confounded by comorbidities and are discussed as part of safety events of interest in Section 9.5.4. Subject 1844-00365-3221 had AKI and sudden cardiac death and is discussed the deaths section above.

The most frequent DMEs were neutropenia, seizure, and rhabdomyolysis. Notable DMEs reported across the Phase 3 trials in subjects who received B/F/TAF are detailed further in this section including:

- Neutropenia,
- Seizure,
- Rhabdomyolysis, and
- Anaphylaxis.

Neutropenia and Seizure- Related Causality

Two DMEs considered related to B/F/TAF in the four Phase 3 trials were neutropenia and generalized tonic clonic seizure that are detailed below. In both cases, study drug was continued.

- Subject 1489-01691-1596 is a 23 yo male with a baseline WBC of 2.62 $X10^3$ cells/ul with 50% neutrophils who developed Grade 1 neutropenia on D28-55 (two lab values) with a WBC count of 2.44$X10^3$ cells/ul with 38% neutrophils, that then rose to 4.72$X10^3$ cells/ul with 64% neutrophils on D72. This was considered related to study drug but study drug was continued. This neutropenia was transient and could be related to the study drug or another phenomenon. Interestingly, this subject had a Grade 1 hyperbilirubinemia, which is not a DME, and is described in the Hepatobiliary analysis (Section 9.4.10).
- Subject 1489-11563-1530 is a 45 yo male with a history of epileptic disorder had a SAE of Grade 3 tonic clonic seizure on D21 (see Section 9.4.2). The subject was hospitalized and study drug was continued. The subject was reportedly a poor historian and the history of prior epilepsy was obtained after the reported event; if this information was available before the event, the causality may not have been assessed as related to study drug.

In the comparator treatment arms the two DMEs of neutropenia occurred that were considered related to study drug and where the study drugs were also continued.

- Subject 1490-00986-2656 is a 43 yo male on DTG/F/TAF with transient Grade 2 neutropenia on D60-89.
- Subject 1878-00986-4655 is a 38 yo female on SBR with transient Grade 1neutropenia on D57-85.

There is no non-clinical finding or mechanistic hypothesis that links neutropenia or seizure DME events to B/F/TAF, despite the causality listed as related. Further neutropenia can be confounded by HIV or concomitant infections including upper respiratory illness. Four Neutropenia AEs occurred in the B/F/TAF arms and seven events occurred in the comparator treatment arms. The majority of the neutropenia events were Grade 1 or Grade 2. Like the neutropenia cases above, generally the neutropenia events were transient. A Grade 3 protracted neutropenia from D57-D220 considered not related to B/F/TAF treatment occurred early after initiating therapy in a HIV-1 treatment naïve subject (Subject 1489-02316-1012) with a CD4 count on D1 of 0 cells/uL.

One other seizure event occurred in the B/F/TAF arm, while the comparator arms had four other seizure events (one on ABC/DTG/3TC, one on DTG/F/TAF, and two on SBR). The etiology of seizures can be multifactorial including prior seizure disorder, CNS injury or pathology, or substance abuse, and thus, the causality to study drug is often confounded. Despite the temporal association to study drug, these cases of neutropenia and seizure were not sufficiently compelling to consider labeling for these events, particularly because the events did not lead to drug discontinuation and resolved despite continued treatment.

Rhabdomyolysis

Two subjects on B/F/TAF in Trial 1490 reported rhabdomyolysis, and one subject on ABC/DTG/3TC in Trial 1844 reported rhabdomyolysis. Subject 1490-02316-2033 on B/F/TAF had Grade 3 rhabdomyolysis due to viral illness that required hospitalization from D180-206. Study drug was interrupted, the subject was treated with IV hydration and improved, and study drug was later resumed without further problems. The other B/F/TAF subject had a transient elevation of CPK levels, considered not related to study drug, and study drug was continued despite the laboratory abnormality.

Anaphylaxis

One subject (subject 1490-00731-2251) reported an episode of anaphylaxis on D16-18. The subject was treated for syphilis with ceftriaxone on D14. The data included the reported term of 'ceftriaxone allergy' on D16 (no end date) and the preferred term of 'drug hypersensitivity' on D16. Study drug was continued. Based on review of the data, and the fact that study drug was not interrupted, this reviewer attributes the anaphylaxis to ceftriaxone used for treatment of syphilis and not B/F/TAF.

Other Selected DMEs

A subject with sudden cardiac death on B/F/TAF is described above in Section 9.4.1 Deaths. One subject in Trial 1878 had sensorineural deafness on B/F/TAF on D244 that is ongoing with B/F/TAF continued.

One subject reported pancreatitis on DTG/F/TAF. This event is interesting in that, despite high laboratory parameters, there were no clinically related signs or symptoms of pancreatitis reported. Additionally, TAF, a component of B/F/TAF, has been associated with pancreatitis in patients being treated for hepatitis B and is a labeled adverse reaction.

- Subject 1490-02191-2123 received DTG/F/TAF and had baseline Grade 3 amylase elevation of 418 U/L (normal 28-140 U/L) and Grade 4 lipase of 793 U/L (normal 1-100). On D4, the subject had Grade 1 pancreatitis, considered not related to study drug. This subject had intermittent elevations in amylase that were more frequent after initiation of study drug, with a maximum Grade 4 amylase elevation of 1519 U/L at D85 and a concomitant Grade 4 lipase elevation (4653 U/L) without related clinical AEs. He had three normal amylase values over the 48 weeks and Week 48 labs showed a Grade 3 amylase elevation of 217 U/L and a Grade 3 lipase elevation of 413 U/L, both lower than baseline.

No other subjects across the phase 3 trials had pancreatitis events.

The other DMEs not discussed above were single reports, and/or confounded, and did not generate concern for a signal that is not evaluated elsewhere in this NDA review. Overall, the review of the DMEs found most cases were transient, had alternate risk factors or related medical conditions or other confounding issues, and most did not result in permanent discontinuation of study drug.

9.4.5 Common Adverse Events and Adverse Reactions

The most common treatment-emergent AEs (≥ 5%) reported for B/F/TAF in the HIV-treatment naive Phase 3 trials were diarrhea, headache, nausea, nasopharyngitis, and fatigue (see Table 60). The most common AEs in the virologically suppressed treatment groups were generally similar to the treatment-naïve population; however, nausea was much less frequently reported in this treatment-experienced population.

Table 60: Treatment-emergent AEs Reported (≥ 5%) of Subjects in Any Treatment Group in Trials 1489 and 1490

Dictionary Derived Term	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Diarrhea	77 (12%)	41 (13%)	39 (12%)
Headache	76 (12%)	43 (14%)	40 (12%)
Nausea	57 (9%)	72 (23%)	29 (9%)
Nasopharyngitis	45 (7%)	29 (9%)	31 (10%)
Fatigue	38 (6%)	27 (9%)	26 (8%)
Upper respiratory tract infection	35 (6%)	34 (11%)	23 (7%)
Cough	31 (5%)	8 (3%)	16 (5%)
Insomnia	30 (5%)	20 (6%)	14 (4%)
Arthralgia	27 (4%)	19 (6%)	9 (3%)
Vomiting	26 (4%)	17 (5%)	10 (3%)
Back pain	25 (4%)	15 (5%)	20 (6%)
Pyrexia	24 (4%)	12 (4%)	21 (6%)
Lymphadenopathy	24 (4%)	9 (3%)	18 (6%)
Syphilis	23 (4%)	25 (8%)	12 (4%)
Oropharyngeal pain	23 (4%)	12 (4%)	4 (1%)
Depression	23 (4%)	11 (3%)	10 (3%)
Influenza	22 (3%)	6 (2%)	10 (3%)
Abdominal pain	21 (3%)	16 (5%)	6 (2%)
Dizziness	19 (3%)	14 (4%)	12 (4%)
Hypertension	19 (3%)	5 (2%)	10 (3%)
Gonorrhea	18 (3%)	9 (3%)	12 (4%)
Anogenital warts	17 (3%)	9 (3%)	5 (2%)
Constipation	17 (3%)	8 (3%)	10 (3%)
Rash	17 (3%)	15 (5%)	15 (5%)
Anxiety	16 (3%)	11 (3%)	15 (5%)
Bronchitis	15 (2%)	16 (5%)	13 (4%)

Source: ADAE Trials 1489 and 1490

Table 53 summarizes the TEAEs for Trial 1844, and Table 54 summarized the TEAEs for Trial 1878. Unlike Trial 1844 that was randomized and double- blinded, Trial 1878 was a randomized open- labeled switch study in virologically suppressed HIV-1 infected subjects. TEAEs were reported more frequently in the B/F/TAF arm compared to the SBR arm, which may have been due to the open-label design of this study (See Table 62). Regardless, overall, the most commonly reported TEAEs (headache, diarrhea, upper respiratory tract infection and nasopharyngitis) were similar to both the treatment naïve population and those observed in Trial 1844.

Table 61: Treatment-emergent AEs Reported (≥ 2%) of Subjects in Either Treatment Group for Trial 1844

Dictionary Derived Term	B/F/TAF N=282	ABC/DTG/3TC N=281
Upper respiratory tract infection	29 (10%)	27 (10%)
Diarrhea	24 (9%)	14 (5%)
Nasopharyngitis	20 (7%)	22 (8%)
Headache	19 (7%)	21 (7%)
Arthralgia	19 (7%)	10 (4%)
Sinusitis	11 (4%)	11 (4%)
Insomnia	8 (3%)	14 (5%)
Fatigue	8 (3%)	13 (5%)

Source: ADAE 1844

Table 62: Treatment-emergent AEs Reported (≥ 2%) of Subjects in Either Treatment Group for Trial 1878

Dictionary Derived Term	B/F/TAF N=290	SBR N=287
Headache	35 (12%)	13 (5%)
Diarrhea	25 (9%)	19 (7%)
Upper respiratory tract infection	21 (7%)	24 (8%)
Nasopharyngitis	21 (7%)	34(12%)
Back pain	14 (5%)	17 (6%)
Cough	14 (5%)	8 (3%)
Constipation	13 (4%)	9 (3%)
Arthralgia	12 (4%)	15 (5%)
Influenza	8 (3%)	14 (5%)

Source: ADAE 1878

Common Adverse Drug Reactions

Drug related adverse events (ADRs) are defined as adverse events considered by the Investigator to be at least possibly related to study drug (including, B/F/TAF or comparator drug regimen). Table 63 summarizes ADRs reported in at least 2% of subjects in the pooled naïve Phase 3 registrational trials for B/F/TAF. Overall, the ADRs reported with B/F/TAF are similar to the ADRs observed with use of the comparator arms, with the notable difference of ABC/DTG/3TC having higher rates (17%) of nausea. Additionally, the reported rate of nausea in

Trial 1489 is greater than that seen in the registrational trial for Tivicay (FDC of ABC/DTG/3TC) as described in the USPI where the rate of nausea is <1%.

Table 63: Treatment-emergent ADRs Reported in ≥ 1% of Subjects in Trials 1489 and 1490, All Grades

Dictionary Derived Term	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Diarrhea	29 (5%)	13 (4%)	11 (3%)
Headache	29 (5%)	15 (5%)	10 (3%)
Nausea	26 (4%)	55 (17%)	17 (5%)
Fatigue	16 (3%)	10 (3%)	7 (2%)
Dizziness	13 (2%)	9 (3%)	2 (1%)
Insomnia	11 (2%)	9 (3%)	1 (<1%)
Abnormal dreams	9 (1%)	8 (3%)	2 (1%)
Constipation	7 (1%)	2 (1%)	3 (1%)
Abdominal distension	7 (1%)	5 (2%)	4 (1%)
Flatulence	6 (1%)	2 (1%)	7 (2%)
Vomiting	6 (1%)	5 (2%)	2 (1%)
Depressed mood	5 (1%)	0	0
Nightmare	4 (1%)	2 (1%)	1 (<1%)
Somnolence	4 (1%)	3 (1%)	2 (1%)
Abdominal discomfort	4 (1%)	4 (1%)	3 (1%)
Dyspepsia	4 (1%)	4 (1%)	3 (1%)
Decreased appetite	3 (<1%)	3 (1%)	2 (1%)
Sleep disorder	3 (<1%)	5 (2%)	0
Abdominal pain	3 (<1%)	6 (2%)	2 (1%)
Pollakiuria	2 (<1%)	0	2 (1%)
Alopecia	2 (<1%)	0	2 (1%)
Pruritus generalized	2 (<1%)	0	2 (1%)
Asthenia	1 (<1%)	1 (<1%)	2 (1%)
Depression	1 (<1%)	2 (1%)	0
Frequent bowel movements	1 (<1%)	2 (1%)	0
Hyperhidrosis	1 (<1%)	2 (1%)	1 (<1%)
Myalgia	1 (<1%)	2 (1%)	2 (1%)
Anxiety	1 (<1%)	3 (1%)	1 (<1%)
Hyperuricemia	0	0	2 (1%)
Hypoesthesia	0	1 (<1%)	3 (1%)
Flushing	0	2 (1%)	0
Gastroesophageal reflux disease	0	2 (1%)	0

Source: ADAE Trials 1489 and 1490

Table 64 summarizes ADRs by the individual treatment naïve trials, Trial 1489 and 1490, and by treatment arm. The sponsor had proposed (b) (4) in labeling. However, the review team disagreed (b) (4)

(b) (4) Additionally, the review team believes that presenting ADRs at a 2% or higher occurrence in the B/F/TAF arm is appropriate, as this presentation will include dizziness, abnormal dreams, and insomnia, (b) (4) . Table 64 is proposed by the review team for Section 6 of the product label. In addition, additional ADRs occurring in less than 2% of subjects who received B/F/TAF in Trials 1489 and 1490 including vomiting, flatulence, dyspepsia, and abdominal pain were proposed for labeling by the Applicant. The review team agreed with these ADRs being included but in addition, requested depression be added to this list. Further discussion of depression is in Section 9.5 of this review.

Table 64: Percentage Incidence of Treatment-emergent ADRs for Trials 1489 and 1490 Listed Separately ≥ 2%, All Grades

	Trial 1489		Trial 1490	
Dictionary Derived Term	B/F/TAF N=314	ABC/DTG/3TC N=315	B/F/TAF N=320	DTG + F/TAF N=325
Diarrhea	6%	4%	3%	3%
Nausea	5%	18%	3%	5%
Headache	5%	5%	4%	3%
Fatigue	3%	3%	2%	2%
Dizziness	2%	3%	2%	1%
Insomnia	2%	3%	2%	<1%
Abnormal dreams	3%	3%	<1%	1%

Source: ADAE Trials 1489 and 1490

ADRs in Virologically Suppressed Subjects- Trials 1844 and 1878

Overall, the reported ADRs were similar to the treatment-naïve population; however, ADRs were less frequently reported in general, across all treatment arms in the virologically suppressed population as shown in Table 65 and Table 66. The proposed labeling by the Applicant states that overall the safety profile in virologically suppressed adult subjects in Trials 1844 and 1878 was similar to that in treatment naïve subjects. The review team agrees with this proposal.

Table 65: Treatment-emergent ADRs Reported in ≥ 1% of Subjects in Trial 1844, All Grades

Dictionary Derived Term	B/F/TAF N=282	ABC/DTG/3TC N=281
Headache	7 (2%)	8 (3%)
Vomiting	2 (1%)	0
Diarrhea	2 (1%)	4 (1%)
Irritability	1 (0%)	2 (1%)
Fatigue	1 (0%)	3 (1%)
Abnormal dreams	1 (<1%)	5 (2%)
Insomnia	0	3 (1%)
Flatulence	0	5 (2%)
Nausea	0	5 (2%)

Source: ADAE Trial 1844

Table 66: Treatment-emergent ADRs Reported in ≥ 1% of Subjects in Trial 1878, All Grades

Dictionary Derived Term	B/F/TAF N=290	SBR N=287
Headache	14 (5%)	0
Nausea	7 (2%)	1 (<1%)
Flatulence	7 (2%)	0
Diarrhea	6 (2%)	1 (<1%)
Constipation	5 (2%)	0
Fatigue	4 (1%)	0
Abdominal distension	4 (1%)	0
Insomnia	3 (1%)	0
Rash	2 (1%)	0
Abnormal dreams	2 (1%)	0
Paresthesia	2 (1%)	0
Arthralgia	2 (1%)	0
Dysgeusia	2 (1%)	0
Dizziness	2 (1%)	0

Source: ADAE Trial 1878

9.4.6 Laboratory Findings

Treatment-Emergent Laboratory Abnormalities- Trials 1489 and 1490

This section summarizes the treatment-emergent graded laboratory abnormalities analyses completed for chemistry and hematology parameters, except for selected liver enzyme tests and renal function tests that are discussed in Section 9.5 of the review. These analyses represent the worst change from baseline per subject. As shown in Table 67 and

Table 68, for most parameters in the treatment naïve trials, Grade 3 and 4 abnormalities occurred infrequently and at a similar rate in subjects treated with B/F/TAF and the comparator arms.

The Applicant proposed to include laboratory abnormalities (Grades 3-4) occurring in at least 2% of subjects receiving B/F/TAF in Trials 1489 and 1490. These parameters include amylase, AST, creatinine kinase, neutrophils, and LDL-cholesterol (fasted). AST abnormalities are discussed in the hepatobiliary analyses in Section 9.5.

Table 67: Selected Chemistry Lab Results Change from Baseline in Trials 1489 and 1490, All Grades

Parameter and Maximum Analysis Toxicity Grade	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Alkaline Phosphatase (U/L)			
Grade 1 (1.25x to 2.5x ULN)	11 (2%)	9 (3%)	7 (2%)
Grade 2 (>2.5x to 5x ULN)	2 (<1%)	1 (<1%)	0
Grade 3 (>5x to 10x ULN)	1 (<1%)	0	0
Amylase (U/L)			
Grade 1 (>1x to 1.5x ULN)	75 (12%)	34 (11%)	28 (9%)
Grade 2 (>1.5x to 2x ULN)	25 (4%)	14 (4%)	16 (5%)
Grade 3 (>2x to 5x ULN)	11 (2%)	6 (2%)	5 (2%)
Grade 4 (>5x ULN)	1 (<1%)	1 (<1%)	1 (<1%)
Creatine Kinase (U/L)			
Grade 1 (3x to 6x ULN)	26 (4%)	15 (5%)	19 (6%)
Grade 2 (6x to 10x ULN)	15 (2%)	6 (2%)	2 (1%)
Grade 3 (10x to 20x ULN)	9 (1%)	6 (2%)	2 (1%)
Grade 4 (<20X ULN)	13 (2%)	4 (1%)	5 (2%)
Fasting LDL Cholesterol (mg/dL)			
Grade 1 (130 to 160)	126 (20%)	42 (13%)	57 (18%)
Grade 2 (>160 to 190)	42 (7%)	29 (9%)	19 (6%)
Grade 3 (>190)	16 (3%)	8 (3%)	11 (3%)
Fasting Triglycerides (mg/dL)			
Grade 1 N/A	0	0	0
Grade 2 (500 to 750)	7 (1%)	4 (1%)	2 (1%)
Grade 3 (>750 to 1200)	3 (<1%)	0	2 (1%)

Grade 4 (>1200)	1 (<1%)	0	1 (<1%)

Source: ADSL and ADLB Trials 1489 and 1490

Table 68: Hematology Parameters Change from Baseline in Trials 1489 and 1490, All Grades

Parameter and Maximum Analysis Toxicity Grade	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Hemoglobin (g/dL)			
Grade 1 (8.5 to 10)	7 (1%)	5 (2%)	3 (1%)
Grade 2 (7.5 to <8.5)	3 (<1%)	0	0
Grade 3 (6.5 to <7.5)	1 (<1%)	1 (<1%)	0
Grade 4 (<6.5)	1 (<1%)	1 (<1%)	0
Leukocytes (/mm^3)			
Grade 1 (2,000 to 2,500)	11 (2%)	11 (3%)	4 (1%)
Grade 2 (1,500 to <2,000)	3 (<1%)	3 (1%)	1 (<1%)
Grade 3 (1,000 to <1,500)	2 (<1%)	0	0
Grade 4 (<1,000)	1 (<1%)	0	0
Neutrophils, Segmented (/mm^3)			
Grade 1 (1,000 to 1,300)	49 (8%)	19 (6%)	25 (8%)
Grade 2 (750 to <1,000)	22 (3%)	9 (3%)	14 (4%)
Grade 3 (500 to <750)	9 (1%)	6 (2%)	2 (1%)
Grade 4	2 (<1%)	4 (1%)	0
Platelets (/mm^3)			
Grade 1 (100,000 to <125,000)	7 (1%)	5 (2%)	3 (1%)
Grade 2 (50,000 to <100,000	4 (1%)	1 (<1%)	0
Grade 3 (25,000 to <50,000)	1 (<1%)	0	0
Grade 4 (<25,000)	0	1 (<1%)	0

Source: ADSL and ADLB Trials 1489, -1490

Treatment-Emergent Laboratory Abnormalities- Trials 1844 and 1878

This section summarizes the treatment-emergent graded laboratory abnormalities analyses

completed for chemistry and hematology parameters in virologically suppressed subjects in Trials 1844 and 1878. These analyses represent the worst change from baseline per subject. In Trial 1844 (
Table 69), Grade 3 and 4 abnormalities occurred infrequently and at a similar rate in subjects treated with B/F/TAF and the ABC/DTG/3TC arm. More Grade 3 amylase elevations occurred in the B/F/TAF arm (2% versus 0%); however, no pancreatitis or AEs attributable to elevated amylase were reported. No subjects in the B/F/TAF arm in Trial 1844 had a Grade 3 or 4 hematology laboratory event (Data not shown) and Grade 1 or 2 hematology changes were similar. Two subjects had Grade 3 or 4 decreases in neutrophils in the ABC/DTG/3TC arm.

Table 69: Selected Chemistry Lab Change from Baseline Results in Trial 1844, All Grades*

Parameter and Maximum Analysis Toxicity Grade	B/F/TAF N=282	ABC/DTG/3TC N=281
Alkaline Phosphatase (U/L)		
Grade 1	6 (2%)	2 (1%)
Grade 2	1 (<1%)	0
Amylase (U/L)		
Grade 1	31 (11%)	25 (9%)
Grade 2	6 (2%)	11 (4%)
Grade 3	7 (2%)	0
Creatine Kinase (U/L)		
Grade 1	16 (6%)	12 (4%)
Grade 2	3 (1%)	5 (2%)
Grade 3	3 (1%)	3 (1%)
Grade 4	3 (1%)	3 (1%)
Fasting Cholesterol (mg/dL)		
Grade 1	40 (14%)	43 (15%)
Grade 2	29 (10%)	35 (12%)
Grade 3	4 (1%)	4 (1%)
Fasting LDL Cholesterol (mg/dL)		
Grade 1	38 (13%)	45 (16%)
Grade 2	26 (9%)	31 (11%)
Grade 3	14 (5%)	13 (5%)
Fasting Triglycerides (mg/dL)		
Grade 1	0	0
Grade 2	3 (1%)	4 (1%)
Grade 3	2 (1%)	2 (1%)
Grade 4	1 (<1%)	0
Triacylglycerol Lipase (U/L)		
Grade 1	1 (<1%)	2 (1%)
Grade 2	3 (1%)	1 (<1%)
Grade 3	2 (1%)	3 (1%)

Source: ADSL, ADLB -1844

*Reference ranges for the Graded abnormalities are the same as in Table 67

In Trial 1878 (Table 70 and Table 71), Grade 3 and 4 abnormalities occurred infrequently in subjects treated with B/F/TAF and at a similar rate to the SBR arm. It is notable, that despite subjects remaining on boosted protease inhibitors in the SBR arm, the graded abnormalities in fasting cholesterol, fasting LDL, and triglycerides were similar between the treatment arms. Further, treatment with lipid modifying agents among subjects with Grade 3 or 4 elevations of these cholesterol parameters were similar between the treatment arms: seven (2%) B/F/TAF subjects and eight (3%) of SBR subjects also had Grade 3 and 4 elevations of these cholesterol parameters. Abnormal (decreased) neutrophils was the only hematology parameter that occurred in ≥ 2% of subjects in Trial 1878 (Table 71), at 2% in B/F/TAF versus 1% in SBR. These abnormalities were generally transient.

Table 70: Selected Chemistry Lab Change from Baseline Results Trial 1878, All Grades*

Parameter and Maximum Analysis Toxicity Grade	B/F/TAF N=290	SBR N=287
Alkaline phosphatase (U/L)		
Grade 1	1 (<1%)	8 (3%)
Grade 2	0	2 (1%)
Amylase (U/L)		
Grade 1	37 (13%)	36 (13%)
Grade 2	10 (3%)	14 (5%)
Grade 3	6 (2%)	6 (2%)
Creatine Kinase (U/L)		
Grade 1	7 (2%)	5 (2%)
Grade 2	2 (1%)	3 (1%)
Grade 3	3 (1%)	0
Grade 4	1 (<1%)	4 (1%)
Fasting Cholesterol (mg/dL)		
Grade 1	46 (16%)	37 (13%)
Grade 2	32 (11%)	33 (11%)
Grade 3	2 (1%)	6 (2%)
Fasting LDL Cholesterol (mg/dL)		
Grade 1	52 (18%)	55 (19%)
Grade 2	26 (9%)	23 (8%)
Grade 3	11 (4%)	11 (4%)
Fasting Triglycerides (mg/dL)		
Grade 1	0	0
Grade 2	6 (2%)	4 (1%)
Grade 3	2 (1%)	4 (1%)
Grade 4	2 (1%)	0
Triacylglycerol Lipase (U/L)		

Grade 1	2 (1%)	4 (1%)
Grade 2	2 (1%)	2 (1%)
Grade 3	1 (<1%)	1 (<1%)

Source: ADSL and ADLB Trial 1878
*Reference ranges for the Graded abnormalities in this Table are in Table 67

Table 71: Selected Hematology Parameters Change from Baseline in Trial 1878, All Grades*

Parameter and Maximum Analysis Toxicity Grade	B/F/TAF N=290	SBR N=287
Hemoglobin (g/dL)		
Grade 1	4 (1%)	2 (1%)
Grade 2	0	0
Grade 3	0	1 (<1%)
Leukocytes (/mm^3)		
Grade 1	3 (1%)	2 (1%)
Grade 2	1 (<1%)	2 (1%)
Grade 3	1 (<1%)	1 (<1%)
Neutrophils, Segmented (/mm^3)		
Grade 1	7 (2%)	12 (4%)
Grade 2	1 (<1%)	2 (1%)
Grade 3	4 (1%)	3 (1%)
Grade 4	1 (<1%)	0

Source: ADSL and ADLB Trial 1878
*Reference ranges for the Graded abnormalities in this Table are in

Table 68

9.4.7 Vital Signs

Vital signs were assessed at least every 12 weeks in phase 3 trials, and more frequently at study initiation. No clinically relevant pattern of changes in vital signs (systolic and diastolic blood

pressure, pulse) were identified in B/F/TAF or comparator treatment groups across the phase 3 trials.

9.4.8 Electrocardiograms (ECGs)

Five subjects had clinically significant shifts in ECG parameters, reported as AEs, at Week 48 in Study GS-US-380-1489 (B/F/TAF 3 subjects; ABC/DTG/3TC 2 subjects), all of which were nonserious AEs. One ECG-related AE (ABC/DTG/3TC group) was considered related to study drugs and led to interruption of study drugs. All other ECG-related AEs were considered not related to study drugs, and none led to discontinuation of study drugs. B/F/TAF did not cause meaningful ECG changes or concerns based on the Phase 3 trials, as well as the thorough QT trial (see Section 9.4.9).

9.4.9 QT

The potential for bictegravir to cause QT prolongation was evaluated under IND 121318 in April 2016. The conclusion from the data submitted from a thorough QT study was that bictegravir does not lead to significant QTc prolongation effect.

One subject in Trial 1878 reported 'prolonged QT syndrome' could be attributed to a concomitant medication. Subject 1878-00828-4037 on B/F/TAF is a 44 yo male with history of substance abuse and schizoaffective disorder who had a reported term of 'prolonged QT syndrome' and a preferred term of 'long QT syndrome'. His baseline ECG showed sinus tachycardia at a rate of 109 with a normal QT/QTc of 388/469 ms. On D337, he had AE of methadone withdrawal not related to study drug, and on D338, AE of 'prolonged QT syndrome' of moderate severity was reported with a QT/QTc of 420/490 ms that was attributed to asenapine maleate, which is treatment for schizoaffective disorder. After discontinuation of asenapine maleate, on D359, ECG was normal. QT prolongation is listed as a warning per the USPI for asenapine maleate.

9.4.10 Immunogenicity

Because bictegravir is a small molecule, immunogenicity issues were not anticipated and not specifically addressed during the clinical trials. Similarly, emtricitabine and tenofovir alafenamide are small molecules.

9.5 Analysis of Submission-Specific Safety Issues

The following adverse events and laboratory abnormalities of special interest were reviewed because these were identified as adverse events and laboratory abnormalities of special interest with INSTIs or tenofovir containing regimens:

- Hepatobiliary analysis (hepatobiliary AEs and hepatic laboratory analysis)
- Psychiatric AEs of interest
- Rash and hypersensitivity reactions

- Renal analysis (renal AEs, acute renal failure, and renal laboratory analysis)
- Bone analysis (fractures and Dual Energy X-ray Absorptiometry scan results)

9.5.1 Hepatobiliary Analysis

A detailed hepatobiliary analysis was performed to evaluate the potential for hepatotoxicity from B/F/TAF because the hepatobiliary system (with gastrointestinal intolerance) was identified as the target organ of toxicity in repeat-dose toxicology studies in mice, rats, and monkeys, and because antiretroviral drugs in general have been associated with hepatotoxicity.

This section summarizes the following analyses:
1) Review of hepatobiliary AEs,
2) Hepatic events in subjects coinfected with Hepatitis A, B or C,
3) Review of hepatic laboratory abnormalities,
4) Overview of Potential Drug-Induced Liver Injury and Hy's Law Cases, and
5) Summary of hepatobiliary analysis

Hepatobiliary Adverse Events

In Trials 1489 and 1490, adverse events from the Hepatobiliary Disorder SOC in Trials 1489 and 1490 are described in Table 72 below. In these two trials, hepatobiliary AEs occurred infrequently (1%) and were similar in severity and rate across all treatment arms.

Table 72: Hepatobiliary SOC AEs in Trials 1489 and 1490

Hepatobiliary Disorders SOC	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Any Subject with Hepatobiliary Event – n (%)	5 (1%)	2 (1%)	2 (1%)
Hepatobiliary SAEs – n (%)	0	0	0
D/C Due to Hepatobiliary AEs – n (%)	0	0	0
Maximum Toxicity Grade			
1	3 (<1%)	1 (<1%)	2 (1%)
2	1 (<1%)	1 (<1%)	0
3	1 (<1%)	0 (<1%)	0
Related Hepatobiliary Events – n (%)			
Hyperbilirubinemia	1 (<1%)	0	0

Source: ADSL and ADAE Trials 1489 and 1490

One subject was reported to have a Grade 1 hyperbilirubin elevation considered related to B/F/TAF; all other hepatobiliary AEs across the treatment naïve trials were considered not

related. Subject 1489-001691-1596 is a 23 yo male with Grade 1 hyperbilirubinemia that started on D174 (1.5mg/dL) and normalized on D257 (0.7mg/dL) while continuing study drug.

One subject had a Grade 3 hepatic failure (and renal failure) AE described in the database; however, the reported associated laboratory abnormalities were not supportive of severe organ dysfunction. Subject 1489-00031-1540 is a 48 yo female with reported Grade 3 acute hepatic (ALT maximum 51 mg/dL) and renal failure (creatinine maximum 1.15 mg/dL) due to acetaminophen overdose on D67. Study drug was withdrawn and resumed on D81.

In Trial 1844, hepatobiliary events were reported in two subjects (1%) in the B/F/TAF arm and one subject (<1%) in the ABC/DTG/3TC arm. No SAEs occurred in the B/F/TAF arm and one SAE occurred in the comparator arm. None of the three total events were considered related to study drug. These events, that are all considered unrelated to study drug, are briefly described as follows:

B/F/TAF

- Subject 1844-05580-3393 is a 36 yo male with Grade 1 cholelithiasis on D199 reported as ongoing.
- Subject 1844-00959-3296 is a 46 yo male with Grade 1 gallbladder polyp on D201 ongoing.

DTG+F/TAF

- Subject 1844-02838-3234 is a 35 yo female Grade 3 bile duct stone (SAE) on D244-248 and study drug was interrupted.

In Trial 1878, the hepatobiliary disorders and hepatic labs in the SBR arm were influenced by the concomitant use of boosted atazanavir by 46% of the subjects. Atazanavir can cause an increase in bilirubin levels. Hepatobiliary SOC AEs in Trial 1878 is displayed in Table 73. Trial 1878 also included subjects with hepatitis A, B, and C coinfections (described in the next section).

Table 73: Hepatobiliary SOC AEs in Trial 1878

Hepatobiliary Disorders SOC	B/F/TAF N=290	SBR N=287
Any Subject with Hepatobiliary Event – n (%)	4 (1%)	6 (2%)
Hepatobiliary SAEs – n (%)	0	1 (<1%)
D/C Due to Hepatobiliary AEs – n (%)	0	0
Maximum Toxicity Grade		
1	2 (<1%)	3 (1%)
2	2 (<1%)	1 (<1%)
3	0	2 (1%)
Related Hepatobiliary Events – n (%)	0	1 (<1%)

Source: ADSL and ADAE Trials 1489 and 1490

In total, four hepatic AEs occurred in the B/F/TAF arm. Three subjects had Grade 1 or 2 hepatic steatosis with either Grade 1 or no associated ALT elevation; all subjects continued study drug. There was one subject who developed a significant hepatitis while on treatment; however, his course was confounded by influenza infection, concomitant medications, and alcohol use. The details are provided below:

- Subject 1878-00698-4125 is a 51 yo male with Grade 2 liver injury D338 who had influenza diagnosed prior to the reported liver injury. The subject had flu like illness with sore throat and myalgia. He was treated with a five-day course of Tamiflu, NSAIDS, and over the counter cough medications; additionally, the subject reported alcohol use. This subject had a Grade 4 ALT elevation of 1006 mg/dL at Week 48. The subject continued to work and his symptoms improved. His liver tests declined over the course of three months with frequent follow up and at last report, he had a Grade 2 ALT elevation at 145 U/L (see Table 74 below). Investigator and Applicant portray his liver injury as multifactorial causes including influenza, alcohol, and over the counter medication use. The Applicant cited an article by Polakos et. al., describing in vivo evaluation of hepatitis in influenza infection.[6]

Table 74: Liver Biochemistry Laboratory Tests for Subject 1878-00698-4125

Liver Function Tests								
Visit	Lab Date (Study Day)	ALT (U/L)	AST (U/L)	Alk Phos (U/L)	Total Bili (mg/dL)	Direct Bili (mg/dL)	Indirect Bili (mg/dL)	Creatine Kinase (U/L)
Normal Range		6~43	11~36	35~131	0.2~1.2	0.1~0.4	0~1.2	39~308
Unscheduled	2017-05-19 (360)	510 (11.9x)	270 (7.5x)	76	1.0	0.3	0.7	185
Unscheduled	2017-05-26 (367)	600 (14.0x)	288 (8.0x)	73	0.8	0.2	0.6	138
Unscheduled	2017-06-02 (374)	358 (8.3x)	188 (5.2x)	88	0.5	0.2	0.3	84
Unscheduled	2017-06-14 (386)	332 (7.7x)	167 (4.6x)	59	0.7	0.2	0.5	207
Unscheduled	2017-07-14 (416)	275 (6.4x)	162 (4.5x)	58	0.7	0.2	0.5	126
Week 60	2017-07-20 (422)	279 (6.5x)	166 (4.6x)	58	0.5	0.2	0.3	113
Unscheduled	2017-08-30	145 (3.4x)	77 (2.1x)	62	0.7	0.2	0.5	100

Source: Gilead communication for NDA 210215 in SN 0015

In the SBR arm, six subjects had hepatobiliary AEs: two subjects with cholelithiasis, one subject with hepatic cirrhosis, one subjects with acute hepatitis (HAV), and two subjects with jaundice. The only hepatobiliary event considered related to study drug in the SBR arm was in a subject on boosted atazanavir who developed jaundice on D58.

Hepatic Events in Subjects Coinfected with Hepatitis A, B or C

Hepatitis A, B, and C viruses account for co-infections in HIV infected patients and can confound evaluation of both liver-related AEs and laboratory tests. Subjects co-infected (either acutely or chronically) with these hepatitis virus infections across the Phase 3 trials are described below and are displayed by the individual viruses.

Hepatitis A virus

Two subjects in Trial 1490, one on B/F/TAF and one subject on DTG + F/TAF, and three subjects, two subjects on B/F/TAF and one subject on SBR, in Trial 1878 had hepatitis A virus infection reported as an AE, and some reported as an SAE because of hospitalization. These five subjects had Grade 3 or 4 ALT and/or AST abnormalities that decreased and resolved through Week 48 with continued study drug treatment. One subject with Hepatitis A on B/F/TAF (Subject 1878-6748-4244) had a Grade 3 ALT, Grade 2 AST, and Grade 4 bilirubin increase because of acute hepatitis A.

Hepatitis B

Generally, subjects with HIV and hepatitis (HBV) coinfection did not have graded post baseline liver test abnormalities except where hepatic flares occurred. Trials 1490 and 1878 permitted HIV/HBV-coinfected subjects to enroll, while Trials 1489 and 1844 excluded HIV/HBV coinfected subjects.

In Trial 1490, fourteen (2%) subjects in Trial 1490 had HBV coinfection: eight (3%) subjects in the B/F/TAF arm and six (2%) subjects in the DTG+ F/TAF arm. None of these subjects had tenofovir containing products as concomitant medication prior to enrollment into the trial. The AEs reported by HIV/HBV baseline coinfected subjects were generally similar to those reported by HIV mono-infected subjects in this study.

During the study, no subjects with HIV/HBV coinfection at baseline reported a hepatic AE; and ALT values remained at baseline values except for two subjects who experienced a HBV flare with Grade 3 or higher ALT elevation (detailed below). One subject in the DTG+F/TAF group experienced Grade 1 ALT and AST elevations; the other five subjects in this arm did not have graded post-baseline elevations in ALT. In all cases, study drug was continued.

Subject 1490-00994-2530 with HIV/HBV baseline-coinfection on B/F/TAF had a confirmed on-treatment ALT flare reported as a Grade 2 AE of immune reconstitution inflammatory syndrome during the study. Baseline ALT was 118 U/L (Grade 2) and AST was 64 U/L (Grade 1). ALT increased to 1477 U/L (Grade 4) and AST to 551 U/L (Grade 4) at Week 12. Both parameters

returned to normal limits at Week 24. Study drug was continued. HBV DNA was > 170,000,000 IU/mL at baseline, decreasing to 128,000 IU/mL at Week 12 and < 20 IU/mL at Week 48.

Subject 1490-00986-2654 in the B/F/TAF group, with HIV/HBV baseline-coinfection and normal ALT (30 U/L) and AST (24 U/L) at baseline, experienced Grade 3 ALT (316 U/L) and Grade 2 AST (136 U/L) at Week 8, both of which resolved to within the normal range by Week 24 while study drug was continued.

In Trial 1878, 8 (3%) subjects on B/F/TAF and 6 (2%) subjects on SBR had baseline HBV infection; all but one were on a tenofovir based regimen (one in SBR was on 3TC) prior to being randomized. Three of the eight subjects with HBV on B/F/TAF had post baseline Grade 1 ALT elevations. In the SBR arm, none of the HBV/HIV co-infected subjects had graded post baseline ALT elevations.

Hepatitis C virus

In Trial 1489, at baseline, four subjects (1%) in the ABC/DTG/3TC group versus none in the B/F/TAF group had HIV/HCV coinfection. These subjects had Grade 1 or 2 liver function abnormalities. Three subjects in the ABC/DTG/3TC group developed possible acute HCV infection. All three subjects had a nonserious AE of hepatitis C or acute hepatitis C associated with the infection during the study; two of the three subjects had Grade 3 or 4 ALT and/or AST abnormalities. One of these two subjects had treatment interrupted. None of the HCV AEs resulted in discontinuation of study drugs, and none was considered related to study drugs HCV AEs were reported as ongoing for two subjects. No other hepatic AEs occurred in this group of subjects.

In Trial 1490, at baseline, a total of 10 subjects had HIV/HCV co-infection, 5 (2%) subjects in both treatment arms. Eight of the 10 subjects with HIV/HCV baseline-coinfection continued study treatment through Week 48, one subject discontinued (lost to follow up) and one subject had a treatment interruption because of the elevated liver tests but subsequently resumed therapy with study drug. One subject in each treatment arm with HIV/HCV baseline coinfection experienced a treatment-emergent Grade 3 or 4 hepatic laboratory abnormality and the others experienced Grade 1 or 2 ALT and/or AST changes.

In Trial 1844, one subject had baseline HCV coinfection in the ABC/DTG/3TC arm without graded liver function abnormalities or hepatic AEs.

In Trial 1878, five subjects (2%) in each arm had baseline HCV infection. For these ten subjects, no hepatic AEs occurred and study drug was continued. One subject on B/F/TAF with baseline HCV coinfection and one subject with incident HCV had Grade 3 or 4 ALT and/or AST elevation. One subject on B/F/TAF with baseline HCV coinfection received HCV treatment with ledipasvir/sofosbuvir during study, and reported a Grade 1 ALT abnormality. One subject in the SBR arm had Grade 3 ALT elevation and was treated with sofosbuvir/velpatasvir.

The small number of HIV-1 patients coinfected with acute or chronic hepatitis A, B, or C viruses generally tolerated antiretroviral treatment well, did not show evidence of increased hepatobiliary risk, and in most cases, could continue study drug without interruption or discontinuation in the Phase 3 trials. These subjects, albeit small numbers, with acute or chronic hepatitis A, B, or C viruses account for some of the Grade 3 or 4 elevations in ALT, AST, and/or bilirubin observed in the Phase 3 trials.

Review of Hepatic Laboratory Abnormalities

In Trials 1489 and 1490, Grade 1-4 ALT and AST post baseline changes were similar across the three treatment arms. Grade 1 post baseline elevations occurred in 8-9% of subjects (Table 75). The normal range of ALT level for the Phase 3 trials was 6-42 mg/dL. Graded total bilirubin increases were observed in 12% of subjects administered B/F/TAF through Week 48. Increases were primarily Grade 1 (1.0 to 1.5 x ULN) in 9% of subjects and Grade 2 (1.5 to 2.5 x ULN) in 3% of subjects. These post baseline elevations were not associated with hepatic AEs or other liver enzyme test abnormalities. There were no discontinuations due to hepatic adverse events through Week 48 in the B/F/TAF arms. Total bilirubin increases in the ABC/DTG/3TC, and DTG+FTC/TAF groups, were 4% and 6%, respectively, and these increases were primarily Grade 1 (3% of subjects on ABC/DTG/3TC and 5% of subjects on DTG+FTC/TAF) or Grade 2 (1% ABC/DTG/3TC and DTG+FTC/TAF, respectively). Grade 3-4 AST elevations occurred in 1-2% in each treatment arm and were similar.

Table 75: Liver Laboratories Post-Baseline Changes in Trials 1489 and 1490, All Grades

Parameter and max Analysis Toxicity Grade	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Alanine Aminotransferase (U/L)			
Grade 1 (1.25x to 2.5x ULN)	50 (8%)	28 (9%)	30 (9%)
Grade 2 (>2.5x to 5x ULN)	12 (2%)	12 (4%)	6 (2%)
Grade 3 (>5x to 10x ULN)	6 (1%)	2 (1%)	0
Grade 4 (>10x ULN)	3 (<1%)	2 (1%)	3 (1%)
Aspartate Aminotransferase (U/L)			
Grade 1 (1.25x to 2.5x ULN)	53 (8%)	32 (10%)	26 (8%)
Grade 2 (>2.5x to 5x ULN)	19 (3%)	12 (4%)	2 (1%)
Grade 3 (>5x to 10x ULN)	8 (1%)	3 (1%)	6 (2%)
Grade 4 (>10x ULN)	2 (<1%)	1 (<1%)	2 (1%)
Bilirubin (mg/dL)			
Grade 1 (>1 to 1.5x ULN)	54 (9%)	8 (3%)	16 (5%)
Grade 2 (>1.5x to 2.5x ULN)	17 (3%)	4 (1%)	3 (1%)
Grade 3 (>2.5 to 5x ULN)	2 (<1%)	1 (<1%)	0
Grade 4 (>5x ULN)	0	0	0

Source: ADLB for Trials 1489 and 1490

In Trials 1844 and 1878, Grade 1 (1.25 to 2.5 x ULN) ALT increases were observed in 15% of subjects in Trial 1844 (Table 76) and in 17% of subjects in Trial 1878 (Table 77) through 48 weeks on B/F/TAF. In comparison to the comparator arm, Grade 1 increases were observed in Trial 1844 in 8% of subjects in the ABC/DTG/3TC arm and in Trial 1878 in 7% of subjects in the SBR arm. This reviewer evaluated the timing of these Grade 1 elevations and did not discern any sustained elevation or consistency in timing of the elevations. There were no discontinuations of B/F/TAF due to Grade 1 ALT increases. The Applicant provided additional laboratory analysis data (NDA 210215 SN 0017) showing a similar pattern of Grade 1 ALT increases after a switch to a new ART regimen, including data from Genvoya® (elvitegravir/cobicistat/F/TAF), Complera® (F/rilpivirine/TDF), and Atripla® (efavirenz/F/TDF). Notably the greatest magnitude of the difference was in a Complera® switch trial where the Grade 1 ALT post baseline changes in the Complera® arm were observed in 31% of subjects compared with 8% of subjects in the SBR arm. This 23% difference between the new switched regimen and the SBR arm, is greater than the 10% difference observed between arms in Trial 1878. The review team decided that the Grade 1 ALT increases do not need to be described in the label because these Grade 1 ALT increases were transient, not treatment limiting, and a similar pattern has been observed in other switch trials.

Table 76: Trial 1844, Liver Laboratories Post-Baseline Changes, All Grades*

Parameter and max Analysis Toxicity Grade	B/F/TAF N=282	ABC/DTG/3TC N=281
Alanine Aminotransferase (U/L)		
Grade 1	41 (15%)	22 (8%)
Grade 2	5 (2%)	5 (2%)
Grade 3	4 (1%)	0
Grade 4	2 (1%)	0
Aspartate Aminotransferase (U/L)		
Grade 1	31 (11%)	19 (7%)
Grade 2	11 (4%)	7 (2%)
Grade 3	2 (1%)	1 (<1%)
Grade 4	2 (1%)	0
Bilirubin (mg/dL)		
Grade 1	14 (5%)	7 (2%)
Grade 2	5 (2%)	3 (1%)
Grade 3	2 (1%)	0

Source: ADLB Trial 1844
*Reference ranges for the Graded abnormalities in this Table are in Table 75

Table 77: Liver Laboratories Post-Baseline Changes Trial 1878

Parameter and max Analysis Toxicity Grade	B/F/TAF N=290	SBR N=287
Alanine Aminotransferase (U/L)		
Grade 1	48 (17%)	19 (7%)
Grade 2	14 (5%)	7 (2%)
Grade 3	2 (1%)	1 (<1%)
Grade 4	4 (1%)	3 (1%)
Aspartate Aminotransferase (U/L)		
Grade 1	30 (10%)	18 (6%)
Grade 2	8 (3%)	7 (2%)
Grade 3	2 (1%)	1 (<1%)
Grade 4	3 (1%)	3 (1%)
Bilirubin (mg/dL)		
Grade 1	10 (3%)	20 (7%)
Grade 2	4 (1%)	32 (11%)
Grade 3	0	41 (14%)
Grade 4	2 (1%)	3 (1%)

Source: ADLB Trial 1878
*Reference ranges for the Graded abnormalities in this Table are in Table 75

Overview of Potential Drug-Induced Liver Injury and Hy's Law Analysis

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e. aminotransferase elevation) accompanied by jaundice had a mortality of 10-50%. Hepatocellular injury sufficient to impair bilirubin excretion has been used by the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as an indicator of clinical concern for drug-induced liver injury includes the following: ALT or AST > 3x upper limit of normal (ULN), total bilirubin > 2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (for example, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury).

No subjects met the laboratory and/or clinical criteria of Hy's Law across any of the four Phase 3 pivotal trials or in the Phase 2 comparative Trial 1495.

Summary of Hepatobiliary Analysis

This reviewer evaluated hepatic AEs, hepatitis viruses of special interests, and liver laboratory tests as part of a comprehensive hepatobiliary analysis.

B/F/TAF was determined to be relatively safe from the hepatic standpoint. Grade 1 and 2 hyperbilirubinemia in the naïve trials was more frequently observed in subjects on B/F/TAF

than in subjects in the comparator arms. Grade 1 ALT abnormalities were observed at a rate 10% higher in the virologically suppressed population on B/F/TAF than in those on the comparator arms, or for those on B/F/TAF in the treatment naïve trials; however, based on data from other development programs, these low grade elevations of ALT have been previously observed after a change in ART regimen. The clinical review team agrees with including bilirubin laboratory findings in Section 6 of the label as proposed by the Applicant. The review team decided not to recommend describing Grade 1 ALT increases observed in the virologically suppressed population in the label because they were transient, not treatment limiting, and have been observed in other switch trials. Both bilirubin elevations and ALT elevations were not associated with increased hepatic AEs or discontinuation of therapy. Grade 3-4 AST elevations occurred in 1-2% in each treatment arm and were similar. Additionally, it is reassuring that no subjects met Hy's Law criteria.

9.5.2 Psychiatric AEs of Interest

HIV infected patients have high rates of psychiatric comorbidities compared with the HIV-uninfected population. Some antiretroviral agents have been associated with, or may exacerbate pre-existing psychiatric illnesses. Suicidal ideation and behavior, particularly in subjects with a pre-existing history of psychiatric illness, has been described and are labeled in association with use of raltegravir, dolutegravir, and elvitegravir, all INSTIs, and efavirenz, an NNRTI. Depression has been described and is labeled in association with raltegravir, dolutegravir, and elvitegravir.

This section summarizes the analyses of psychiatric disorders and depression in the treatment naïve trials and virologically suppressed trials, including relevant SAEs. The Applicant did not propose any language or inclusion of psychiatric disorders in the initial proposed label. Although insomnia is captured under the psychiatric disorders SOC, this section does not discuss insomnia, as these analyses are included in the Section 9.4.5 under TEAE above.

Trials 1489 and 1490

The proportion of subjects having psychiatric adverse events ranged from 15% to 21% in the treatment naïve trials (

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Table 78), with 18% of B/F/TAF subjects reporting any psychiatric AE. Psychiatric AEs considered by the investigator to be related to the drug (or adverse drug reactions, ADRs) for B/F/TAF were 5% (

Table 78), which was in the middle of the range of 2%-8% observed in the treatment naïve trials. Subjects in the DTG+F/TAF treatment arm had the lowest overall rate (15%) of psychiatric AEs, regardless of causality.

One case is notable due to the temporal relationship of the onset of the psychiatric AEs with the initiation of study drug and reported improvement with discontinuation. Subject 1490-06259-2604 experienced Grade 1 depression and Grade 1 insomnia on Day 63 of study drug. All AEs worsened during treatment and the subject discontinued treatment on Day 65 and switched to Complera. The events were reported as improved within a day or two of discontinuation of study drug (D67). This subject is also described in the Section 9.4.3 Dropouts and/or Discontinuations Due to Adverse Events above.

Table 78: Psychiatric AEs in Trials 1489 and 1490 ≥ 1% in the B/F/TAF Arms, All Grades

	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Any Subject with Psychiatric Disorder SOC – n (%)	114 (18%)	66 (21%)	50 (15%)
Preferred Term			
Insomnia	30 (5%)	20 (6%)	14 (4%)
Depression	23 (4%)	11 (3%)	11 (3%)
Anxiety	17 (3%)	11 (3%)	15 (5%)
Abnormal dreams	11 (2%)	10 (3%)	3 (1%)
Depressed mood	11 (2%)	0	3 (1%)
Sleep disorder	8 (1%)	10 (3%)	0
Libido decreased	6 (1%)	3 (1%)	3 (1%)
Nightmare	6 (1%)	2 (1%)	2 (1%)
Stress	5 (1%)	1 (<1%)	1 (<1%)

Source: ADSL and ADAE Trials 1489 and 1490

Table 79: ADR Psychiatric Events, All Grades

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	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Any Subject with Related Psychiatric Disorder SOC – n (%)	31 (5%)	25 (8%)	7 (2%)
Preferred Term			
Insomnia	11 (2%)	9 (3%)	1 (<1%)
Abnormal dreams	9 (1%)	8 (3%)	2 (1%)
Depressed mood	5 (1%)	0	0
Nightmare	4 (1%)	2 (1%)	1 (<1%)
Sleep disorder	3 (<1%)	5 (2%)	0
Libido decreased	2 (<1%)	0	0
Anxiety	1 (<1%)	3 (1%)	1 (<1%)
Bruxism	1 (<1%)	0	0
Depression	1 (<1%)	2 (1%)	0
Disorientation	1 (<1%)	0	0
Middle insomnia	1 (<1%)	0	0
Suicide attempt	1 (<1%)	0	0
Initial insomnia	0	0	1 (<1%)
Loss of libido	0	0	1 (<1%)
Mood swings	0	0	1 (<1%)

Source: ADSL and ADAE Trials 1489 and 1490

The rate of psychiatric SAEs in the HIV treatment naïve trials was similar across treatment arms and occurred in 2% in the B/F/TAF arms (Table 80). In general, the subjects experiencing psychiatric SAEs were young men between the ages of 20-34 years old, and most events describe a history of psychiatric illness and social stressors. The most frequent preferred term for the psychiatric SAE was 'suicide attempt' (n=3) followed by 'major depression" (n=2). 'Suicide attempt' and 'depression suicidal' and 'suicidal ideation' were reviewed and are confounded by underlying psychiatric illness and/or situational stressors which makes the causality to study drug difficult to discern. Additionally, there is no pattern to the timing of events. However, depression and suicidal ideation or suicidal attempt has been associated with other drugs in the INSTI class and therefore, remains an adverse event of interest for B/F/TAF.

Table 80: Psychiatric SAEs Trials 1489 and 1490, All Grades

	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Any Subject with Psychiatric D/O SOC SAE – n (%)	12 (2%)	4 (1%)	3 (1%)
Preferred Term			
Suicide attempt	3 (<1%)	0	1 (<1%)
Major depression	2 (<1%)	0	0
Delirium tremens	1 (<1%)	0	0
Depression	1 (<1%)	2 (1%)	0
Depression suicidal	1 (<1%)	0	0
Drug abuse	1 (<1%)	0	0
Mental disorder	1 (<1%)	0	0
Psychotic disorder	1 (<1%)	0	0
Suicidal ideation	1 (<1%)	2 (1%)	0
Bipolar disorder	0	0	1 (<1%)
Seasonal affective disorder	0	0	1 (<1%)

Source: ADSL and ADAE Trials 1489 and 1490

Further analyses were completed evaluating depression and suicidal events using MedDRA HLTs of 'Depressive Disorders', 'Mood Alterations with Depressive Symptoms', and 'Suicidal and Self-Injurious Behavior'. The subjects with depression or suicidal events considered related to study drug were similar across the treatment arms (See). The majority of the events were Grade 1 or 2.

Table 81: Depression and Suicidal Events* in Trials 1489 and 1490: All Cause, All Grades

	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Any Subject with Depression or Suicidal Event –	41 (6%)	14 (4%)	16 (5%)
Depression or Suicidal Event SAEs – n (%)	8 (1%)	4 (1%)	1 (<1%)
D/C Due to Depression or Suicidal Event AEs – n	1 (<1%)	1 (<1%)	0
Preferred Term			
Depression	23 (4%)	11 (3%)	11 (3%)
Depressed mood	11 (2%)	0	3 (1%)
Suicidal ideation	3 (<1%)	3 (1%)	1 (<1%)
Suicide attempt	3 (<1%)	0	1 (<1%)
Major depression	2 (<1%)	2 (1%)	0
Depression suicidal	1 (<1%)	0	0
Depressive symptom	1 (<1%)	0	0
Maximum Toxicity Grade			
1	18 (3%)	3 (1%)	10 (3%)
2	16 (3%)	9 (3%)	4 (1%)
3	4 (1%)	1 (<1%)	0
4	3 (<1%)	1 (<1%)	1 (<1%)
Any Subject with Related Depression or Suicidal Event – n (%)	7 (1%)	2 (1%)	0
Depressed mood	5 (1%)	0	0
Depression	1 (<1%)	2 (1%)	0
Suicide attempt	1 (<1%)	0	0

Source: ADSL and ADAE Trials 1489 and 1490
*Defined by MedDRA HLTs: Depressive Disorders, Mood Alterations with Depressive Symptoms, Suicidal and Self-Injurious Behavior

Trials 1844 and 1878

The analyses in the virologically-suppressed population are described separately because the drug classes used in the comparator arms are different (INSTI versus boosted protease inhibitor) and the open label nature of Trial 1878 may influence patient and investigator perception of the relatedness of an AE to study drug. In Trial 1844, fewer subjects on B/F/TAF reported psychiatric disorders, regardless of causality, compared to ABC/DTG/3TC (See Table 82 and

Table 83). Three subjects (1%) reported five SAEs (two suicidal ideations, one alcohol abuse, one depression suicidal, one suicide attempt) in the B/F/TAF arm, and 4 (1%) subjects reported 4 SAEs (one suicidal ideation, one schizophrenia, one bipolar disorder, and one abnormal

behavior) in the ABC/DTG/3TC arm. In the B/F/TAF arm, the three suicide attempt events: one depression suicidal and two suicidal ideations are further detailed as follows:

- Subject 1844-07881-3397 is 29 yo male with history of depression treated with quetiapine, escitalopram, and mephedrone who had Grade 4 suicidal ideation on D8-18 reportedly following alcohol intake at a wedding. The event resolved and was considered not related to study medication. While this event occurred shortly after starting study drug, suggesting a temporal relationship to study drug, prior depression and the social situation may have also played a role. This subject had another Grade 3 suicidal ideation on D206 and study drug was then withdrawn and the event was considered ongoing. At the time of the 48-week analysis this was considered not to be related to study drug; however, the causality was subsequently updated to "related".

- Subject 1844-01624-3360 is a 46 yo female without a documented psychiatric history who reported a Grade 4 suicidal ideation on D165-169. The event resolved with additional medical intervention. The SAE was considered not related to study medication. The subject was found dead by her mother on D311.

- Subject 1844-04838-3219 is 21 yo male with history of bipolar disorder who was hospitalized D253-258 for Grade 3 suicidal ideation. The event was considered not related to study drug and study drug was continued.

Table 82: Psychiatric AEs in Trial 1844 ≥ 1% in the B/F/TAF arms

	B/F/TAF N=282	ABC/DTG/3TC N=279
Any Subject with Psychiatric Disorder SOC – n (%)	26 (9%)	45 (16%)
Preferred Term		
Insomnia	8 (3%)	14 (5%)
Libido decreased	3 (1%)	2 (1%)
Depression	3 (1%)	10 (4%)
Anxiety	2 (1%)	4 (1%)
Sleep disorder	2 (1%)	0
Irritability	2 (1%)	3 (1%)
Substance abuse	2 (1%)	0
Abnormal dreams	2 (1%)	7 (2%)
Suicidal ideation	2 (1%)	1 (<1%)

Source: ADSL and ADAE Trial 1844

Table 83: Psychiatric ADRs in Trial 1844 ≥ 1% in the B/F/TAF arms

	B/F/TAF N=282	ABC/DTG/3TC N=279
Any Subject with Related Psychiatric Disorder SOC – n (%)	3 (1%)	13 (5%)
Preferred Term		
Abnormal dreams	1(<1%)	5 (2%)
Mood swings	1(<1%)	0
Aggression	1(<1%)	0
Irritability	1(<1%)	2 (1%)
Sleep disorder	1(<1%)	0
Mood altered	0	1(<1%)
Nightmare	0	1(<1%)
Anxiety	0	1(<1%)
Agitation	0	1 (<1%)
Depressed mood	0	1(<1%)
Insomnia	0	3 (1%)

Source: ADSL and ADAE Trial 1844

In Trial 1844, there were fewer subjects with psychiatric SOC AEs on B/F/TAF (9%) than on ABC/DTG/3TC (16%). This was largely driven by insomnia and depression which occurred less frequently in the B/F/TAF arm (3% and 1%, respectively) than in the ABC/DTG/3TC arm (5%, and 4%, respectively) in the AE analysis.

In the psychiatric ADR analysis, no subjects in either treatment arm had depression reported as an ADR; however, one subject in the ABC/DTG/3TC arm reported an ADR of 'depressed mood'. In the ADR analysis, the preferred terms in the ABC/DTG/3TC arm that account for a greater incidence of events were 'abnormal dreams', 'irritability' and 'insomnia'; albeit, at only 1-2% of subjects.

Further analysis of depression and suicidal events was completed using MedDRA HLTs of 'Depressive Disorders', 'Mood Alterations with Depressive Symptoms', and 'Suicidal and Self-Injurious Behavior'. B/F/TAF had a lower rate of depression at 3% compared to ABC/DTG/3TC at 6%; other events were reported at either similar rates or reported in a single subject in either arm. The rates of depression and suicidal events considered related to study drug were similar among the treatment arms.

In contrast to Trial 1844, the rate of any subject with a psychiatric disorder in the open label Trial 1878 was 14% in the B/F/TAF arm compared with 8% in the comparator arm of SBR (See Table 84). The rate of psychiatric disorders considered related to study drug was 3% for B/F/TAF and 0% in the SBR arm (Table 85). It is likely that the imbalance in psychiatric disorder events, regardless of causality, between the B/F/TAF and SBR treatment arms relates to the switching to a new treatment regimen in an open label clinical trial. Two (<1%) psychiatric SAEs (schizoaffective disorder and schizophrenia) occurred in the B/F/TAF arm in Trial 1878 and 2 (<1%) SAEs (schizoaffective disorder and suicide attempt) occurred in the SBR arm. These SAEs cases are detailed as follows:

- Subject 1878-07880-4237 is a 24 yo male without a history of psychiatric illness who was hospitalized on D233 for Grade 3 paranoid schizophrenia. The subject discontinued study drug on D247 and the trial on D274 due to this AE. This SAE of paranoid schizophrenia was considered related to study drug by the investigator.

- Subject 1878-00651-4040, is a 39 yo female who experienced schizoaffective disorder on D69. The subject subsequently experienced a worsening of schizoaffective disorder on D117 which required hospitalization, the study drug was interrupted, and outcome was reported as resolving.

Table 84: Psychiatric AEs in Trial 1878 ≥ 1% in the B/F/TAF arms

	B/F/TAF N=290	SBR N=287
Any Subject with Psychiatric Disorder SOC – n (%)	41 (14%)	22 (8%)
Preferred Term		
Insomnia	11 (4%)	6 (2%)
Anxiety	10 (3%)	5 (2%)
Depression	4 (1%)	4 (1%)
Abnormal dreams	3 (1%)	0
Panic attack	2 (1%)	2 (1%)
Major depression	2 (1%)	1 (<1%)
Depressed mood	2 (1%)	0
Nightmare	2 (1%)	0

Source: ADSL and ADAE Trial 1878

Table 85: Psychiatric ADRs in Trial 1878 ≥ 1% in the B/F/TAF arms

	B/F/TAF N=290	SBR N=287
Any Subject with Related Psychiatric Disorder SOC – n (%)	9 (3%)	0
Preferred Term		
Insomnia	3 (1%)	0
Abnormal dreams	2 (1%)	0
Middle Insomnia	1 (<1%)	0
Schizophrenia	1 (<1%)	0
Somnambulism	1 (<1%)	0
Anxiety	1 (<1%)	0

Source: ADSL and ADAE Trial 1878

In Trial 1878, further analyses of depression and suicidal events using MedDRA HLTs of 'Depressive Disorders', 'Mood Alterations with Depressive Symptoms', and 'Suicidal and Self-Injurious Behavior' also were similar among the treatment arms at approximately 3% and none were considered related to study drug (Table 86).

Table 86: Depression and Suicidal Events*: All Cause, All Grades

	B/F/TAF N=290	SBR N=287
Any Subject with Depression or Suicidal Event – n	9 (3%)	6 (2%)
Depression or Suicidal Event SAEs – n (%)	8 (1%)	4 (1%)
D/C Due to Depression or Suicidal Event AEs – n	1 (<1%)	1 (<1%)
Preferred Term		
Depression	4 (1%)	4 (1%)
Depressed mood	2 (1%)	0
Major depression	2 (1%)	1 (<1%)
Seasonal affective disorder	1 (<1%)	0
Suicide attempt	0	1 (<1%)
Maximum Toxicity Grade		
1	5 (2%)	2 (1%)
2	4 (1%)	3 (1%)
3	0	1 (<1%)
4	0	0
Any Subject with Related Depression or Suicidal Event – n (%)	0	0

Source: ADSL and ADAE Trial 1878
*Defined by MedDRA HLTs: Depressive Disorders, Mood Alterations with Depressive Symptoms, Suicidal and Self-Injurious Behavior

In summary, psychiatric disorders, including depression and insomnia, occurred in all four registrational trials. In the treatment naïve trials, the psychiatric disorders SOC and depression

pooled HLTs in B/F/TAF were comparable to ABC/DTG/3TC and more frequent than DTG/F/TAF. In Trial 1844, the rates of psychiatric disorder ADRs in the B/F/TAF arm were lower than the rates in the ABC/DTG/3TC arm; this was primarily driven by higher rates of insomnia and abnormal dreams observed in the ABC/DTG/3TC arm. In Trial 1878, B/F/TAF had a higher incidence of events in the psychiatric disorders SOC compared to SBR, but in the pooled depression HLT analysis the rates of events in the B/F/TAF arm were similar to SBR. Psychiatric disorder SAEs occurred in all trials, some of which were considered related to study drug. Subject 1490-06259-2604 did have a constellation of symptoms including depression and insomnia soon after starting therapy that improved when the subject discontinued B/F/TAF.

Depression and psychiatric comorbidities are common in HIV infected patients and confound the assessment of causality for these events. In the overall assessment of depression and psychiatric disorders, the data appears similar to other integrase inhibitors, such as raltegravir, dolutegravir and elvitegravir where labeling for depression, insomnia, and suicidal ideation or behavior are present. Because of the similar frequency of events in the pooled treatment naïve trials, the resolution of depression in some cases after discontinuation of study drug, and the types and patterns of SAEs, the review team believes that depression, suicidal ideation or behavior, and insomnia should be included in Section 6 of the product label.

9.5.3 Rash and Hypersensitivity Reactions

Compared to the general population, HIV-1 infected subjects have a higher incidence of drug skin rash and hypersensitivity and these events are associated with many antiretroviral drugs, including INSTIs, NNRTIs and PIs. The raltegravir (Isentress) label includes a Warnings and Precautions for rash events, including severe rash such as (b) (4) Stevens-Johnson syndrome.

Rash was identified as an AE of special interest in the Phase 2 trial 1475. A description of the subject with a skin event leading to discontinuation of the drug follows.

- Subject 1912-6075 is a 21 yo AAM with history of asthma, eczema, peanut and shellfish allergies, and idiopathic urticaria developed Grade 3 urticaria on D130. This event was assessed as related to drug and the study drug was withdrawn. The AE end date was D163. The presentation of his urticaria was waxing and waning and notably he had concomitant medications of hydrocortisone, cetirizine, and epinephrine pen as needed. After initiation of B/F/TAF, he had a hive-like total body rash on D8 that resolved with Benadryl on D9. Subsequently he had waxing and waning of rash that was noted as consistent with eczema on D129. Examination by dermatology consult on D133 described the rash as consistent with a cutaneous allergic reaction, though it was felt safe to resume study medication. He was given topical steroid and antifungal medications. Study drug was permanently discontinued on D162 and the rash was noted to have resolved on D162. The subject was unblinded and started on ABC/3TC/DTG. In subsequent follow-up, he continued to have waxing and waning rashes. This was diagnosed as eczema and was treated with topical steroid and oral antihistamines.

Evaluation of Skin SOC in the naïve Phase 3 registrational trials showed a 3% incidence of related skin or subcutaneous AEs in the B/F/TAF arms in the naïve trials that was similar to the comparator arms (Table 87). No SAEs or discontinuation due to Skin SOC AEs occurred. In Trial 1844, the related skin and subcutaneous SOC AEs were less frequent than in the naïve population, occurring in approximately 1% or less of subjects in either arm. In Trial 1878, the related skin and subcutaneous SOC AEs were higher at 3%, although similar to the naïve trials; in contrast, no related skin and subcutaneous SOC AEs occurred in the SBR arm (Table 88). Trial 1878 was an open label trial and half the subjects switched from the protease inhibitor class of medications to the INSTI class of medications. Because subjects knew they were on a new drug, it is possible that the rashes were then considered attributable to a changed antiretroviral regimen.

Table 87: Skin or Subcutaneous Tissue SOC Analyses of Trials 1489 and 1490

	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Any Subject with Skin or Subcutaneous Tissue Event – n (%)	125 (20%)	64 (20%)	58 (18%)
Skin or Subcutaneous Tissue SAEs – n (%)	0	0	0
D/C Due to Skin or Subcutaneous Tissue AEs – n (%)	0	1 (<1%)	1 (<1%)
Maximum Toxicity Grade			
1	102 (16%)	49 (16%)	51 (16%)
2	22 (3%)	13 (4%)	7 (2%)
3	1 (<1%)	2 (1%)	0
Related Skin or Subcutaneous Tissue AEs – n (%)	17 (3%)	7 (2%)	6 (2%)
Alopecia	2 (<1%)	0	2 (1%)
Pruritus generalized	2 (<1%)	0	2 (1%)
Angioedema	1 (<1%)	0	0
Eczema	1 (<1%)	0	0
Hyperhidrosis	1 (<1%)	2 (1%)	1 (<1%)
Nail bed disorder	1 (<1%)	0	0
Pruritus	1 (<1%)	0	1 (<1%)
Rash	1 (<1%)	1 (<1%)	1 (<1%)
Rash generalized	1 (<1%)	1 (<1%)	0
Skin lesion	1 (<1%)	0	0
Skin mass	1 (<1%)	0	0
Skin odor abnormal	1 (<1%)	0	0
Dermatitis	0	1 (<1%)	0
Dermatitis contact	0	1 (<1%)	0
Drug eruption	0	1 (<1%)	0

Source: ADSL and ADAE Trial 1878

Table 88: Skin or Subcutaneous Tissue SOC Analyses of Trial 1878

	B/F/TAF N=290	SBR N=287
Any Subject with Skin or Subcutaneous Tissue Event – n (%)	43 (15%)	23 (8%)
Skin or Subcutaneous Tissue SAEs – n (%)	0	0
D/C Due to Skin or Subcutaneous Tissue AEs – n (%)	1	0
Maximum Toxicity Grade		
1	35 (12%)	19 (7%)
2	12 (4%)	3 (1%)
3	0	1 (<1%)
Related Skin or Subcutaneous Tissue AEs – n (%)	17 (3%)	0
Rash	2 (1%)	0
Rash maculopapular	1 (<1%)	0
Urticaria	1 (<1%)	0
Night Sweats	1 (<1%)	0
Onychoclasis	1 (<1%)	0
Ecchymosis	1 (<1%)	0
Acne	1 (<1%)	0

Source: ADSL and ADAE Trial 1878

One B/F/TAF subject (1878-01221-4195) discontinued study drug due to a Grade 2 rash on D6 on his arms that continued after discontinuation. The subject had Grade 1 flu like symptoms 2 days prior to the rash. The investigator assessed the rash as not related to study drug.

Further rash analysis was completed by exploring events that had any of the following preferred terms: rash, exfoliative rash, rash erythematous, rash follicular, rash generalized, rash macular, rash papular, rash maculopapular, rash pruritic, rash vesicular, drug eruption. In the pooled naïve trials, rash events occurred less commonly in the B/F/TAF arm 4% compared with 6% in the B/F/TAF arm and 9% in the ABC/DTG/3TC arm, respectively (Table 89).

Table 89: Rash Event* in Trials 1489 and 1490

	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Any Subject with Rash Event – n (%)	26 (4%)	27 (9%)	19 (6%)
Rash SAEs – n (%)	0	0	0
D/C Due to Rash AEs – n (%)	0	1 (<1%)	1 (<1%)
Maximum Toxicity Grade			
1	25 (4%)	22 (7%)	19 (6%)
2	1 (<1%)	4 (1%)	0
3	0	1 (<1%)	0
Related Rash Event – n (%)	2 (<1%)	3 (1%)	1 (<1%)
Rash	1 (<1%)	1 (<1%)	1 (<1%)
Rash generalized	1 (<1%)	1 (<1%)	0
Drug eruption	0	1 (<1%)	0

Source: ADSL and ADAE Trials 1489 and 1490

*Based on TIVICAY label: Includes pooled terms: rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and drug eruption plus added 'rash papular, rash pustular'

There were two angioedema events in subjects receiving B/F/TAF across the Phase 3 trials, both continued study drug despite the reported angioedema. One subject (Subject 1490-1808-1160) had Grade 2 angioedema D28-30, not serious and was treated with antihistamine. One subject (Subject 1844-00315-3209) had Grade 3 angioedema on Day 114-119 reported to be related to study drug and treated with epinephrine, prednisone, and famotidine; however, the subject had eaten shell fish the night prior to the event and subsequently reported a similar shellfish reaction prior to entering the trial. The Investigator changed the causality to 'not related' to study drug after submission of the NDA.

In Trials 1490 and 1844, abacavir (ABC) is one of the comparator drugs. A serious safety risk associated with use of ABC is a well characterized drug-related hypersensitivity reaction (ABC HSR), which is generally manageable by stopping drug and avoiding rechallenge. The genetic version of HLA-B, known as HLA-B*5701 has been highly associated with a high risk of developing ABC HSR. The product labeling recommends pre-therapy screening to exclude patients who carry the HLA-B*5701 allele from any ABC containing treatment regimen. Consistent with product labeling, all subjects in Trials 1490 and 1844 were required to have a negative screening for HLA-B*5701 prior to starting therapy.

Evaluation of the Hypersensitivity SMQ using MAED for Trials 1475, 1489, 1490, 1844, and 1878 revealed no new signals to suggest hypersensitivity reactions from B/F/TAF. The Hypersensitivity SMQ narrow search found similar rates in the B/F/TAF and the comparator arms at 6%-9%, except for Trial 1878 (Table 90). In Trial 1878, any hypersensitivity event occurred in 12% of B/F/TAF subjects compared with 6% of subjects in the SBR arm; the most frequent AE was rash in 4% of subjects in the B/F/TAF arm compared with <1% of subjects in the SBR arm. The AEs were Grade 1 or Grade 2 in the B/F/TAF arm. One new SAE of Grade 2

asthma was identified with the Hypersensitivity SMQ analysis in the B/F/TAF arm but was not related to study drug and likely due to asthma itself and not drug hypersensitivity. There was one discontinuation due to AE (Subject 1878-1221-4195**)** of rash described above (Section 9.5.3). Overall, the analysis of Hypersensitivity SMQ narrow search for Trial 1878 did not raise concern for hypersensitivity or serious allergic type reaction from B/F/TAF and the SAE was due to underlying illness and not B/F/TAF.

Table 90: Hypersensitivity (SMQ, Narrow Search) for Trial 1878

	B/F/TAF N=290	SBR N=287
Any Subject with Hypersensitivity Event – n (%)	34 (12%)	16 (6%)
Rash	12 (4%)	1 (<1%)
Eczema	5 (2%)	0
Asthma	4 (1%)	1 (<1%)
Conjunctivitis	4 (1%)	5 (2%)
Pruritus	4 (1%)	3 (1%)
Dermatitis	2 (1%)	1 (<1%)
Stomatitis	2 (1%)	0
Urticaria	2 (1%)	1 (<1%)
Blister	1 (<1%)	2 (1%)
Hypersensitivity	1 (<1%)	1 (<1%)
Wheezing	1 (<1%)	1 (<1%)
SAEs – n (%)	1 (<1%)	0
D/C Due to AEs – n (%)	1 (<1%)	0
Maximum Toxicity Grade		
1	21 (7%)	11 (4%)
2	13 (4%)	4 (1%)
3	0	1 (<1%)
Related Events – n (%)		
Rash	2 (1%)	0
Urticaria	1 (<1%)	0

Source: MAED SMQ Output -ADAE Trial 1848

In summary, rash and urticaria associated with B/F/TAF have been reported in the Phase 2 and 3 trials. However, in general, the rash events have been mild to moderate and few subjects have discontinued due to rash, regardless of causality. One subject in phase 2, may have had an allergic skin issue that was considered related to study drug, as evaluated by dermatology, however, the subject continued study drug through 48 weeks, despite the ongoing rash issue. Two cases of Grade 2 and Grade 3 “angioedema’ also occurred that although initially considered related to B/F/TAF, however, B/F/TAF was continued. Serious rashes such as erythema multiforme, Stevens Johnson’s syndrome and toxic epidermal necrolysis syndrome

were not reported in the overall safety database for B/F/TAF. The Applicant is proposing to list rash an ADR in Section 6 and this is adequate given review of the evidence.

9.5.4 Renal Analysis

Tenofovir has been associated with the development of Fanconi's syndrome and acute and chronic renal failure. With tenofovir disoproxil fumarate (TDF), the incidence of nephrotoxicity is severe enough to warrant discontinuation in TDF in about 1% of patients with < 0.2% experiencing severe renal failure. Renal toxicity is thought to be due to TFV exposure concentrations making the lower TFV exposures with TAF attractive as potentially renal function sparing. Tenofovir alafenamide is believed to have lower impact on the renal proximal tubules due to its lowered serum tenofovir exposures.

Differences in serum creatinine favoring TAF over TDF have been demonstrated in the data submitted in the Genvoya® and Vemlidy® applications. The Applicant did not include a Warning and Precaution for renal impairment or recommendations for monitoring in their proposed labeling despite these warnings being in current TDF and TAF containing product labels.

Bictegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Indeed, iohexol studies submitted with this application show GFR is preserved on treatment even if creatinine increases slightly (see Section 6.2.2 *Effect of BIC on serum creatinine via inhibition of renal transporters)*. In Trial 1490, the $eGFR_{CG}$ had to be ≥ 30 mL/min, while in the other Phase 3 trials of this application, the estimated $eGFR_{CG}$ had to be ≥ 50 mL/min.

This section describes renal adverse events and changes in laboratory patterns for creatinine.

<u>Renal Adverse Events- Trials 1489 and 1490</u>
In the pooled naïve trials, overall, 6% of B/F/TAF subjects reported any renal AE, which was similar to the comparator arms at 4% of subjects who reported any renal AE. Renal AEs that were considered related to study drug occurred in four subjects (<1%) in the B/F/TAF arms, 3 (1%) subjects in the DTG+F/TAF arm and none of the ABC/DTG/3TC arm (Table 91). SAEs were reported in <1% of subjects across all the treatment arms. The two subjects who reported renal SAEs in the B/F/TAF arm were subjects with diabetes mellitus, which likely contributed to the renal SAE.

Two subjects on B/F/TAF in the treatment naïve trials reported Acute Kidney Injury (AKI), or acute renal failure, assessed as not related to B/F/TAF. The events of AKI were precipitated by concomitant medication or comorbid disease.

- Subject 1489-00031-1540 is a 48 yo male on B/F/TAF who had a Grade 4 'stress induced overdose' (reported term) with Tylenol, cocaine, and Seroquel on D67-76 and developed Grade 3 AKI, Grade 2 acute liver injury, and Grade 2 hepatic encephalopathy with the overdose. Study drug was interrupted and resumed later.

- Subject 1490-02843-2211 is a 62 yo Diabetic male with poor circulation to bilateral lower extremities who was hospitalized for hypoglycemia and bilateral lower extremity edema. He had the incidental finding of Grade 2 acute kidney injury (creatinine 2.57 mg/dL) that improved with hydration. Study drug was continued. His diabetes may have contributed to his AKI.

One subject had proteinuria that was considered related to B/F/TAF. Subject 1490-03976-2387 is a 37 yo WM who had baseline proteinuria 1+ and hypophosphatemia 1.7 mg/dL (normal range 2.2-5.1 mg/dL). After starting B/F/TAF, the phosphate level normalized. On Day 57, the subject again had hypophosphatemia (AE and lab abnormality) with a value of 1.9 mg/dL which subsequently improved to 3.1 mg/dL on D86. The subject also had trace protein on Days 29, 57, and 170, and an AE of proteinuria reported on Day 170-256. He had no proteinuria on Days 86, 254, and 302. He did not have glycosuria. This subject's creatinine was baseline of 1.03 mg/dL, 1.06 mg/dL at D86, 1.12 mg/dL at D168, 1.16 mg/dL at D254, and 1.01 mg/dL at D302. This subject had hypertension on D87 with a blood pressure of 149/99 mmHg and on D302 of 154/93 mmHg. He was normotensive at the other visits and was not on antihypertensives. Study drug was continued throughout these events. Taken together, though hypophosphatemia and proteinuria may be concerning for the diagnosis of Fanconi's syndrome, this subject had baseline hypophosphatemia (which corrected on treatment) and proteinuria and no reported glycosuria. Additionally, hypertension can cause transient proteinuria. Based on review of the available data, the clinical reviewer concludes that in this case, hypophosphatemia was not associated with B/F/TAF.

Table 91: Renal Events in Trials 1489 and 1490

Renal and Urinary Disorders SOC	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Any Subject with Renal Event – n (%)	41 (6%)	12 (4%)	13 (4%)
Renal SAEs – n (%)	2 (<1%)	1 (<1%)	1 (<1%)
D/C Due to Renal AEs – n (%)	0	0	0
Maximum Toxicity Grade			
1	33 (5%)	8 (3%)	12 (4%)
2	6 (1%)	3 (1%)	2 (1%)
3	2 (<1%)	1 (<1%)	0
4	1 (<1%)	0	0
Related Renal Events – n (%)	4 (1%)	0	3 (1%)
Pollakiuria	2 (<1%)	0	2 (1%)
Polyuria	1 (<1%)	0	0
Proteinuria	1 (<1%)	0	1 (<1%)

Source: ADSL and ADAE Trials 1489 and 1490

Renal Adverse Events - Trials 1844 and 1878

Generally, the rates of renal AEs were similar across the treatment arms in Trials 1844 and 1878 (interrupted for four days during hospitalization.

Table 92 and Table 93). One subject with AKI (Trial 1844) and an SAE of ureterolithiasis (Trial 1878) are described below; both events were considered not related to B/F/TAF.

- Subject 1844-01534-3169 on B/F/TAF reported an AE of AKI. He is a 58 yo male with Grade 1 AKI with a creatinine that peaked at 1.62 mg/dL (normal 0.45-1.35 mg/dL) on D58 and then gradually declined. Study drug was continued. The subject was taking the concomitant medication of ibuprofen that may have contributed to AKI. The AE of AKI is confounded and the renal function improved despite continuation of study drug.

- Subject 1878-00417-4205 developed an SAE of Grade 3 ureterolithiasis D241-246, for which he was hospitalized. The SAE was considered not related to B/F/TAF, and study drug was interrupted for four days during hospitalization.

Table 92: Renal Events in Trial 1844

Renal and Urinary Disorders SOC	B/F/TAF N=282	ABC/DTG/3TC N=281
Any Subject with Renal Event – n (%)	9 (3%)	14 (5%)
Renal SAEs – n (%)	0	2 (1%)
D/C Due to Renal AEs – n (%)	0	0
Maximum Toxicity Grade		
2	2 (1%)	2 (1%)
3	0	1 (<1%)
4	0	0
Related Renal Events – n (%)	1 (<1%)	1 (<1%)
Proteinuria	0	1 (<1%)
Polyuria	1 (<1%)	0

Source: ADSL and ADAE Trial 1844

Table 93: Renal Events in Trial 1878

Renal and Urinary Disorders SOC	B/F/TAF N=290	SBR N=287
Any Subject with Renal Event – n (%)	10 (3%)	17 (6%)
Renal SAEs – n (%)	1 (<1%)	2 (1%)
D/C Due to Renal AEs – n (%)	0	1 (<1%)
Maximum Toxicity Grade		
2	1 (<1%)	2 (1%)
3	2 (1%)	1 (<1%)
4	1 (<1%)	0
Related Renal Events – n (%)	0	2 (1%)
Proteinuria	0	2 (1%)

Source: ADSL and ADAE Trial 1844

Across all four Phase 3 trials, there were no cases of Fanconi's syndrome and no discontinuation due to renal AEs.

Changes in Renal Laboratory Parameters

In the pooled naïve trials, increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48 (see Table 94). The median serum creatinine increased by 0.10 (0.03, 0.17) mg per dL, 0.11 (0.03, 0.18) mg per dL, and 0.11 (0.04, 0.19) mg per dL from baseline to Week 48 in the B/F/TAF, ABC/DTG/3TC, and DTG+FTC/TAF groups, respectively.

Table 94: Pooled analysis of Trial 1489 & 1490 for Creatinine changes at Week 4 and 48 from Baseline

	Treatment Arm		
	B/F/TAF (N=634)	ABC/DTG/3TC (N=315)	DTG/F/TAF (N=325)
Baseline			
N	634	315	325
Mean (SD)	0.924 (0.249)	0.915 (0.168)	0.894 (0.156)
Median	0.9	0.91	0.89
Q1, Q3	0.8, 1.01	0.81, 0.99	0.79, 1.0
Range (Min, Max)	0.4, 4.93	0.53, 2.09	0.51, 1.33
Change at Week 4 from Baseline (Completer Analysis)			
N	625	309	325
Mean (SD)	0.098 (0.210)	0.113 (0.098)	0.110 (0.125)
Median	0.1	0.11	0.11
Q1, Q3	0.04, 0.16	0.05, 0.17	0.03 0.18
Range (Min, Max)	-3.62, 2.64	-0.22, 0.46	-0.34, 1.09
Change at Week 48 from Baseline (Completer Analysis)			
N	580	301	306
Mean (SD)	0.104 (0.229)	0.108 (0.155)	0.120 (0.117)

Median	0.1	0.11	0.11
Q1, Q3	0.03, 0.17	0.03, 0.17	0.04, 0.19
Range (Min, Max)	-3.71, 5.54	-0.39, 1.85	-0.19, 0.47

Source: ADLB-1489 and 1490
Analysis completed by Wen Zeng, PhD

One subject on B/F/TAF developed markedly elevated creatinine while on treatment. Subject 1490-02140-2217 is a 32 yo diabetic AAM with baseline creatinine of 3.08 mg/dL who had an SAE of hyperkalemia nine months after starting study drug. In the investigator's opinion, the pre-existing conditions of HIV-1, diabetes and chronic kidney disorder were all possible etiological factors for the worsening of his renal function while on treatment. This subject also had hyperphosphatemia and metabolic acidosis. Since hypophosphatemia occurs with Fanconi's syndrome, hyperphosphatemia makes Fanconi's less likely.

Analyses of graded creatinine laboratory abnormalities across the Phase 3 trials are summarized in Table 95. Generally, the elevations in creatinine are Grade 1 in all treatment arms across the Phase 3 trials. In the pooled naïve trials the Grade 1 elevations were reported in 16 (3%), 5 (2%), and 14 (4%) subjects in the B/F/TAF, ABC/DTG/3TC and DTG+FTAF arms, respectively. In the virologically suppressed trials, the rates of Grade 1 elevations in creatinine were similar between the treatment arms.

Table 95: Graded Creatinine Postbaseline Elevations in the Phase 3 Trials

Creatinine mg/dL	Trials 1489 and 1490		
	B/F/TAF N=634	ABC/DTG/3TC N=315	DTG + F/TAF N=325
Grade 1 (>1.5 to 2 mg/dL)	16 (3%)	5 (2%)	14 (4%)
Grade 2 (2 to 3 mg/dL)	2 (<1%)	1 (<1%)	1 (<1%)
Grade 3 (3 to 6 mg/dL)	1 (<1%)	1 (<1%)	0
Grade 4 (>6 mg/dL)	1 (<1%)	0	0
	Trial 1844		
	B/F/TAF N=282	ABC/DTG/3TC N=281	
Grade 1	21 (7%)	13 (5%)	
Grade 2	0	1 (<1%)	
	Trial 1878		
	B/F/TAF N=290	SBR N=287	
Grade 1	8 (3%)	5 (2%)	

Source: ADLB Trials 1489, 1490, 1844, and 1878

In conclusion, the Applicant proposed labeling limited to describing changes in creatinine in the naïve trials and did not include the TAF-related renal Warnings and Precautions language or recommendations for monitoring in their proposed labeling. The Division has consulted the Cardiovascular and Renal Products under other Gilead-sponsored TAF-containing NDAs. Based

on the review of the available data, the Cardio-Renal consultant has recommended retaining the warning in TAF containing products. Consistency across labeling for TAF containing products is also recommended. The Warnings and Precautions for renal impairment and recommendations for monitoring are included in the labeling for Genvoya®, Descovy®, and Vemlidy® (all TAF containing drugs) and should be included in the B/F/TAF label. The review team has recommended inclusion of the Warnings and Precautions language, and the monitoring language in the B/F/TAF label to be consistent with the other TAF-containing products.

One advantage of B/F/TAF is that it provides an unboosted INSTI FDC treatment option for those with moderate renal impairment because it can be dosed in subjects with $eGFR_{CG} \geq 30$ ml/min. ABC/DTG/3TC FDC is limited to patients with eGFR ≥ 50 ml/min.

9.5.5 Bone Analysis

Low bone mineral density (BMD) occurs in HIV infected patients. Many factors, including HIV disease itself, host characteristics, and antiretroviral treatment contribute to osteopenia. TDF has been shown to have effects on bone metabolism and renal function in both animal models and in human clinical trials. The exact mechanisms underlying decreased bone mineral density from TDF are not fully understood but are thought to involve the renal effects of the active antiviral tenofovir diphosphate (TFV) and to be proportional to its systemic exposure. TDF has been associated with enhanced BMD decline and nonpathological fractures in HIV infected patients on TDF compared with other antiretrovirals. Associated with its 90% lower TFV systemic exposure, TAF is anticipated to have a more favorable bone toxicity profile. Bone safety data in trials with Genvoya® favored the TAF containing regimen (Genvoya®) over the TDF containing regimen (Stribild®).

Changes in bone mineral density (BMD) were a pre-specified safety endpoint when the comparator to B/F/TAF was ABC/DTG/3TC in Trials 1489 and 1844. Bone loss in HIV infected patients is greatest during the first two years of initiation of antiretroviral therapy by 2-6%.[7] Thus, it is expected that a higher percentage of bone loss may be observed in the treatment-naïve Trial 1489 compared to Trial 1844, in a treatment experienced population. This section describes the analyses including BMD changes and fractures.

<u>Bone Mineral Density</u>
In Trials 1489 and 1844, Dual Energy X-ray Absorptiometry (DXA) scans of lumbar spine and hip were performed on all subjects at screening, every 24 weeks, and at early discontinuation, if not done within the previous 12 weeks. Not all subjects in these trials had DXA scans. DXA measurements include BMD changes at the hip and the lumbar spine. Clinically significant BMD changes, as also defined by prior consults with DBRUP for other TDF and TAF containing regimens, include BMD changes of ≥7% of the femoral neck and ≥ 5% of the lumbar spine.

The Applicant's analyses of BMD were submitted to the FDA as the ADDXA dataset and the changes were replicated and with only minor, clinically insignificant differences from the Applicant's results. Differences in BMD between the arms were not statistically significant.

Mean percentage (SD) changes from baseline at Week 48 (SD) in BMD (Source: ADDXA dataset)

Trial 1489

- Femoral neck: B/F/TAF −0.77% (2.22%) vs. ABC/DTG/3TC −1.02% (2.31%)
- Spine: B/F/TAF −0.83% (3.20%) vs. ABC/DTG/3TC −0.60% (3.10%)

Trial 1844

- Femoral neck: B/F/TAF 0.16% (2.21%) vs. ABC/DTG/3TC 0.3% (2.11%)
- Spine: B/F/TAF 0.69% (3.13%) vs. ABC/DTG/3TC 0.42% (3.00%)

Subjects with clinically significant declines of ≥7% at the femoral neck and ≥5% at the lumbar spine from baseline to Week 48 (Source: ADDXA dataset) are summarized as follows:

BMD declines of ≥7% at the femoral neck

- 1489 B/F/TAF 6/257 subjects (2%), ABC/DTG/3TC 4/270 subjects (4%)
- 1844 B/F/TAF 3/229 subjects (1%), ABC/DTG/3TC 2/242 subjects (1%)

BMD declines of ≥5% at the lumbar spine

- 1489 B/F/TAF 28/267 subjects (11%) vs. ABC/DTG/3TC 18/274 subjects (7%)
- 1844 B/F/TAF 4/233 subjects (2%) vs. ABC/DTG/3TC 7/244 subjects (3%)

Fracture analyses

AEs of fractures were evaluated across the Phase 3 trials. Fractures were captured under the Injury, Poisoning, and Procedures SOC as 'Bone and Joint Fractures'. In general, no type of fracture AE occurred more than once in any individual trial and most were consistent with accidents and trauma; the events were not suggestive of bone pathology from treatment. There were no spine or hip fractures in the B/F/TAF arms.

Conclusions

Mean BMD changes and clinically significant changes in femoral neck and lumbar spine were comparable with ABC/DTG/3TC in Trials 1489 and 1844. Mean BMD declines were approximately 0.6-1.03% in the Trial 1489 among treatment naïve individuals. Mean BMD were increased 0.16-0.69% in Trial 1844 among HIV virologically suppressed individuals. The fracture patterns in all four phase 3 trials were not suggestive of fractures due to decreased BMD. The Applicant did not propose language to describe BMD changes in the USPI, based on the available data, the review team agreed that specific BMD data did not need to be included in the label. No new signals were identified in this analysis.

9.6 Safety Analyses by Demographic Subgroups

Safety analyses by gender and race were performed for safety events in key subgroups focusing on AEs by body system organ class and TEAEs by DDT. No specific pattern of concern was identified in the safety analyses by race, gender, and age.

9.7 Specific Safety Studies/Clinical Trials

Not Applicable

9.8 Additional Safety Explorations

9.8.1 Human Carcinogenicity or Tumor Development

B/F/TAF clinical trial findings do not indicate the potential for carcinogenicity. Most of the neoplasms in phase 2/3 clinical trials were benign cutaneous neoplasms, and all identified malignancies were reported as not related to study drug. There was no signal found in the nonclinical toxicology studies for the components of B/F/TAF. Two cases of Kaposi's Sarcoma, a malignancy related to HIV infection, occurred. One subject in Trial 1878 developed metastatic lung cancer and is described in Section 9.4.1 Deaths.

9.8.2 Pregnancy

No teratogenicity was observed in animal studies. Effects on male or female fertility, and parturition were not observed in animal reproductive and developmental toxicity studies. In rabbits, increased maternal developmental toxicities, including spontaneous abortion, increased clinical signs, and decreased body weight, occurred at approximately 1.4 times higher than human exposure of bictegravir.

Pregnant women were excluded from B/F/TAF clinical trials, and pregnancy was a pre-specified withdrawal criteria in these trials. At the time of NDA data cut-off, a total of 11 pregnancies were reported in subjects in the Phase 3 trials, and of these, six were in the B/F/TAF arm. Of the six that all discontinued therapy, there were three live healthy births, one outcome ongoing, one spontaneous abortion, and one intrauterine demise. In the safety update report, one new pregnancy on B/F/TAF in Trial 1844 was reported. Study drug was discontinued and the pregnancy was reported as uncomplicated and ongoing. No pregnancies occurred in the Phase 2 trial.

No adequate and well-controlled trials of bictegravir have been conducted in the pregnant population. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk.

9.8.3. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Limited clinical experience is available at doses higher than the therapeutic doses of BIC, FTC, or TAF. As BIC is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. Up to 30% of the FTC dose may be removed by hemodialysis. TFV is removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether FTC or TFV may be removed by peritoneal dialysis.

If an overdose with B/F/TAF occurs, the patient must be monitored for evidence of toxicity, and be provided with general supportive measures as necessary, including observation of the clinical status of the patient and monitoring of vital signs.

No safety issues concerning the abuse or misuse of B/F/TAF tablets are anticipated from the available data.

B/F/TAF labeling will contain a boxed warning regarding the potential for severe acute exacerbations of hepatitis B with discontinuation of B/F/TAF therapy in patients coinfected with HIV-1 and HBV, due to the anti-hepatitis B activity of the FTC and TAF components of B/F/TAF. Patients coinfected with HIV-1 and HBV who discontinue B/F/TAF should be closely monitored with both clinical- and laboratory-follow up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted with discontinuation of B/F/TAF.

9.9 Safety in the Postmarket Setting

9.9.1 Safety Concerns Identified Through Postmarket Experience

The FDC of B/F/TAF as a complete regimen is not available on the US market or in any foreign market; therefore, no previous postmarket information is available for this specific three drug complete regimen. Approved drugs for the treatment of HIV have included emtricitabine since 2003 and tenofovir alafenamide since 2015. Additionally, another prodrug of tenofovir, tenofovir disoproxil fumarate has been approved for the treatment of HIV since 2001. Identified safety concerns described in the emtricitabine and TAF labels are included in the proposed labeling for B/F/TAF.

9.9.2 Expectations on Safety in the Postmarket Setting

The safety of B/F/TAF is expected to be similar to the individual drug products and aligned with what was seen in the NDA application. Routine pharmacovigilance will be conducted to continue to monitor for unlabeled or unexpected adverse events.

9.10 Integrated Assessment of Safety

Bictegravir, the new molecular entity, demonstrates thus far, a generally comparable safety profile to other INSTIs. Approved components of the FDC with bictegravir include emtricitabine, FDA approved since 2003, and tenofovir alafenamide, FDA approved since 2015. There is robust clinical trial and post-marketing safety information for F/TAF.

The most common ADRs (≥ 2%) reported for B/F/TAF in the HIV-treatment naive Phase 3 trials were diarrhea, headache, nausea, nasopharyngitis, fatigue, dizziness, and insomnia. The rates of these ADRs were similar to the comparator groups except for nausea, which occurred more frequently with ABC/DTG/3TC. In the virologically suppressed Phase 3 trials, the ADRs were generally similar for subjects treated with B/F/TAF, except nausea was infrequently reported. Grade 3 or 4 laboratory abnormalities were generally comparable between B/F/TAF and the comparator arms with the exception of amylase elevations in Trial 1844. However, the amylase elevations in subjects taking B/F/TAF were transient and not associated with clinical pancreatitis.

Adverse events of special interest were evaluated based on the drug profile of bictegravir, experience with other INSTIs including hepatobiliary AEs, psychiatric AEs, and rash and hypersensitivity reactions, and known adverse reactions related to F/TAF including renal and bone safety. The most notable issues identified were mild to moderate increases in bilirubin and ALT laboratory parameters. Increases of Grade 1 and 2 bilirubin elevations were observed more frequently in the naïve treatment Trials 1489 and 1490, and increased Grade 1 ALT were seen in the trials in the virologically suppressed Trials 1844 and 1878. Both findings did not result in related SAEs or discontinuation of the study drug, and no subjects met Hy's Law criteria. Suicidal ideation, suicide attempt, and depression suicidal occurred in <1% of subjects administered B/F/TAF; all events were serious and primarily occurred in subjects with a preexisting history of depression, prior suicide attempt or psychiatric illness. Depression, suicidal ideation, suicide attempt and depression suicidal were recommended by the review team to be added to product labeling. Rashes were generally mild to moderate and occurred at <2% and no stigmata of hypersensitivity reaction, erythema multiforme, or Stevens Johnson Syndrome occurred.

Analyses of renal events and laboratory data did not reveal significant AEs, novel safety issues, or events of Fanconi's syndrome. However, tenofovir alafenamide is a prodrug of tenofovir, which has been associated with acute renal failure and Fanconi's syndrome and therefore, while the exposures of TAF are lower than tenofovir disoproxil fumarate, the risk of renal toxicity remains. Renal warnings, therefore, should be retained in the product labeling as they are in other TAF containing products. Analyses of bone related AEs and laboratory parameters showed no significant fragility fractures and BMD changes were comparable to ABC/DTG/3TC in both treatment naïve and virologically suppressed subjects.

10 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for this NDA because there are previously approved drugs in this ARV class, available safety data did not reveal issues that were unexpected for the class, and efficacy results from phase 3 trials did not pose specific concerns. No other external consultations were made for this NDA for the same reasons as specified above.

11 Pediatrics

No studies in the pediatric population have been submitted in the NDA application. A Proposed Pediatric Study Plan (PPSP) was submitted and reviewed by DAVP and the Pediatric Review Committee (PeRC). An agreed upon PSP dated May 31, 2016, proposes a program of formulation development, clinical pharmacology, and clinical trials. Final study reports will be submitted by March 2022.

Typically, the review process for HIV pediatric trials involves matching pediatric and adult pharmacokinetic data which in turn is used to extrapolate efficacy between adults and pediatric patients. We do this because we presume the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c).

Trial GS-US-380-1474, is being conducted first. The protocol and ICF have been reviewed by the Division. This is an open-label, multi-center study of the pharmacokinetics, safety, and antiviral activity of age-appropriate B/F/TAF formulations in HIV-1 infected virologically suppressed adolescents and children. PK parameters derived from adults and adolescents will inform dosing in younger pediatric patients from 6-12 years, who will be studied later.

(b) (4)

A deferral was requested for subjects 4 weeks to <18 years of age since it is dependent on staged PK information from the cohorts of Trials 1474 and (b) (4). A waiver was requested for pediatric subjects from birth to < 4 week of age studies are highly impractical (see Section 14 Postmarketing Requirements and Commitments for further discussion of the waiver).

(b) (4)

12 Labeling Recommendations

12.1 Prescribing Information

HIGHLIGHTS and TABLE OF CONTENTS were revised for consistency with the rest of the Prescribing Information.

BOXED WARNING
The following statement is removed from the boxed warning, (b) (4) (b) (4) (b) (4). Both emtricitabine and tenofovir alafenamide are treatment guidelines recommended drugs for the treatment of chronic HBV, and both are approved with established safety profiles for the treatment of HBV. While we are not providing an indication for HIV-1/HBV coinfection for B/F/TAF in Section 1 of the label, the statement in the proposed Boxed Warning is not consistent with current clinical practice and lessens the message regarding the potential for post-treatment acute exacerbation of HBV which is the reason for the Boxed Warning.

1 INDICATIONS AND USAGE
The indications statement was revised to: 1) add complete regimen, 2) replace (b) (4) with have no antiretroviral treatment history, and 3) further define the switch population to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with BIKTARVY
Renal testing language was added for consistency with other FDCs containing FTC and TAF.

2.4 Not Recommended in Patients with Severe Hepatic Impairment
This subsection was added with cross reference to subsections 8.7 and 12.3 for additional information, which is also consistent with other HIV labels with similar restrictions.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV
Specification was added that HBV testing should be done before or when initiating antiretroviral therapy. (b) (4) was deleted for consistency with edits made to the Boxed Warning.

The following subsection regarding the importance of certain drug interactions was added to W&P for consistency with other HIV FDCs:

5.2 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions
The concomitant use of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4) and Drug Interactions (7.5)]:*

- Loss of therapeutic effect of BIKTARVY and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during BIKTARVY therapy; review concomitant medications during BIKTARVY therapy; and monitor for the adverse reactions associated with the concomitant drugs.

The following subsection regarding renal impairment was added for consistency with other labels containing TAF:

5.4 New Onset or Worsening Renal Impairment
Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of BIKTARVY, there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). In clinical trials of BIKTARVY in subjects with no antiretroviral treatment history with eGFRs greater than 30 mL per minute, and in virologically suppressed subjects switched to BIKTARVY with eGFRs greater than 50 mL per minute, renal serious adverse events were encountered in less than 1% of subjects treated with BIKTARVY through Week 48 *[see Adverse Reactions (6.1)].* BIKTARVY is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus.

Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

6 ADVERSE REACTIONS

6.1 CLINICAL TRIALS EXPERIENCE

The safety results including adverse reactions and laboratory abnormalities for Trials 1489 and 1490 were displayed separately by treatment arm because the trials had different comparators [redacted] (b) (4) Suicidal ideations, suicidal attempt, and depression suicidal were observed in the trials in proportion similar to those observed in other INSTI labels therefore these events were added. Total bilirubin increases for the two comparator arms were added.

7 DRUG INTERACTIONS

7.1 Other Antiretroviral Medications

The following text was incorporated: "Comprehensive information regarding potential drug-drug interactions with other antiretroviral medications is not provided because the safety and efficacy of concomitant HIV-1 antiretroviral therapy is unknown." See Section 6.2.3. of the review for rationale.

7.2 Potential for BIKTARVY to Affect Other Drugs

The statement that BIKTARVY with [redacted] (b) (4) was removed. A clinical comment related to drug interaction with metformin was added to Table 3. Additional changes were made to provide more clinically relevant information in this section.

7.3 Potential Effect of Other Drugs on One or More Components of BIKTARVY

Section 7.4 Drugs Affecting Renal Function was added to describe the potential for increase in adverse reactions when BIKTARVY is co-administered with drugs that reduce renal function or compete for active tubular secretion.

7.5 Established and Potentially Significant Drug Interactions

- Drugs listed in the contraindication section were included in Table 3 per 21 CRF 201.57(c)(8)(i).
- All references to [redacted] (b) (4) were deleted to be consistent with Section 7.1.
- Clinical comment related to co-administration of BIKTARVY with medications or oral supplements containing polyvalent cations was revised. Please refer to Section 6.2.3 of this review for the rationale and final recommendations.

- Clinical comment related to co-administration of BIKTARVY with metformin was revised. Please refer to Section 6.2.3 of this review for the rationale and final recommendation.

7.6 Drugs without Clinically Significant Interactions with BIKTARVY

Drugs included in this section were only those for which the results of a drug-drug interaction study did not show a significant drug-drug interaction. See Section 6.2.3 of this review for the rationale.

8 USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Animal data showing developmental toxicities including spontaneous abortion, increased clinical signs and decreased body weight in rabbits at maternally toxic dose was added to the risk statement and animal data.

8.7 Hepatic Impairment

BIKTARVY is not recommended for use in patients with severe hepatic impairment was added.

10 OVERDOSAGE

Per regulation, overdosage information that did not communicate potential toxicities and compilations associated with an overdosage was deleted.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

For the ADME data displayed Table 4, measures of variability for all PK parameters were added. (b) (4) were removed. Under Drug Interaction Studies sub-section, in vitro information related to the effect of B or TAF on enzymes and transporters was incorporated. See Section 6.2.3 of this review for the rationale.

12.4 Microbiology

Antiviral Activity in Cell Culture

(b) (4) was removed (b) (4) (b) (4)

Resistance:

Under clinical trials in subjects with no antiretroviral treatment history, the following information was added:

Definition of the resistance analysis population;
Because genotypic resistance pathways for BIC have not been identified, clarification was made to the language regarding resistance development in treatment-failure subjects. The applicant proposed (b) (4) however, this was changed to "No specific amino acid substitutions emerged consistently in the 8 treatment failure subjects with evaluable genotypic resistance data and failed to establish an association with genotypic BIC resistance. There were no treatment-emergent NRTI resistance-associated substitutions detected in the 8 evaluated treatment failure isolates"; and phenotypic resistance analysis data of failure isolates.

Under *clinical trials in virologically suppressed subjects:* the resistance analysis results from the 2 switch trials were combined.

Cross-Resistance:
Bictegravir: cell-culture cross-resistance data were detailed to show the cross-resistance profile of BIC.

14 CLINICAL STUDIES

14.2 Clinical Trial Results in HIV-1 Subjects with No Antiretroviral Treatment History
Description and results of Trials 1489 and 1490 are displayed separately rather than pooled as the comparators were different in the two trials. (b) (4)

14.3 Clinical Trial Results in HIV-1 Virologically-Suppressed Subjects Who Switched to BIKTARVY
(b) (4) were removed for both Trials 1844 and 1878 as the treatment difference and CI are included in the efficacy table.

16 HOW SUPPLIED/STORAGE AND HANDLING
The strength of each of the components of BIKTARVY was added per 21 CFR 201.57(c)(17).

17 PATIENT COUNSELING INFORMATION
Counseling points for drug interactions and renal impairment were added for consistency with edits to the rest of the PI.

12.2 Patient Labeling

The patient labeling was edited for consistency with the rest of the PI and per the standards.

13 Risk Evaluation and Mitigation Strategies (REMS)

No identified safety issues warrant consideration of REMS.

14 Postmarketing Requirements and Commitments

The following are the three Postmarketing Requirement (PMR) studies proposed by the review team for B/F/TAF as required under the Pediatric Research Equity Act (PREA). These studies are deferred as per the timelines provided.

- Conduct a study in HIV-1 infected, treatment naïve patients at least 4 weeks and weighing 4 to 12 kg to assess the pharmacokinetics, safety and tolerability, and antiviral activity of bictegravir/emtricitabine/tenofovir alafenamide. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.

  Final Protocol Submission: 08/2019
  Study/Trial Completion: 02/2022
  Final Report Submission: 06/2022

- Conduct a study in patients 2 years to <18 years old who are HIV-1 infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of bictegravir/emtricitabine/tenofovir alafenamide as part of an fixed dose combination (FDC) product. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.

  Final Protocol Submission: 08/2018
  Study/Trial Completion: 12/2020
  Final Report Submission: 05/2021

- Conduct a study to evaluate bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in neonates (birth to less than 4 weeks of age) who are HIV-1 infected or exposed and at high risk of infection to identify the appropriate dose and establish the safety of B/F/TAF.

  Final Protocol Submission: 01/2021
  Study/Trial Completion: 02/2022
  Final Report Submission: 06/2022


(b) (4)

15 Appendices

15.1 References

1. Centers for Disease Control and Prevention, HIV/AIDS Statistics Overview, HIV Surveillance Report. Retrieved December 19, 2017, available at: https://www.cdc.gov/hiv/statistics/overview/index.html

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6. Polakos NK, Cornejo JC, Murray DA, Wright KO, Treanor JJ, Crispe IN, et al. Kupffer Cell-Dependent Hepatitis Occurs during Influenza Infection. Am J Pathol 2006; 168 (4):1169-78.

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15.2 Financial Disclosure

There were over 2500 investigators involved in the four pivotal studies, and 97 investigators received payments from the Applicant in excess of $25,000. Twenty-eight investigators had significant equity interest in the Applicant of >$50,000. Fifteen investigators had significant payments in excess of $25,000 and significant equity interests in excess of $50,000. Four investigators have compensation for the study where the value could be influenced by the

outcome of the study. In total, 114 investigators had disclosable financial interest(s). The total number of investigators with disclosable financial interest is 4% (114/2560).

Site-specific metrics provided by the Sponsor identified 41 sites with investigators and sub-investigators with disclosable financial interests. The majority of the sites with investigators and sub-investigators with disclosable financial interests enrolled (b) (4) or less of the subjects in the individual trials. Sites that enrolled more than (b) (4) include the following by trial number:

Trial 1489

- Site #698-PI Edwin DeJesus enrolled (b) (4) of the treated subjects
- Site #2106-PI Olayemi Osiyemi enrolled (b) (4) of the treated subjects

Trial 1490

- Site #698-PI Edwin DeJesus enrolled (b) (4) of the treated subjects

Trial 1844

- Site #1950- PI Moti Ramgopal enrolled (b) (4) of the treated subjects
- Site #2728-PI Anthony Mills enrolled (b) (4) of the treated subjects

Trial 1878

None

The Division selected Sites #698, #2106, and #2728 for inspections because of their high enrollment and having investigators or sub-investigators with disclosable financial interests.

The four investigators that had compensation for the study where the value could be influenced by the outcome of the study were all from one site (b) (4)

(b) (4)

This financial disclosure information is not likely to affect the overall results because each investigator enrolled (b) (4) or fewer subjects in each trial with the majority of the sites having investigators or sub-investigators with disclosable financial interests enrolling under (b) (4) of the subjects. The Division selected three of the four sites enrolling greater than (b) (4) of the subjects in the trials for investigation. There were no significant findings in the clinical trial site inspections. In addition, efficacy for the pursued HIV treatment indication relies on an objective endpoint, HIV viral load, based on laboratory results and not subjective investigator-based endpoints, thereby limiting the ability of investigators to influence the efficacy results. Lastly, any investigator related bias is unlikely to influence overall outcomes in three of the four trials that were double-blinded (Trials 1489, 1490, and 1844).

Covered Clinical Study (Name and/or Number): Trials 1489, 1490, 1844, and 1878

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2560		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 41		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 4 Significant payments of other sorts: 97 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 28		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15.3 Clinical Virology NGS Data Analysis Appendix

Overview

The sponsor performed next generation sequencing (NGS) analyses using the deepType HIV assay by Seq-IT (Kaiserslautern, Germany), which utilizes the Illumina MiSeq platform, to determine the baseline genotypes of the integrase (IN), protease (PR), and reverse transcriptase (RT) genes derived from the plasma viral RNA of HIV-1-infected subjects in clinical trials GS-US-380-1489 and GS-US-380-1490. No IN genotyping was conducted at screening in

the study, but baseline IN genotypic data were obtained retrospectively for 1267 of 1274 subjects. The baseline IN genotyping for 7 subjects was missing or failed primarily due to low viral load.

Baseline IN, PR and RT sequences were analyzed for the presence of previously identified resistance-associated substitution to study drugs consisting of TAF, FTC, ABC, 3TC, BIC, and DTG depending on the study design (Table 96). Detection of resistance substitutions to TAF, FTC, 3TC, or ABC excluded subjects from enrollment. HIV-1 genotyping of the PR/RT genes was conducted at screening using the GenoSure® MG assay (Monogram Biosciences) to assess for preexisting resistance as part of the enrollment criteria for all 1274 subjects in the FAS from Studies GS-US-380-1489 and GS-US-380-1490.

Table 96. Resistance-associated substitutions (Table 2, page 14, Integrated Virology Study Report).

Resistance Associated Substitutions[a]	
Mutation Groups	**Codon Mutations**
Primary Integrase Strand Transfer Inhibitor (INSTI) Resistance (-R) substitutions	T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI-R substitutions	M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A
Primary Nucleoside and Nucleotide Reverse Transcriptase Inhibitor (N(t)RTI)-R substitutions	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R
Thymidine Analogue Mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F, K219Q/N/E/R
Tenofovir (TFV) resistance associated substitutions	K65R/E/N, K70E
Emtricitabine (FTC) and lamivudine (3TC) resistance associated substitutions	M184V/I
Abacavir (ABC) resistance associated substitutions	K65R/E/N, K70E, L74V, Y115F, M184V/I
Secondary NRTI-R substitutions	E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, T215A/C/D/E/G/H/I/L/N/S/V[b]
Primary Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-R substitutions	L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230L/I
Secondary NNRTI-R substitutions	V90I, A98G, K101H, V106I, V179D/F/T
Primary Protease Inhibitor (PI)-R substitutions	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
Atazanavir (ATV) or Darunavir (DRV) resistance associated substitutions	I47V, I50L/V, I54M/L, L76V, I84V, N88S

a Adapted from the current IAS-USA list with some modifications {Wensing 2017}
b Reversion mutations at RT codon T215 including T215A/C/D/E/G/H/I/L/N/S/V have not been definitively shown to be associated with reduced response to either emtricitabine or tenofovir DF.

Methods

deepType HIV assay by Seq-IT used by GS. The sponsor reported that next generation sequencing was performed using the deepType HIV assay by Seq-IT (Kaiserslautern, Germany) employing the Illumina MiSeq platform. According to the sponsor, amplicons encoding subject-derived HIV-1 IN, PR, and/or RT coding sequences were processed by Seq-IT, which included

library preparation, multiplexing, and deep sequencing. The HIV-1 IN, PR, and RT NGS protocols utilized by Seq-IT were provided and were appropriate. The sponsor stated that NGS data were received from Seq-IT as a set of paired-end fastq files for each sample and these were generated by using only 100% matched barcodes to bin the reads. Software developed internally at Gilead was used to process and align sequencing data via a multi-step method (Table 97).

Table 97. **Overview of GS NGS analysis pipeline** (Table 1, page 5, NGS Description of Illumina MiSeq).

Step	Description
1	For HIV Integrase, assemble baseline sequence using VICUNA and enhance the assembly by aligning raw reads to the assembled sequence. For HIV Protease and Reverse Transcriptase, identify patient baseline population sequence.
2	Merge Paired-End FASTQ files using PEAR[a]
3	Split FASTQ files into FASTA and QUAL
4	Remove sequences based on low quality scores: starting from 5' end, look for score < 15 and remove 3' when found
5	Filter FASTA file for any sequences < 50 bp or without a corresponding quality sequence in QUAL file
6	Execute MOSAIK alignment tool on filtered reads, using the sample's baseline population sequence or the assembled sequence as the reference sequence
7	Conduct quality checks on aligned reads per criteria listed below: a. Read contains an 'N' in the sequence = Does Not Pass b. Average quality score of the read is < 30 = Does Not Pass
8	Correct reading frame from where first position of 5' end aligns with reference sequence
9	If insertions/deletions (indels) are detected and they produce a frame shift, the longest fragment between two indels will be kept If indel(s) don't produce a frame shift, they will be translated and aligned to an amino acid sequence to identify amino acid indels. Using the amino acid alignment, the nucleotide sequence is then inferred with the correct positioning of indels.
10	Use "sliding window" algorithm to exclude all bases within 15 bases of end of read in variant tabulation a. Sliding window not applied if base position within first 15 bases of 5' end of amplicon b. Sliding window not applied if base position within first 200 bases of 3' end of amplicon
11	Mutations and indels tabulated at the amino acid level: a. Only mutations with more than one hit included in the final analysis b. Insertions will be reported as a variant with additional nucleotides or amino acids (e.g. T69S.S) c. Deletions will be reported as a dash (e.g. T69-)

a. PEAR – Paired End Read Merger (http://sco.h-its.org/exelixis/web/software/pear/doc.html)

GS used a 15% frequency cutoff for calling resistance-associated substitutions (RAS) previously described and listed in Table 96.

MaxiHIVE used by FDA. Given that next generation sequencing is an emerging technology with no current standards for analysis, the division requested raw data in fastq format so that an independent analysis could be performed on the NGS data. For the independent analyses, an independent mapping of reads to the subtype B NL4-3 reference sequence (Accession: AF003887) was performed for each sample using an optimized NGS analysis pipeline in the High-Performance Integrative Virtual Environment (HIVE) using the maximum security credentials (MaxiHIVE) to ensure the security and confidentiality of the data being analyzed.

From the read mappings, variants were called and variant tables were generated for each nucleotide sequence using the built in variant caller in HIVE (Simonyan et al., 2017). The variant call tables were converted into amino acid frequency tables using the HIVE Viral Mutation Comparator tool. Below are descriptions of the variant caller and frequency table:

1. HIVE variant detector – calls variants from a read mapping using the Heptagon Sequence Profiler tool (Simonyan et al., 2017). Following alignment, the reference-based variant profile is computed by mapping nucleotides of short read sequences and counting occurrences of distinct bases at every genomic position on the reference. This variant-calling procedure produces consensus, per-base, forward/reverse, and total coverage maps for all reference segments of the specified reference genomes/sets. The frequencies of each variant call are then computed relative to the reference genome or relative to the accumulated consensus genome, depending on user specifications. Amino acids (AA) are called based on the contribution of every read and its alignment in relation to an annotated open reading frame (ORF). AA substitution calls are made from codon translations of individual reads, based on mapping to annotated open reading frames. This is to contrast the variant calling from a consensus based AA calling procedure.
2. Frequency tables – Tables were generated using the HIVE Viral Mutation Comparator tool. This table contains information for each position of each gene and each subject for which variation from the reference occurs. The frequency table contains the following columns: unique subject identifier (USUBJID), treatment regimen (ARM), visit (VISIT), the amino acid position within the gene of interest (AAPOS), total coverage at the nucleotide position (TCOV), the amino acid found in the reference sequence (AAREF), the amino acid substitution (AASUB), the coverage at the nucleotide level for the variant (VCOV), and the frequency by which the variant was detected (AAFREQ). Frequency tables are generated using the following criteria:
    a. The variant tables were combined by arm and gene
    b. The variant tables were filtered to remove synonymous substitutions (codon change encoding the same amino acid)
    c. The variant tables were reformatted to be directly comparable to the frequency tables submitted by the sponsor
    d. Any amino acid substitution ≥1% was presented in the table.

For the independent analyses, substitutions were called using a 10% frequency cutoff, consistent with DAVP guidelines. The results of the independent assessment were compared with those reported by the sponsor.

Comparison of results. The sponsor provided summary tables of primary and secondary RAS (listed in Table 96) for INSTI, RT (NNRTI and NRTI) and PI that was compiled from their NGS analyses of baseline samples collected from subjects infected with HIV-1 that were enrolled in clinical trials GS-US-380-1489 and GS-US-380-1490. DAVP generated frequency tables for each

study and each gene and then generated similar tables for comparison. Of note, the DAVP analysis was performed using a more stringent 10% cutoff compared to the 15% cutoff used by the sponsor. Therefore, some differences in results could be attributed to differences in frequencies used to make variant calls.

Results

The following RAS were analyzed by the sponsor and reported in two summary tables (, one for each clinical trial:

Integrase:

- Primary INSTI RAS: T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, and R263K
- Secondary INSTI RAS: M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, and E170A

Reverse Transcriptase:

- Primary NNRTI RAS: L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, and M230L/I
- Secondary NNRTI RAS: V90I, A98G, K101H, V106I, V179D/F/T
- Primary NRTI RAS: M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, and K219E/Q/N/R
- Secondary NRTI RAS: E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, and T215A/C/D/E/G/H/I/L/N/S/V

Protease:

- Primary PI RAS: D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M

Baseline Resistance Analysis for GS-US-380-1489

The sponsor summarized primary and secondary INSTI RAS, primary NNRTI and NRTI RAS and primary PI RAS for subjects infected with HIV-1 who enrolled in trial GS-US-380-1489 (Table 98).

Table 98. **GS-US-380-1489: Summary of IN, RT, and PR RAS detected pretreatment** (Table 8, page 28 and 29, Integrated Virology Study Report).

	Number of Subjects, n (%)		
Mutation Class[a]	B/F/TAF (N = 314)	ABC/DTG/3TC (N = 315)	All (N = 629)
Primary INSTI-R[b]	3 (1.0)	4 (1.3)	7 (1.1)
Average Number of Primary INSTI-R Mutations	1.0	1.0	1.0
T97A	2 (0.6)	4 (1.3)	6 (1.0)
Q148H	1 (0.3)	0	1 (0.2)
Secondary INSTI-R[b]	149 (47.5)	152 (48.4)	301 (47.9)
Average Number of Secondary INSTI-R Mutations	1.1	1.2	1.2
M50I	44 (14.0)	47 (15.0)	91 (14.5)
H51Y	0	1 (0.3)	1 (0.2)
L68V	0	2 (0.6)	2 (0.3)
V72T	2 (0.6)	1 (0.3)	3 (0.5)
L74M	1 (0.3)	5 (1.6)	6 (1.0)
Q95K	1 (0.3)	0	1 (0.2)
S119P/R/T	96 (30.6)	103 (32.8)	199 (31.7)
A128T	1 (0.3)	0	1 (0.2)
E138A/K	0	2 (0.6)	2 (0.3)
G140S	1 (0.3)	0	1 (0.2)
Q146R	1 (0.3)	0	1 (0.2)
S153A	2 (0.6)	1 (0.3)	3 (0.5)
E157K/Q	16 (5.1)	12 (3.8)	28 (4.5)
G163K/R	2 (0.6)	5 (1.6)	7 (1.1)

Primary NRTI-R	6 (1.9)	5 (1.6)	11 (1.7)
Average Number of Primary NRTI-R Mutations	1.0	1.0	1.0
Any TAM	6 (1.9)	4 (1.3)	10 (1.6)
M41L	2 (0.6)	2 (0.6)	4 (0.6)
K65R/E/N	0	0	0
D67N	1 (0.3)	1 (0.3)	2 (0.3)
K70R	1 (0.3)	0	1 (0.2)
Y115F	0	1 (0.3)	1 (0.2)
K219Q/R	2 (0.6)	1 (0.3)	3 (0.5)
Primary NNRTI-R	36 (11.5)	51 (16.2)	87 (13.8)
Average Number of Primary NNRTI-R Mutations	1.2	1.1	1.1
L100I	2 (0.6)	0	2 (0.3)
K101E	1 (0.3)	2 (0.6)	3 (0.5)
K103N/S	23 (7.3)	27 (8.6)	50 (7.9)
V106A	0	1 (0.3)	1 (0.2)
V108I	0	3 (1.0)	3 (0.5)
E138A/G/K/Q	7 (2.2)	16 (5.1)	23 (3.7)
Y181C	3 (1.0)	2 (0.6)	5 (0.8)
Y188L	1 (0.3)	2 (0.6)	3 (0.5)
G190A/S	3 (1.0)	1 (0.3)	4 (0.6)
H221Y	1 (0.3)	1 (0.3)	2 (0.3)
P225H	1 (0.3)	1 (0.3)	2 (0.3)
Primary PI-R	12 (3.8)	11 (3.5)	23 (3.7)
Average Number of Primary PI-R Mutations	1.3	1.0	1.1
D30N	1 (0.3)	1 (0.3)	2 (0.3)
V32I	1 (0.3)	0	1 (0.2)
M46I/L	4 (1.3)	3 (1.0)	7 (1.1)
I50L	1 (0.3)	0	1 (0.2)
Q58E	3 (1.0)	5 (1.6)	8 (1.3)
V82A	2 (0.6)	0	2 (0.3)
L90M	3 (1.0)	2 (0.6)	5 (0.8)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance; TAM = thymidine analogue mutation
a Drug resistance mutations are defined in Table 2.
b Denominator for the IN gene analyses are 314 B/F/TAF; 314 ABC/DTG/3TC; 628 All.
Source: GS-US-380-1489 Virology Listing 1 and Virology Listing 2

A similar analysis was performed by DAVP and comparable results for each viral target protein (IN, PR, and RT) were generated separately (see Table 99, Table 100,

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Table 101, Table 103, and Table 105). In addition, secondary RAS were summarized for NNRTI and NRTI (Table 102 and Table 104). The results of the primary INSTI RAS T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, and R263K are shown in Table 99.

Table 99. Primary INSTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1489 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=314)	ABC/DTG/3TC (n=315)	ALL (n=629)	
Primary INSTI-R	6	5	11	GS reported 7
T97A	4	4	8	1 subs <15% cutoff; HIVE missed 1 RAS
Y143C	1	0	1	not detected by GS, <15% cutoff
S147G	0	1	1	not detected by GS, <15% cutoff
Q148H	1	0	1	AGREE

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the secondary INSTI RAS M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, and E170A are shown in Table 100.

Table 100. Secondary INSTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1489 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=314)	ABC/DTG/3TC (n=315)	ALL (n=629)	
Secondary INSTI-R	**160**	**163**	**323**	GS reported 301; there were significant differences between GS and HIVE
M50I	49	47	96	GS reported: 44 and 47 RAS, respectively; 2 RAS <15% cutoff
H51Y	0	0	0	GS detected 1 RAS
L68I/V	2	3	5	GS reported 0 and 2 RAS, respectively; 1 RAS <15% cutoff
V72T	1	3	4	GS reported 2 and 1 RAS, respectively; 2 RAS <15% cutoff
L74M	1	3	4	GS reported 1 and 5 RAS, respectively
Q95K	1	0	1	AGREE
S119P/R/T	81	88	169	GS reported: 96 and 103 RAS, respectively
A128T	2	0	2	1 RAS <15% cutoff
E138K	0	1	1	HIVE missed one sub
G140S	1	0	1	AGREE
Q146R	1	1	2	differences in frequencies
S153A	2	1	3	HIVE missed 1 RAS
E157K/Q	17	11	28	GS reported 16 and 12 RAS, respectively; 2 RAS <15% cutoff
G163K/R	2	5	7	AGREE

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the primary NNRTI RAS L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, and M230L/I are shown in

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Table 101.

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Table 101. Primary NNRTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1489 (DAVP analysis).

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Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=314)	ABC/DTG/3TC (n=315)	ALL (n=629)	
Primary NNRTI-R	43	58	101	GS reported 87
L100I	2	0	2	AGREE
K101E	1	2	3	AGREE
K103N	24	28	52	GS missed 2 RAS
V106A	0	1	1	AGREE
V108I	1	5	6	2 <15% cutoff, GS missed 1 RAS
E138A/K/Q	7	16	23	AGREE
Y181C	3	2	5	AGREE
Y188L/C	2	2	4	GS missed 1 RAS
G190E/S/A	3	2	5	GS missed 1 RAS
H221Y	2	1	3	1 RAS <15% cutoff
P225H	0	1	1	AGREE

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the secondary NNRTI RAS V90I, A98G, K101H, V106I, V179D/F/T are shown in Table 102

Table 102. Secondary NNRTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1489 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=314)	ABC/DTG/3TC (n=315)	ALL (n=629)	
Secondary NNRTI-R	33	32	65	Not reported by GS
V90I	13	14	27	
A98G	1	1	2	
K101H	1	0	1	
V106I	10	9	19	
V179D/T	8	8	16	

The results of the primary NRTI RAS M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, and K219E/Q/N/R are shown in Table 103

Table 103. Primary NRTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1489 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=314)	ABC/DTG/3TC (n=315)	ALL (n=629)	
Primary NRTI-R	13	17	30	GS reported 11
M41L	2	2	4	AGREE
K65R/E/N	1	2	3	1 sub <15% cutoff; 2 RAS missed by GS
D67N	1	2	3	GS missed 1 RAS
T69S	5	4	9	no data reported by GS
K70R	1	1	2	1 RAS missed by GS
Y115F	0	0	0	<10% cutoff
M184I/V	0	2	2	no data reported by GS
K219Q/R/E	3	4	7	GS reported 2 and 1, respectively but did not report K219E

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the secondary NRTI RAS E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, and T215A/C/D/E/G/H/I/L/N/S/V are shown in Table 104.

Table 104. Secondary NRTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1489 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=314)	ABC/DTG/3TC (n=315)	ALL (n=629)	
Secondary NRTI-R	31	30	61	Not reported by GS
A62V	1	4	5	
T69N	3	3	6	
V75I	1	1	2	
F77L	1	0	1	
F116Y	0	1	1	
V118I	16	17	33	
T215S/C/A/D/I	9	4	13	

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the primary PI RAS D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M are shown in Table 105.

Table 105. Primary PI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1489 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=314)	ABC/DTG/3TC (n=315)	ALL (n=629)	
Primary PI-R	**15**	**16**	**31**	GS reported 23 RAS in total but the table was incorrect. It should have reported 26
D30N	1	2	3	GS missed one
V32I	1	1	2	1 RAS <15% cutoff
M46I/L	4	5	9	2 RAS <15% cutoff
I47V	0	1	1	Not detected by GS
I50L	1	0	1	AGREE
Q58E	3	5	8	AGREE
V82A	2	0	2	AGREE
L90M	3	2	5	AGREE

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

Overall, the independent analysis confirmed many of the RAS detected and reported by GS, but there were several disagreements. Some of the differences could be accounted for as differences in the frequencies used to call variants (10% for DAVP and 15% for GS); however, there were still several examples of substitutions that were missed by one or the other analysis.

Baseline Resistance Analysis for GS-US-380-1490

Similar analyses were performed by DAVP for trial GS-US-380-1490 and results for each viral target protein (IN, PR, RT) were generated separately (see Table 106, Table 107,

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Table 108, Table 110, and Table 112). In addition, secondary RAS were summarized for NNRTI and NRTI (Table 109 and Table 111). The results of the primary INSTI RAS T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, and R263K are shown in Table 106.

Table 106. Primary INSTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1490 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=320)	DTG/F/TAF (n=325)	ALL (n=645)	
Primary INSTI-R	5	5	10	GS reported 9 RAS
E92G	1	0	1	not detected by GS
T97A	4	5	9	1 RAS <15% cutoff; HIVE missed 1 RAS
Q148H	1	0	1	not detected by GS
R263K	0	1	1	not detected by GS

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the secondary INSTI RAS M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, and E170A are shown in Table 107.

Table 107. Secondary INSTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1490 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=320)	DTG/F/TAF (n=325)	ALL (n=645)	
Secondary INSTI-R	**178**	**157**	**335**	GS reported 334 RAS; there were significant differences between GS and HIVE
M50I	68	55	123	GS reported 80 and 60 RAS, respectively
H51Y	1	1	2	1 RAS <15% cutoff
L68I/V	5	2	7	3 RAS <15% cutoff; GS reported 4 and 2 RAS, respectively
V72T	0	3	3	HIVE missed 1 RAS
L74M	0	2	2	AGREE
S119P/R/T	82	75	157	GS reported 101 and 99 RAS, respectively
A128T	2	0	2	AGREE
E138K	0	2	2	HIVE missed 1 RAS
S153A	1	1	2	HIVE missed 1 RAS
E157K/Q	13	11	24	GS reported 19 and 12 RAS, respectively
G163K/R	6	5	11	3 RAS <15% cutoff

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the primary NNRTI RAS L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, and M230L/I are shown in

Table 108.

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Table 108. Primary NNRTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1490 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=320)	DTG/F/TAF (n=325)	ALL (n=645)	
Primary NNRTI-R	52	43	95	GS reported a total of 81 RAS
L100I	1	0	1	AGREE
K101E	4	0	4	AGREE
K103N/S	18	22	40	1 RAS <15% cutoff
V106A	0	0	0	GS reported 0 and 2 RAS, respectively
V108I	1	2	3	GS missed 1 RAS
E138A/K/Q/G	21	13	34	1 RAS <15% cutoff; GS missed 3 RAS
V179L	0	0	0	GS reported 0 and 1 RAS, respectively
Y181C	0	2	2	GS missed 1 RAS
Y188L/C	0	1	1	AGREE
G190E/Q/A	4	2	6	GS reported 2 and 3 RAS, respectively; 2 RAS were <15% cutoff
P225H	2	1	3	AGREE
M230I	1	0	1	AGREE

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the secondary NNRTI RAS V90I, A98G, K101H, V106I, V179D/F/T are shown in Table 109.

Table 109. Secondary NNRTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1490 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=320)	DTG/F/TAF (n=325)	ALL (n=645)	
Secondary NNRTI-R	25	28	53	Not reported by GS
V90I	12	11	23	
V106I	5	8	13	
V179D/T	8	9	17	

The results of the primary NRTI RAS M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, and K219E/Q/N/R are shown in Table 110.

Table 110. Primary NRTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1490 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=320)	DTG/F/TAF (n=325)	ALL (n=645)	
Primary NRTI-R	16	9	25	GS reported 15
M41L	1	1	2	HIVE missed 1 RAS
K65E	1	0	1	GS missed 1 RAS
D67N	2	2	4	1 RAS <15% cutoff; GS missed 1 RAS
T69S	1	3	4	Not reported by GS
K70R	3	1	4	1 RAS <15% cutoff; GS missed 1 RAS
L74V	1	0	1	AGREE
M184V	2	0	2	Not reported by GS; both RAS <15% cutoff
L210W	1	1	2	1 RAS <15% cutoff
K219Q/R/N	4	1	5	GS reported 7 and 2 RAS, respectively; HIVE missed 3 and 1 RAS, respectively

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

The results of the secondary NRTI RAS E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, and T215A/C/D/E/G/H/I/L/N/S/V are shown in Table 111.

Table 111. Secondary NRTI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1490 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=320)	DTG/F/TAF (n=325)	ALL (n=645)	
Secondary NRTI-R	37	40	77	Not reported by GS
E44D	0	2	2	
A62V	2	0	2	
T69N	7	3	10	
V75I	1	1	2	
F77L	1	0	1	
V118I	19	24	43	
T215S/C/A/D/I/E/G	7	10	17	

The results of the primary PI RAS D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M are shown in Table 112.

Table 112. Primary PI RAS identified at baseline in HIV-1 infected subjects enrolled in GS-US-380-1490 (DAVP analysis).

Substitution Class	Number of Subjects			Compared to GS
	B/F/TAF (n=314)	ABC/DTG/3TC (n=315)	ALL (n=629)	
Primary PI-R	**15**	**16**	**31**	GS reported 23 RAS in total but the table was incorrect. It should have reported 26
D30N	1	2	3	GS missed one
V32I	1	1	2	1 RAS <15% cutoff
M46I/L	4	5	9	2 RAS <15% cutoff
I47V	0	1	1	Not detected by GS
I50L	1	0	1	AGREE
Q58E	3	5	8	AGREE
V82A	2	0	2	AGREE
L90M	3	2	5	AGREE

GS, Gilead analysis; HIVE, DAVP analysis; RAS, resistance-associated substitution.

Overall, the independent analysis confirmed many of the RAS detected and reported by GS, but there were several disagreements. Some of the differences could be accounted for as differences in the frequencies used to call variants (10% for DAVP and 15% for GS); however, there were still several examples of substitutions that were missed by one or the other analysis.

When comparing treatment-emergent RAS, a third analysis platform is used by DAVP to reanalyze positions where disagreements occurred. Given that there were only baseline sequences available and there were a limited number of treatment failures in these two studies, a third algorithm was not used to resolve disagreements. Instead, DAVP compared the

RAS detected at baseline for subjects in the resistance analysis population (as determined by virology review Sung Rhee, Ph.D.) to see if any major differences occurred for these subjects (Table 113).

Table 113. Comparison of NGS data results for the resistance analysis population from clinical trials 1489 and 1490 (DAVP Analysis).

Trial	Subject ID	Treatment	INSTI		NNRTI		NRTI		PI		Compare
			GS	HIVE	GS	HIVE	GS	HIVE	GS	HIVE	
1489	00729-1609	B/F/TAF									AGREE
	01598-1106	ABC/DTG/3TC	S119P	S119P							AGREE
	02825-1085	ABC/DTG/3TC	S119T	S119T							AGREE
	02838-1390	ABC/DTG/3TC									AGREE
1490	00031-2093	B/F/TAF									AGREE
	01543-2111	B/F/TAF	S119P	S119P	V179D	N/D					V179D not detected by HIVE
	01624-2140	B/F/TAF									AGREE
	01624-2534	B/F/TAF	N/D	S119P (99%)							S119P not detected by GS
	02035-2333	B/F/TAF	N/D N/D	S119P (100%) E157K (51%)							S119P and E157K not detected by GS
	02511-2326	B/F/TAF	V72T/I S119P	V72T/I S119P							AGREE
	11678-2182	B/F/TAF									AGREE
	00031-2272	DTG+F/TAF	M50I	M50I	K103N	K103N	N/D	T69S (100%)			T69S not detected by GS
	00310-2435	DTG+F/TAF	M50I E157K	M50I E157K			T69D	T69D			AGREE
	00310-2556	DTG+F/TAF									AGREE
	01942-2507	DTG+F/TAF									AGREE
	02106-2037	DTG+F/TAF									AGREE

GS, analyses results from Seq-IT reported by the sponsor; HIVE, analyses results reported by Clinical Virology; Blue, subjects treated with B/F/TAF; N/D, not detected; %, frequency by which a substitution was detected with HIVE.

Differences observed between the DAVP and GS analyses were limited to 4 RAS (V179D, S119P (n=2), E157K, and T69S) in the resistance analysis population, and all of these occurred in subjects who failed treatment in clinical trial GS-US-380-1490 (1 from the DTG+F/TAF arm and 3 from the B/F/TAF arm) (Table 113). Given that all four of these baseline RAS were observed in the HIV-1 from multiple subjects from both clinical trials and most of these subjects were successfully treated, it is unlikely that the differences reported by the two analysis platforms would impact the overall resistance assessment for B/F/TAF.

Conclusion

For the independent analyses, Clinical Virology used Maxi-HIVE to align all of the fastq sequences in clinical trials GS-US-380-1489 and GS-US-380-1490 to the appropriate IN, PR, or RT gene, using the NL3-4 HIV-1 reference genome, and to call variants and generate frequency tables. For the independent analysis, Clinical Virology used the SUBS10 criteria, which used a ≥10% frequency cutoff to define substitutions. Overall, there was general agreement between the results reported by the sponsor and those determined by DAVP but there were several substitutions that were reported by one and not the other analyses platform. The variation that was observed was not completely explained by the differences in frequencies used to call substitutions. A comparison of baseline resistance-associated substitutions identified by each

method for subjects in the Clinical Virology resistance analysis population was performed to see if the incongruence in the variant calls at baseline could determine potential baseline resistance-associated substitutions against B/F/TAF. The results of this comparison indicated that there were no major known resistance-associated substitutions missed by either method and that the resulting differences were not likely to impact overall resistance conclusions.

15.4 OB Appendices (Technical documents supporting OB recommendations)

Table 114: Demographic and Baseline characteristics of Trial 1489 (FAS)

Category	B/F/TAF	ABC/DTG/3TC	Total
Treated (FAS)			
N	314	315	629
Gender			
F	29(9.2%)	33(10.5%)	62(9.9%)
M	285(90.8%)	282(89.5%)	567(90.1%)
Race Category			
WHITE	180(57.3%)	179(56.8%)	359(57.1%)
BLACK OR AFRICAN AMERICAN	114(36.3%)	112(35.6%)	226(35.9%)
ASIAN	6(1.9%)	10(3.2%)	16(2.5%)
AMERICAN INDIAN OR ALASKA NATIVE	2(0.6%)	4(1.3%)	6(1.0%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDS	1(0.3%)	2(0.6%)	3(0.5%)
NOT PERMITTED	2(0.6%)	.(. %)	2(0.3%)
OTHER	9(2.9%)	8(2.5%)	17(2.7%)
Ethnicity			
HISPANIC OR LATINO	72(22.9%)	65(20.6%)	137(21.8%)
NOT HISPANIC / LATINO	240(76.4%)	249(79.0%)	489(77.7%)
NOT PERMITTED	2(0.6%)	1(0.3%)	3(0.5%)
Age (Year)			
Mean (SE)	34.12 (0.615)	34.34 (0.609)	34.23 (0.433)
Median	31.00	32.00	32.00
Range	(18.00, 71.00)	(18.00, 68.00)	(18.00, 71.00)
STD	10.90	10.82	10.85
Age Category 1 (35yrs)			
<=32	200(63.7%)	194(61.6%)	394(62.6%)
>32	114(36.3%)	121(38.4%)	235(37.4%)
Age Category 2 (65yrs)			

<65	312(99.4%)	313(99.4%)	625(99.4%)
>=65	2(0.6%)	2(0.6%)	4(0.6%)
Baseline Weight (kg)			
Mean (SE)	80.10 (0.997)	80.27 (1.037)	80.18 (0.719)
Median	77.15	78.00	77.40
Range	(43.00, 146.5)	(43.60, 194.7)	(43.00, 194.7)
STD	17.66	18.41	18.03
Baseline Height (cm)			
Mean (SE)	175.6 (0.459)	175.2 (0.494)	175.4 (0.337)
Median	175.3	175.3	175.3
Range	(150.0, 203.2)	(149.9, 196.0)	(149.9, 203.2)
STD	8.138	8.773	8.458
Baseline BMI (kg/m^2)			
Mean (SE)	25.94 (0.301)	26.14 (0.323)	26.04 (0.221)
Median	25.09	24.87	25.01
Range	(15.78, 46.47)	(15.52, 64.31)	(15.52, 64.31)
STD	5.331	5.730	5.531
Baseline BMI Category 1 (kg/m^2)			
<=25	153(48.7%)	160(50.8%)	313(49.8%)
25<=, <30	103(32.8%)	94(29.8%)	197(31.3%)
>=30	58(18.5%)	61(19.4%)	119(18.9%)
Baseline BMI Category 2 (kg/m^2)			
<=18.5	13(4.1%)	8(2.5%)	21(3.3%)
18.5<=,<25	140(44.6%)	152(48.3%)	292(46.4%)
25<=, <30	103(32.8%)	94(29.8%)	197(31.3%)
30<=, <35	40(12.7%)	39(12.4%)	79(12.6%)
>=35	18(5.7%)	22(7.0%)	40(6.4%)
Region1			
Ex-US	86(27.4%)	82(26.0%)	168(26.7%)
US	228(72.6%)	233(74.0%)	461(73.3%)
Country			
BEL	4(1.3%)	2(0.6%)	6(1.0%)
CAN	18(5.7%)	15(4.8%)	33(5.2%)
DEU	4(1.3%)	9(2.9%)	13(2.1%)
DOM	2(0.6%)	1(0.3%)	3(0.5%)
ESP	20(6.4%)	23(7.3%)	43(6.8%)
FRA	11(3.5%)	10(3.2%)	21(3.3%)
GBR	20(6.4%)	11(3.5%)	31(4.9%)
ITA	7(2.2%)	11(3.5%)	18(2.9%)
USA	228(72.6%)	233(74.0%)	461(73.3%)
Screening HIV RNA log10 (copies/mL)			
Mean (SE)	4.43 (0.038)	4.48 (0.037)	4.46 (0.027)
Median	4.47	4.55	4.51
Range	(2.70, 6.34)	(2.76, 6.50)	(2.70, 6.50)

STD	0.680	0.655	0.667
Screening HIV RNA Category (copies/mL)			
<=100K	257(81.8%)	257(81.6%)	514(81.7%)
100K<, <=400K	43(13.7%)	42(13.3%)	85(13.5%)
400K<	13(4.1%)	15(4.8%)	28(4.5%)
missing	1(0.3%)	1(0.3%)	2(0.3%)
Baseline HIV RNA log10 (copies/mL)			
Mean (SE)	4.41 (0.036)	4.42 (0.039)	4.42 (0.027)
Median	4.42	4.51	4.47
Range	(2.23, 6.52)	(1.28, 6.19)	(1.28, 6.52)
STD	0.647	0.685	0.665
Baseline HCV RNA Category (IU/mL)			
<=100K	261(83.1%)	265(84.1%)	526(83.6%)
100K<, <=400K	45(14.3%)	38(12.1%)	83(13.2%)
400K<	8(2.5%)	12(3.8%)	20(3.2%)
Screening CD4 Count (/uL)			
Mean (SE)	455.6 (12.46)	478.6 (12.68)	467.1 (8.892)
Median	435.0	471.0	457.0
Range	(3.00, 1374)	(9.00, 1125)	(3.00, 1374)
STD	220.4	225.0	222.8
Screening CD4 Category (/uL)			
<50	7(2.2%)	7(2.2%)	14(2.2%)
50<=, <200	25(8.0%)	23(7.3%)	48(7.6%)
200<=	281(89.5%)	285(90.5%)	566(90.0%)
missing	1(0.3%)	.(. %)	1(0.2%)
Baseline CD4 Count (/uL)			
Mean (SE)	452.8 (12.46)	475.8 (13.04)	464.3 (9.021)
Median	443.0	450.0	444.0
Range	(0.00, 1424)	(2.00, 1332)	(0.00, 1424)
STD	220.8	231.4	226.3
Baseline CD4 Category (/uL)			
<50	7(2.2%)	10(3.2%)	17(2.7%)
50<=, <200	29(9.2%)	22(7.0%)	51(8.1%)
200<=, <350	69(22.0%)	58(18.4%)	127(20.2%)
350<=, <500	87(27.7%)	91(28.9%)	178(28.3%)
500<=	122(38.9%)	134(42.5%)	256(40.7%)
HIV Disease Status			
Asymptomatic	286(91.1%)	286(90.8%)	572(90.9%)
Symptomatic HIV I	16(5.1%)	14(4.4%)	30(4.8%)
AIDS	12(3.8%)	15(4.8%)	27(4.3%)
Baseline eGFR (CG) (mL/min)			
Mean (SE)	131.0 (2.226)	128.8 (1.877)	129.9 (1.455)
Median	125.9	123.0	124.8
Range	(25.00, 376.4)	(52.40, 296.2)	(25.00, 376.4)

STD	39.44	33.32	36.49
Cardiovascular Disease at Baseline			
N	307(97.8%)	306(97.1%)	613(97.5%)
Y	7(2.2%)	9(2.9%)	16(2.5%)
Diabetes Mellitus at Baseline			
N	295(93.9%)	306(97.1%)	601(95.5%)
Y	19(6.1%)	9(2.9%)	28(4.5%)
Hypertension at Baseline			
N	279(88.9%)	274(87.0%)	553(87.9%)
Y	35(11.1%)	41(13.0%)	76(12.1%)
Hyperlipidemia at Baseline			
N	270(86.0%)	281(89.2%)	551(87.6%)
Y	44(14.0%)	34(10.8%)	78(12.4%)

Source: statistical reviewer's analysis

Table 115: Demographic and Baseline characteristics of Trial 1490 (FAS)

Category	B/F/TAF	DTG/F/TAF	Total
Randomized & Treated (FAS)			
N	320	325	645
Gender			
F	40(12.5%)	37(11.4%)	77(11.9%)
M	280(87.5%)	288(88.6%)	568(88.1%)
Race Category			
WHITE	183(57.2%)	195(60.0%)	378(58.6%)
BLACK OR AFRICAN AMERICAN	97(30.3%)	100(30.8%)	197(30.5%)
ASIAN	7(2.2%)	10(3.1%)	17(2.6%)
AMERICAN INDIAN OR OTHER ALAKSA NATIVE	1(0.3%)	1(0.3%)	2(0.3%)
NATIVE HAWAIIAN OR PACIFIC ISLANDS	1(0.3%)	.(. %)	1(0.2%)
OTHER	31(9.7%)	19(5.8%)	50(7.8%)
Ethnicity			
HISPANIC OR LATINO	83(25.9%)	81(24.9%)	164(25.4%)
NOT HISPANIC / LATINO	237(74.1%)	244(75.1%)	481(74.6%)
Age (Year)			
Mean (SE)	36.55 (0.688)	36.86 (0.642)	36.70 (0.470)
Median	33.00	34.00	34.00
Range	(18.00, 71.00)	(18.00, 77.00)	(18.00, 77.00)
STD	12.31	11.58	11.94

Age Category 1 (35yrs)			
<=32	177(55.3%)	170(52.3%)	347(53.8%)
>32	143(44.7%)	155(47.7%)	298(46.2%)
Age Category 2 (65yrs)			
<65	317(99.1%)	323(99.4%)	640(99.2%)
>=65	3(0.9%)	2(0.6%)	5(0.8%)
Baseline Weight (kg)			
Mean (SE)	79.09 (0.981)	80.32 (1.147)	79.71 (0.755)
Median	75.80	76.20	76.00
Range	(43.50, 144.8)	(46.20, 206.3)	(43.50, 206.3)
STD	17.54	20.68	19.18
Baseline Height (cm)			
Mean (SE)	175.0 (0.497)	175.0 (0.444)	175.0 (0.333)
Median	175.3	175.3	175.3
Range	(147.3, 198.1)	(152.4, 198.1)	(147.3, 198.1)
STD	8.892	8.011	8.453
Baseline BMI (kg/m^2)			
Mean (SE)	25.78 (0.281)	26.17 (0.347)	25.98 (0.224)
Median	25.04	24.63	24.84
Range	(16.45, 42.13)	(15.67, 61.67)	(15.67, 61.67)
STD	5.034	6.249	5.678
Baseline BMI Category 1 (kg/m^2)			
<=25	158(49.4%)	174(53.5%)	332(51.5%)
25<=, <30	101(31.6%)	87(26.8%)	188(29.1%)
>=30	61(19.1%)	64(19.7%)	125(19.4%)
Baseline BMI Category 2 (kg/m^2)			
<=18.5	10(3.1%)	5(1.5%)	15(2.3%)
18.5<=,<25	148(46.3%)	169(52.0%)	317(49.1%)
25<=, <30	101(31.6%)	87(26.8%)	188(29.1%)
30<=, <35	43(13.4%)	35(10.8%)	78(12.1%)
>=35	18(5.6%)	29(8.9%)	47(7.3%)
Region1			
Ex-US	127(39.7%)	132(40.6%)	259(40.2%)
US	193(60.3%)	193(59.4%)	386(59.8%)
Country			
AUS	4(1.3%)	10(3.1%)	14(2.2%)
BEL	4(1.3%)	4(1.2%)	8(1.2%)
CAN	12(3.8%)	9(2.8%)	21(3.3%)
DEU	20(6.3%)	28(8.6%)	48(7.4%)
DOM	27(8.4%)	18(5.5%)	45(7.0%)
ESP	17(5.3%)	17(5.2%)	34(5.3%)
FRA	7(2.2%)	5(1.5%)	12(1.9%)
GBR	21(6.6%)	23(7.1%)	44(6.8%)
ITA	15(4.7%)	18(5.5%)	33(5.1%)

USA	193(60.3%)	193(59.4%)	386(59.8%)
Screening HIV RNA log10 (copies/mL)			
Mean (SE)	4.43 (0.041)	4.46 (0.038)	4.45 (0.028)
Median	4.49	4.50	4.49
Range	(2.71, 6.93)	(2.71, 6.29)	(2.71, 6.93)
STD	0.725	0.679	0.702
Screening HIV RNA Category (copies/mL)			
<=100K	261(81.6%)	260(80.0%)	521(80.8%)
100K<, <=400K	46(14.4%)	52(16.0%)	98(15.2%)
400K<	13(4.1%)	12(3.7%)	25(3.9%)
missing	.(. %)	1(0.3%)	1(0.2%)
Baseline HIV RNA log10 (copies/mL)			
Mean (SE)	4.39 (0.041)	4.42 (0.037)	4.41 (0.028)
Median	4.43	4.45	4.44
Range	(2.29, 6.58)	(2.76, 6.15)	(2.29, 6.58)
STD	0.730	0.669	0.700
Baseline HCV RNA Category (IU/mL)			
<=100K	254(79.4%)	271(83.4%)	525(81.4%)
100K<, <=400K	54(16.9%)	41(12.6%)	95(14.7%)
400K<	12(3.8%)	13(4.0%)	25(3.9%)
Screening CD4 Count (/uL)			
Mean (SE)	451.1 (13.42)	460.9 (13.27)	456.0 (9.429)
Median	433.0	441.0	437.0
Range	(6.00, 1434)	(2.00, 1317)	(2.00, 1434)
STD	239.7	239.2	239.3
Screening CD4 Category (/uL)			
<50	11(3.4%)	11(3.4%)	22(3.4%)
50<=, <200	32(10.0%)	31(9.5%)	63(9.8%)
200<=	276(86.3%)	283(87.1%)	559(86.7%)
missing	1(0.3%)	.(. %)	1(0.2%)
Baseline CD4 Count (/uL)			
Mean (SE)	457.2 (14.27)	454.4 (12.84)	455.8 (9.585)
Median	440.0	441.0	440.0
Range	(2.00, 1636)	(3.00, 1458)	(2.00, 1636)
STD	255.3	231.5	243.4
Baseline CD4 Category (/uL)			
<50	15(4.7%)	13(4.0%)	28(4.3%)
50<=, <200	29(9.1%)	21(6.5%)	50(7.8%)
200<=, <350	67(20.9%)	77(23.7%)	144(22.3%)
350<=, <500	91(28.4%)	94(28.9%)	185(28.7%)
500<=	118(36.9%)	120(36.9%)	238(36.9%)
HIV Disease Status			
Asymptomatic	286(89.4%)	288(88.6%)	574(89.0%)
Symptomatic HIV I	10(3.1%)	11(3.4%)	21(3.3%)

AIDS	24(7.5%)	26(8.0%)	50(7.8%)
Baseline eGFR (CG) (mL/min)			
Mean (SE)	122.8 (1.766)	129.2 (2.251)	126.0 (1.437)
Median	120.4	120.6	120.6
Range	(50.00, 241.1)	(51.00, 370.7)	(50.00, 370.7)
STD	31.59	40.57	36.50
Cardiovascular Disease at Baseline			
N	311(97.2%)	319(98.2%)	630(97.7%)
Y	9(2.8%)	6(1.8%)	15(2.3%)
Diabetes Mellitus at Baseline			
N	298(93.1%)	303(93.2%)	601(93.2%)
Y	22(6.9%)	22(6.8%)	44(6.8%)
Hypertension at Baseline			
N	261(81.6%)	263(80.9%)	524(81.2%)
Y	59(18.4%)	62(19.1%)	121(18.8%)
Hyperlipidemia at Baseline			
N	275(85.9%)	281(86.5%)	556(86.2%)
Y	45(14.1%)	44(13.5%)	89(13.8%)

Source: statistical reviewer's analysis

Table 116: Demographic and Baseline characteristics of Trial 1844 (FAS)

Category	B/F/TAF	ABC/DTG/3TC	Total
Treated (FAS)			
N	282	281	563
Gender			
F	35(12.4%)	29(10.3%)	64(11.4%)
M	247(87.6%)	252(89.7%)	499(88.6%)
Race Category			
WHITE	206(73.0%)	202(71.9%)	408(72.5%)
BLACK OR AFRICAN AMERICAN	59(20.9%)	62(22.1%)	121(21.5%)
ASIAN	9(3.2%)	9(3.2%)	18(3.2%)
AMERICAN INDIAN OR ALASKA NATIVE	2(0.7%)	2(0.7%)	4(0.7%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDS	3(1.1%)	(%)	3(0.5%)
NOT PERMITTED	(%)	3(1.1%)	3(0.5%)
OTHER	3(1.1%)	3(1.1%)	6(1.1%)
Ethnicity			
HISPANIC OR LATINO	46(16.3%)	52(18.5%)	98(17.4%)

NOT HISPANIC & LATINO	236(83.7%)	227(80.8%)	463(82.2%)
NOT PERMITTED	(%)	2(0.7%)	2(0.4%)
Age (Year)			
Mean (SE)	45.84 (0.662)	44.93 (0.684)	45.39 (0.476)
Median	47.00	45.00	46.00
Range	(21.00, 71.00)	(20.00, 70.00)	(20.00, 71.00)
STD	11.12	11.47	11.30
Age Category 1 (46yrs)			
<=46	137(48.6%)	147(52.3%)	284(50.4%)
>46	145(51.4%)	134(47.7%)	279(49.6%)
Age Category 2 (65yrs)			
<65	268(95.0%)	271(96.4%)	539(95.7%)
>=65	14(5.0%)	10(3.6%)	24(4.3%)
Baseline Weight (kg)			
Mean (SE)	83.71 (1.103)	83.76 (1.091)	83.74 (0.775)
Median	80.35	80.10	80.20
Range	(44.90, 208.7)	(48.50, 160.2)	(44.90, 208.7)
STD	18.52	18.29	18.39
Baseline Height (cm)			
Mean (SE)	175.0 (0.463)	175.6 (0.519)	175.3 (0.348)
Median	175.3	176.0	175.3
Range	(149.9, 195.6)	(147.3, 197.4)	(147.3, 197.4)
STD	7.781	8.701	8.251
Baseline BMI (kg/m^2)			
Mean (SE)	27.32 (0.350)	27.10 (0.313)	27.21 (0.235)
Median	26.34	25.89	26.09
Range	(16.50, 69.57)	(16.94, 48.71)	(16.50, 69.57)
STD	5.873	5.253	5.568
Baseline BMI Category 1 (kg/m^2)			
<=25	109(38.7%)	112(39.9%)	221(39.3%)
25<=, <30	113(40.1%)	111(39.5%)	224(39.8%)
>=30	60(21.3%)	58(20.6%)	118(21.0%)
Baseline BMI Category 2 (kg/m^2)			
<=18.5	2(0.7%)	5(1.8%)	7(1.2%)
18.5<=,<25	105(37.2%)	107(38.1%)	212(37.7%)
25<=, <30	115(40.8%)	111(39.5%)	226(40.1%)
30<=, <35	31(11.0%)	35(12.5%)	66(11.7%)
>=35	29(10.3%)	23(8.2%)	52(9.2%)
Region1			
US	203(72.0%)	198(70.5%)	401(71.2%)
Ex-US	79(28.0%)	83(29.5%)	162(28.8%)
Country			
AUS	9(3.2%)	6(2.1%)	15(2.7%)

BEL	1(0.4%)	1(0.4%)	2(0.4%)
CAN	13(4.6%)	22(7.8%)	35(6.2%)
DEU	17(6.0%)	11(3.9%)	28(5.0%)
ESP	31(11.0%)	31(11.0%)	62(11.0%)
FRA	4(1.4%)	8(2.8%)	12(2.1%)
GBR	3(1.1%)	3(1.1%)	6(1.1%)
ITA	1(0.4%)	1(0.4%)	2(0.4%)
USA	203(72.0%)	198(70.5%)	401(71.2%)
Baseline HIV-1 RNA Category (IU/mL)			
<50	278(98.6%)	272(96.8%)	550(97.7%)
>=50	4(1.4%)	9(3.2%)	13(2.3%)
Baseline CD4 Count (/uL)			
Mean (SE)	751.8 (18.00)	693.9 (17.39)	722.9 (12.56)
Median	732.0	661.0	695.0
Range	(124.0, 2444)	(125.0, 1570)	(124.0, 2444)
STD	302.2	291.6	298.1
Baseline CD4 Category (/uL)			
50<=, <200	6(2.1%)	4(1.4%)	10(1.8%)
200<=, <350	16(5.7%)	30(10.7%)	46(8.2%)
350<=, <500	33(11.7%)	42(14.9%)	75(13.3%)
500<=	227(80.5%)	205(73.0%)	432(76.7%)
HIV Disease Status			
Asymptomatic	243(86.2%)	245(87.2%)	488(86.7%)
AIDS	30(10.6%)	27(9.6%)	57(10.1%)
Symptomatic HIV I	9(3.2%)	9(3.2%)	18(3.2%)
Baseline eGFR (CG) (mL/min)			
Mean (SE)	104.3 (1.915)	104.9 (1.836)	104.6 (1.325)
Median	100.5	100.7	100.7
Range	(49.90, 319.0)	(52.50, 283.1)	(49.90, 319.0)
STD	32.16	30.78	31.45
Smoking Status at Baseline			
Current Smoker	82(29.1%)	66(23.5%)	148(26.3%)
Former Smoker	58(20.6%)	57(20.3%)	115(20.4%)
Never Smoker	142(50.4%)	158(56.2%)	300(53.3%)
Cardiovascular Disease at Baseline			
N	272(96.5%)	276(98.2%)	548(97.3%)
Y	10(3.5%)	5(1.8%)	15(2.7%)
Diabetes Mellitus at Baseline			
N	260(92.2%)	260(92.5%)	520(92.4%)
Y	22(7.8%)	21(7.5%)	43(7.6%)
Hypertension at Baseline			
N	200(70.9%)	210(74.7%)	410(72.8%)
Y	82(29.1%)	71(25.3%)	153(27.2%)
Hyperlipidemia at Baseline			

N	176(62.4%)	191(68.0%)	367(65.2%)
Y	106(37.6%)	90(32.0%)	196(34.8%)
HIV/HBV Coinfection Status at Baseline			
N	282(100.0%)	281(100.0%)	563(100.0%)
HIV/HCV Coinfection Status at Baseline			
N	282(100.0%)	280(99.6%)	562(99.8%)
Y	(%)	1(0.4%)	1(0.2%)

Source: statistical reviewer's analysis

Table 117: Demographic and Baseline characteristics of Trial 1878 (FAS)

Category	B/F/TAF	SBR	Total
Treated (FAS)			
N	290	287	577
Gender			
F	47(16.2%)	53(18.5%)	100(17.3%)
M	243(83.8%)	234(81.5%)	477(82.7%)
Race Category			
WHITE	188(64.8%)	190(66.2%)	378(65.5%)
BLACK OR AFRICAN AMERICAN	79(27.2%)	72(25.1%)	151(26.2%)
ASIAN	6(2.1%)	10(3.5%)	16(2.8%)
AMERICAN INDIAN OR ALASKA NATIVE	3(1.0%)	3(1.0%)	6(1.0%)
OTHER	14(4.8%)	12(4.2%)	26(4.5%)
Ethnicity			
HISPANIC OR LATINO	60(20.7%)	47(16.4%)	107(18.5%)
NOT HISPANIC & LATINO	230(79.3%)	240(83.6%)	470(81.5%)
Age (Year)			
Mean (SE)	46.76 (0.616)	45.73 (0.617)	46.25 (0.436)
Median	48.00	47.00	48.00
Range	(20.00, 74.00)	(21.00, 79.00)	(20.00, 79.00)
STD	10.48	10.46	10.47
Age Category 1 (48yrs)			
<=48	148(51.0%)	161(56.1%)	309(53.6%)
>48	142(49.0%)	126(43.9%)	268(46.4%)
Age Category 2 (65yrs)			
<65	279(96.2%)	276(96.2%)	555(96.2%)
>=65	11(3.8%)	11(3.8%)	22(3.8%)

Baseline Weight (kg)			
Mean (SE)	82.20 (0.874)	81.43 (1.097)	81.82 (0.700)
Median	80.00	78.50	79.50
Range	(54.90, 142.4)	(42.80, 192.6)	(42.80, 192.6)
STD	14.89	18.59	16.82
Baseline Height (cm)			
Mean (SE)	174.7 (0.535)	173.8 (0.575)	174.2 (0.393)
Median	175.3	174.0	175.0
Range	(147.3, 198.1)	(137.2, 195.6)	(137.2, 198.1)
STD	9.107	9.737	9.430
Baseline BMI (kg/m^2)			
Mean (SE)	26.99 (0.292)	27.01 (0.362)	27.00 (0.232)
Median	26.15	25.88	26.05
Range	(18.14, 53.21)	(17.34, 72.85)	(17.34, 72.85)
STD	4.969	6.127	5.570
Baseline BMI Category 1 (kg/m^2)			
<=25	116(40.0%)	128(44.6%)	244(42.3%)
25<=, <30	115(39.7%)	95(33.1%)	210(36.4%)
>=30	59(20.3%)	64(22.3%)	123(21.3%)
Baseline BMI Category 2 (kg/m^2)			
<=18.5	2(0.7%)	4(1.4%)	6(1.0%)
18.5<=,<25	114(39.3%)	124(43.2%)	238(41.2%)
25<=, <30	115(39.7%)	95(33.1%)	210(36.4%)
30<=, <35	39(13.4%)	41(14.3%)	80(13.9%)
>=35	20(6.9%)	23(8.0%)	43(7.5%)
Region1			
Ex-US	124(42.8%)	123(42.9%)	247(42.8%)
US	166(57.2%)	164(57.1%)	330(57.2%)
Country			
AUS	15(5.2%)	16(5.6%)	31(5.4%)
BEL	2(0.7%)	3(1.0%)	5(0.9%)
CAN	18(6.2%)	15(5.2%)	33(5.7%)
DEU	28(9.7%)	33(11.5%)	61(10.6%)
DOM	4(1.4%)	7(2.4%)	11(1.9%)
ESP	6(2.1%)	4(1.4%)	10(1.7%)
FRA	17(5.9%)	17(5.9%)	34(5.9%)
GBR	31(10.7%)	23(8.0%)	54(9.4%)
ITA	3(1.0%)	5(1.7%)	8(1.4%)
USA	166(57.2%)	164(57.1%)	330(57.2%)
Baseline HCV RNA Category (IU/mL)			
<50	285(98.3%)	277(96.5%)	562(97.4%)
>=50	5(1.7%)	10(3.5%)	15(2.6%)
Baseline CD4 Count (/uL)			
Mean (SE)	669.0 (17.82)	656.8 (16.83)	662.9 (12.25)
Median	616.5	626.0	624.0

Range	(147.0, 2582)	(62.00, 1684)	(62.00, 2582)
STD	303.4	285.0	294.2
Baseline CD4 Category (/uL)			
50<=, <200	4(1.4%)	8(2.8%)	12(2.1%)
200<=, <350	26(9.0%)	30(10.5%)	56(9.7%)
350<=, <500	62(21.4%)	60(20.9%)	122(21.1%)
500<=	198(68.3%)	189(65.9%)	387(67.1%)
Mode of Acquisition HIV			
Heterosexual Sex	83(28.6%)	79(27.5%)	162(28.1%)
Homosexual Sex	195(67.2%)	194(67.6%)	389(67.4%)
IV Drug Use	3(1.0%)	5(1.7%)	8(1.4%)
Transfusion	1(0.3%)	1(0.3%)	2(0.3%)
Unknown	7(2.4%)	6(2.1%)	13(2.3%)
Other	1(0.3%)	2(0.7%)	3(0.5%)
HIV Disease Status			
Asymptomatic	240(82.8%)	234(81.5%)	474(82.1%)
AIDS	34(11.7%)	33(11.5%)	67(11.6%)
Symptomatic HIV I	16(5.5%)	20(7.0%)	36(6.2%)
Baseline eGFR (CG) (mL/min)			
Mean (SE)	109.9 (1.819)	108.4 (1.874)	109.2 (1.305)
median	106.7	104.9	105.6
Range	(42.40, 259.2)	(44.10, 260.1)	(42.40, 260.1)
std	30.97	31.75	31.34
Smoking Status at Baseline			
Current Smoker	88(30.3%)	90(31.4%)	178(30.8%)
Former Smoker	54(18.6%)	61(21.3%)	115(19.9%)
Never Smoker	148(51.0%)	136(47.4%)	284(49.2%)
Cardiovascular Disease at Baseline			
N	269(92.8%)	275(95.8%)	544(94.3%)
Y	21(7.2%)	12(4.2%)	33(5.7%)
Diabetes Mellitus at Baseline			
N	259(89.3%)	270(94.1%)	529(91.7%)
Y	31(10.7%)	17(5.9%)	48(8.3%)
Hypertension at Baseline			
N	213(73.4%)	212(73.9%)	425(73.7%)
Y	77(26.6%)	75(26.1%)	152(26.3%)
Hyperlipidemia at Baseline			
N	185(63.8%)	208(72.5%)	393(68.1%)
Y	105(36.2%)	79(27.5%)	184(31.9%)
HIV/HBV Coinfection Status at Baseline			
N	278(97.2%)	280(97.9%)	558(97.6%)
Y	8(2.8%)	6(2.1%)	14(2.4%)

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HIV/HCV Coinfection Status at Baseline
  N                     283( 98.3%)      282( 98.3%)      565( 98.3%)
  Y                       5(  1.7%)        5(  1.7%)       10(  1.7%)

Stratification Factor - Previous Regimen (TDF vs. Non-TDF)
  TDF                   244( 84.1%)      242( 84.3%)      486( 84.2%)
  Non-TDF                46( 15.9%)       45( 15.7%)       91( 15.8%)

Previous Regimen (4 categories)
  Boosted ATV + FTC/TDF 105( 36.2%)      110( 38.3%)      215( 37.3%)
  Boosted DRV + FTC/TDF 140( 48.3%)      133( 46.3%)      273( 47.3%)
  Boosted ATV + ABC/3TC  21(  7.2%)       23(  8.0%)       44(  7.6%)
  Boosted DRV + ABC/3TC  24(  8.3%)       21(  7.3%)       45(  7.8%)
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Source: statistical reviewer's analysis

Table 118: CD4 Cell Count (cells/µL) changes at Week 48 from Baseline in Trial 1489 (FAS)

	B/F/TAF (N=314)	ABC/DTG/3TC (N=315)
Baseline		
N	314	315
Mean (SD[a])	453 (220.8)	476 (231.4)
Median	443	450
Q1, Q3	299, 590	324, 608
Range (Min, Max)	0, 1424	2, 1332
Week 48		
N	290	301
Mean (SD)	690 (278.5)	711 (285.3)
Median	663.5	692
Q1, Q3	492, 871	524, 877
Range (Min, Max)	88, 2004	145, 1739
Change at Week 48 from Baseline (Completer Analysis)		
N	290	301
Mean (SD)	233 (185.2)	227 (190.2) *
Median	213.5	208
Q1, Q3	105, 317	99, 343
Range (Min, Max)	-170, 1036	-510, 796
Change at Week 48 from Baseline (LOCF Analysis)		
N	314	315
Mean (SD)	229 (185.0)	224 (188.9)*
Median	206.5	208
Q1, Q3	106, 315	99, 330
Range (Min, Max)	-222, 1036	-510, 796
Change at Week 48 from Baseline (BOCF Analysis)		
N	314	315

Mean (SD)	215 (188.4)	217 (191.8)
Median	189	197
Q1, Q3	79, 305	82, 330
Range (Min, Max)	-170, 1036	-510, 796

*: These results are slightly different from the sponsor's results.
[a]: SD: standard deviation
Source: statistical reviewer's analysis

Table 119: CD4 Cell Count (cells/µL) changes at Week 48 from Baseline in Trial 1490 (FAS)

	B/F/TAF (N=320)	DTG/F/TAF (N=325)
Baseline		
N	320	325
Mean (SD)	457 (255.3)	454 (231.5)
Median	440	441
Q1, Q3	289, 591	297, 597
Range (Min, Max)	2, 1636	3, 1458
Week 48		
N	289	304
Mean (SD)	630 (253.1)	656 (279.5)
Median	606	617.5
Q1, Q3	443, 811	471, 807.5
Range (Min, Max)	53, 1472	112, 1814
Change at Week 48 from Baseline (Completer Analysis)		
N	289	304
Mean (SD)	179 (166.0)*	202 (165.9) *
Median	173	180
Q1, Q3	93, 265	98, 298
Range (Min, Max)	-626, 782	-214, 1006
Change at Week 48 from Baseline (LOCF Analysis)		
N	320	325
Mean (SD)	172 (167.7)	192.5 (167.5) *
Median	166	172
Q1, Q3	77, 260.5	90, 292
Range (Min, Max)	-626, 782	-214, 1006
Change at Week 48 from Baseline (BOCF Analysis)		
N	320	325
Mean (SD)	162 (166.5)	188 (167.9)
Median	158	169
Q1, Q3	57, 254.5	78, 291
Range (Min, Max)	-626, 782	-214, 1006

*: These results are slightly different from the sponsor's results.
Source: statistical reviewer's analysis

Table 120: CD4 Cell Count (cells/µL) changes at Week 48 from Baseline in Trial 1844 (FAS)

	B/F/TAF (N=282)	ABC/DTG/3TC (N=281)
Baseline		
N	282	281
Mean (SD)	752 (302.2)	694 (291.6)
Median	732	661
Q1, Q3	554, 936	478, 874
Range (Min, Max)	124, 2444	125, 1570
Week 48		
N	269	268
Mean (SD)	726 (282.9)	690 (300.7)
Median	720	640.5
Q1, Q3	547, 910	476.5, 872.5
Range (Min, Max)	145, 2451	159, 1901
Change at Week 48 from Baseline (Completer Analysis)		
N	269	268
Mean (SD)	-30 (180.2)*	4 (190.6)*
Median	-12	2
Q1, Q3	-124, 73	-93, 84.5
Range (Min, Max)	-989, 494	-541, 962
Change at Week 48 from Baseline (LOCF Analysis)		
N	282	281
Mean (SD)	-24 (182.2)*	6 (194.7)*
Median	-7	3
Q1, Q3	-115, 79	-93, 98
Range (Min, Max)	-989, 506	-541, 962
Change at Week 48 from Baseline (BOCF Analysis)		
N	282	281
Mean (SD)	-29 (176.1)	4 (186.1)
Median	-4.5	0
Q1, Q3	-113, 64	-90, 81
Range (Min, Max)	-989, 494	-541, 962

*: These results are slightly different from the sponsor's results.
Source: statistical reviewer's analysis

Table 121: CD4 Cell Count (cells/µL) changes at Week 48 from Baseline in Trial 1877 (FAS)

	B/F/TAF (N=290)	SBR (N=287)
Baseline		
N	290	287
Mean (SD)	669 (303.4)	657 (285.0)

Median	616.5	626
Q1, Q3	469, 809	437, 821
Range (Min, Max)	147, 2582	62, 1684
Week 48		
N	268	263
Mean (SD)	696 (316.6)	651 (273.6)
Median	639	629
Q1, Q3	490.5, 839	463, 800
Range (Min, Max)	156, 2281	122, 1573
Change at Week 48 from Baseline (Completer Analysis)		
N	268	263
Mean (SD)	26 (151.0)*	-3 (159.3)*
Median	20.5	7
Q1, Q3	-60.5, 116	-79, 78
Range (Min, Max)	-391, 686	-841, 427
Change at Week 48 from Baseline (LOCF Analysis)		
N	290	287
Mean (SD)	23 (151.8)*	-3 (157.0)*
Median	19.5	2
Q1, Q3	-60, 115	-79, 73
Range (Min, Max)	-407, 686	-841, 427
Change at Week 48 from Baseline (BOCF Analysis)		
N	290	287
Mean (SD)	24 (145.3)	-2 (152.4)
Median	12.5	0
Q1, Q3	-51, 113	-69, 66
Range (Min, Max)	-391, 686	-841, 427

*: These results are slightly different from the sponsor's results.
Source: statistical reviewer's analysis

Table 122: Baseline Covariates Subgroup Analysis of the Proportion of Subjects with <50 copies/mL at Week 48 in Trial 1489 (FAS)

Covariates	B/F/TAF	ABC/DTG/3TC	Total
Treated (FAS)			
N	290/314(92.4)	293/315(93.0)	583/629(92.7)
Gender			
F	27/ 29(93.1)	30/ 33(90.9)	57/ 62(91.9)
M	263/285(92.3)	263/282(93.3)	526/567(92.8)
Race Category			

WHITE	169/180(93.9)	168/179(93.9)	337/359(93.9)
BLACK OR AFRICA AMERICAN	104/114(91.2)	105/112(93.8)	209/226(92.5)
ASIAN	6/ 6(100)	9/ 10(90.0)	15/ 16(93.8)
AMERICAN INDIAN OR ALASKA NATIVE	2/ 2(100)	3/ 4(75.0)	5/ 6(83.3)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDS	1/ 1(100)	2/ 2(100)	3/ 3(100)
NOT PERMITTED	2/ 2(100)	./ .(.)	2/ 2(100)
OTHER	6/ 9(66.7)	6/ 8(75.0)	12/ 17(70.6)
Ethnicity			
HISPANIC OR LATION	65/ 72(90.3)	62/ 65(95.4)	127/137(92.7)
NOT HISPANIC OR LATION	223/240(92.9)	230/249(92.4)	453/489(92.6)
NOT PERMITTED	2/ 2(100)	1/ 1(100)	3/ 3(100)
Age Category 1 (32yrs)			
<=32	179/200(89.5)	180/194(92.8)	359/394(91.1)
>32	111/114(97.4)	113/121(93.4)	224/235(95.3)
Age Category 2 (65yrs)			
<65	288/312(92.3)	291/313(93.0)	579/625(92.6)
>=65	2/ 2(100)	2/ 2(100)	4/ 4(100)
Age Category 3 (50yrs)			
<50	250/274(91.2)	256/274(93.4)	506/548(92.3)
>=50	40/ 40(100)	37/ 41(90.2)	77/ 81(95.1)
Baseline BMI Category 1 (kg/m^2)			
<=25	137/153(89.5)	146/160(91.3)	283/313(90.4)
25<=, <30	96/103(93.2)	88/ 94(93.6)	184/197(93.4)
>=30	57/ 58(98.3)	59/ 61(96.7)	116/119(97.5)
Baseline BMI Category 2 (kg/m^2)			
<=18.5	12/ 13(92.3)	6/ 8(75.0)	18/ 21(85.7)
18.5<=,<25	125/140(89.3)	140/152(92.1)	265/292(90.8)
25<=, <30	96/103(93.2)	88/ 94(93.6)	184/197(93.4)
30<=, <35	39/ 40(97.5)	37/ 39(94.9)	76/ 79(96.2)
>=35	18/ 18(100)	22/ 22(100)	40/ 40(100)
Screening HIV RNA Category (copies/mL)			
<=100K	241/257(93.8)	241/257(93.8)	482/514(93.8)
100K<, <=400K	35/ 43(81.4)	38/ 42(90.5)	73/ 85(85.9)
400K<	13/ 13(100)	13/ 15(86.7)	26/ 28(92.9)
missing	1/ 1(100)	1/ 1(100)	2/ 2(100)
Baseline HCV RNA Category (IU/mL)			
<=100K	244/261(93.5)	248/265(93.6)	492/526(93.5)
100K<, <=400K	38/ 45(84.4)	35/ 38(92.1)	73/ 83(88.0)
400K<	8/ 8(100)	10/ 12(83.3)	18/ 20(90.0)
Screening CD4 Category (/uL)			
<50	5/ 7(71.4)	6/ 7(85.7)	11/ 14(78.6)

50<=, <200	22/ 25(88.0)	18/ 23(78.3)	40/ 48(83.3)
200<=	262/281(93.2)	269/285(94.4)	531/566(93.8)
missing	1/ 1(100)	./ .(.)	1/ 1(100)
Baseline CD4 Category (/uL)			
<50	5/ 7(71.4)	7/ 10(70.0)	12/ 17(70.6)
50<=, <200	25/ 29(86.2)	19/ 22(86.4)	44/ 51(86.3)
200<=, <350	63/ 69(91.3)	55/ 58(94.8)	118/127(92.9)
350<=, <500	85/ 87(97.7)	85/ 91(93.4)	170/178(95.5)
500<=	112/122(91.8)	127/134(94.8)	239/256(93.4)
HIV Disease Status			
Asymptomatic	266/286(93.0)	266/286(93.0)	532/572(93.0)
Symptomatic HIV	13/ 16(81.3)	12/ 14(85.7)	25/ 30(83.3)
AIDS	11/ 12(91.7)	15/ 15(100)	26/ 27(96.3)
Cardiovascular Disease at Baseline			
N	283/307(92.2)	286/306(93.5)	569/613(92.8)
Y	7/ 7(100)	7/ 9(77.8)	14/ 16(87.5)
Diabetes Mellitus at Baseline			
N	272/295(92.2)	285/306(93.1)	557/601(92.7)
Y	18/ 19(94.7)	8/ 9(88.9)	26/ 28(92.9)
Hypertension at Baseline			
N	256/279(91.8)	255/274(93.1)	511/553(92.4)
Y	34/ 35(97.1)	38/ 41(92.7)	72/ 76(94.7)
Hyperlipidemia at Baseline			
N	246/270(91.1)	260/281 (92.5)	506/551(91.8)
Y	44/ 44(100)	33/ 34 (97.1)	77/ 78(98.7)
Region1			
Ex-US	78/ 86(90.7)	77/ 82(93.9)	155/168(92.3)
US	212/228(93.0)	216/233(92.7)	428/461(92.8)
Region2			
Region 1	18/ 18(100)	14/ 15(93.3)	32/ 33(97.0)
Region 2	59/ 66(89.4)	62/ 66(93.9)	121/132(91.7)
Region 3	23/ 23(100)	38/ 40(95.0)	61/ 63(96.8)
Region 4	45/ 47(95.7)	53/ 57(93.0)	98/104(94.2)
Region 5	24/ 30(80.0)	19/ 23(82.6)	43/ 53(81.1)
Region 6	17/ 22(77.3)	15/ 17(88.2)	32/ 39(82.1)
Region 7	56/ 57(98.2)	46/ 49(93.9)	102/106(96.2)
Region 8	48/ 51(94.1)	46/ 48(95.8)	94/ 99(94.9)
Country			
BEL	4/ 4(100)	2/ 2(100)	6/ 6(100)
CAN	18/ 18(100)	14/ 15(93.3)	32/ 33(97.0)
DEU	4/ 4(100)	9/ 9(100)	13/ 13(100)
DOM	1/ 2(50.0)	1/ 1(100)	2/ 3(66.7)
ESP	19/ 20(95.0)	22/ 23(95.7)	41/ 43(95.3)
FRA	9/ 11(81.8)	10/ 10(100)	19/ 21(90.5)

GBR	16/ 20(80.0)	8/ 11(72.7)	24/ 31(77.4)
ITA	7/ 7(100)	11/ 11(100)	18/ 18(100)
USA	212/228(93.0)	216/233(92.7)	428/461(92.8)

Source: statistical reviewer's analysis

Table 123: Baseline Covariates Subgroup Analysis of the Proportion of Subjects with <50 copies/mL at Week 48 in Trial 1490 (FAS)

Covariates	B/F/TAF	DTG/F/TAF	Total
Treated (FAS)			
N	286/320(89.4)	302/325(92.9)	588/645(91.2)
Gender			
F	34/ 40(85.0)	32/ 37(86.5)	66/ 77(85.7)
M	252/280(90.0)	270/288(93.8)	522/568(91.9)
Race Category			
WHITE	164/183(89.6)	181/195(92.8)	345/378(91.3)
BLACK OR AFRICA AMERICAN	83/ 97(85.6)	92/100(92.0)	175/197(88.8)
ASIAN	7/ 7(100)	9/ 10(90.0)	16/ 17(94.1)
AMERICAN INDIAN OR OTHER ALAKSA NATIVE	1/ 1(100)	1/ 1(100)	2/ 2(100)
NATIVE HAWAIIAN OR PACIFIC ISLANDS	1/ 1(100)	./ .(.)	1/ 1(100)
OTHER	30/ 31(96.8)	19/ 19(100)	49/ 50(98.0)
Ethnicity			
HISPANIC OR LATINO	77/ 83(92.8)	79/ 81(97.5)	156/164(95.1)
NOT HISPANIC OR LATINO	209/237(88.2)	223/244(91.4)	432/481(89.8)
Age Category 1 (32yrs)			
<=32	154/177(87.0)	154/170(90.6)	308/347(88.8)
>32	132/143(92.3)	148/155(95.5)	280/298(94.0)
Age Category 2 (65yrs)			
<65	284/317(89.6)	300/323(92.9)	584/640(91.3)
>=65	2/ 3(66.7)	2/ 2(100)	4/ 5(80.0)
Baseline BMI Category 1 (kg/m^2)			
<=25	141/158(89.2)	159/174(91.4)	300/332(90.4)
25<=, <30	92/101(91.1)	83/ 87(95.4)	175/188(93.1)
>=30	53/ 61(86.9)	60/ 64(93.8)	113/125(90.4)
Baseline BMI Category 2 (kg/m^2)			
<=18.5	8/ 10(80.0)	5/ 5(100)	13/ 15(86.7)
18.5<, <25	133/148(89.9)	154/169(91.1)	287/317(90.5)
25<=, <30	92/101(91.1)	83/ 87(95.4)	175/188(93.1)
30<=, <35	38/ 43(88.4)	33/ 35(94.3)	71/ 78(91.0)

>=35	15/ 18(83.3)	27/ 29(93.1)	42/ 47(89.4)
Screening HIV RNA Category (copies/mL)			
<=100K	234/261(89.7)	241/260(92.7)	475/521(91.2)
100K<, <=400K	42/ 46(91.3)	49/ 52(94.2)	91/ 98(92.9)
400K<	10/ 13(76.9)	11/ 12(91.7)	21/ 25(84.0)
missing	./ .(.)	1/ 1(100)	1/ 1(100)
Baseline HCV RNA Category (IU/mL)			
<=100K	229/254(90.2)	251/271(92.6)	480/525(91.4)
100K<, <=400K	47/ 54(87.0)	39/ 41(95.1)	86/ 95(90.5)
400K<	10/ 12(83.3)	12/ 13(92.3)	22/ 25(88.0)
Screening CD4 Category (/uL)			
<50	10/ 11(90.9)	11/ 11(100)	21/ 22(95.5)
50<=, <200	30/ 32(93.8)	29/ 31(93.5)	59/ 63(93.7)
200<=	245/276(88.8)	262/283(92.6)	507/559(90.7)
missing	1/ 1(100)	./ .(.)	1/ 1(100)
Baseline CD4 Category (/uL)			
<50	13/ 15(86.7)	13/ 13(100)	26/ 28(92.9)
50<=, <200	29/ 29(100)	21/ 21(100)	50/ 50(100)
200<=, <350	60/ 67(89.6)	69/ 77(89.6)	129/144(89.6)
350<=, <500	81/ 91(89.0)	89/ 94(94.7)	170/185(91.9)
500<=	103/118(87.3)	110/120(91.7)	213/238(89.5)
HIV Disease Status			
Asymptomatic	254/286(88.8)	266/288(92.4)	520/574(90.6)
Symptomatic HIV	10/ 10(100)	10/ 11(90.9)	20/ 21(95.2)
AIDS	22/ 24(91.7)	26/ 26(100)	48/ 50(96.0)
Cardiovascular Disease at Baseline			
N	280/311(90.0)	298/319(93.4)	578/630(91.7)
Y	6/ 9(66.7)	4/ 6(66.7)	10/ 15(66.7)
Diabetes Mellitus at Baseline			
N	265/298(88.9)	281/303(92.7)	546/601(90.8)
Y	21/ 22(95.5)	21/ 22(95.5)	42/ 44(95.5)
Hypertension at Baseline			
N	235/261(90.0)	246/263(93.5)	481/524(91.8)
Y	51/ 59(86.4)	56/ 62(90.3)	107/121(88.4)
Hyperlipidemia at Baseline			
N	246/275(89.5)	264/281(94.0)	510/556(91.7)
Y	40/ 45(88.9)	38/ 44(86.4)	78/ 89(87.6)
Region1			
Ex-US	118/127(92.9)	124/132(93.9)	242/259(93.4)
US	168/193(87.0)	178/193(92.2)	346/386(89.6)
Country			
AUS	3/ 4(75.0)	10/ 10(100)	13/ 14(92.9)

BEL	4/ 4(100)	4/ 4(100)	8/ 8(100)
CAN	11/ 12(91.7)	8/ 9(88.9)	19/ 21(90.5)
DEU	19/ 20(95.0)	26/ 28(92.9)	45/ 48(93.8)
DOM	26/ 27(96.3)	18/ 18(100)	44/ 45(97.8)
ESP	16/ 17(94.1)	15/ 17(88.2)	31/ 34(91.2)
FRA	6/ 7(85.7)	5/ 5(100)	11/ 12(91.7)
GBR	18/ 21(85.7)	21/ 23(91.3)	39/ 44(88.6)
ITA	15/ 15(100)	17/ 18(94.4)	32/ 33(97.0)
USA	168/193(87.0)	178/193(92.2)	346/386(89.6)
Region2			
Region 1	14/ 16(87.5)	18/ 19(94.7)	32/ 35(91.4)
Region 2	78/ 84(92.9)	88/ 95(92.6)	166/179(92.7)
Region 3	15/ 17(88.2)	16/ 18(88.9)	31/ 35(88.6)
Region 4	38/ 45(84.4)	43/ 45(95.6)	81/ 90(90.0)
Region 5	10/ 14(71.4)	18/ 19(94.7)	28/ 33(84.8)
Region 6	18/ 24(75.0)	28/ 30(93.3)	46/ 54(85.2)
Region 7	35/ 37(94.6)	24/ 25(96.0)	59/ 62(95.2)
Region 8	78/ 83(94.0)	67/ 74(90.5)	145/157(92.4)

Source: statistical reviewer's analysis

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/s/

SUZANNE K STRAYHORN
02/06/2018

NDA 210251 CDTL Review and Evaluation – NDA 210251
Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) FDC - BIKTARVY

Application Type	NDA
Application Number(s)	210251
Priority or Standard	Priority
Submit Date(s)	June 10, 2017
Received Date(s)	June 12, 2017
PDUFA Goal Date	February 12, 2018
Division/Office	DAVP/OAP
Review Completion Date	January 12, 2018
Established Name	Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) Fixed-Dose Combination
(Proposed) Trade Name	BIKTARVY™
Pharmacologic Class	Bictegravir is an integrase strand-transfer inhibitor (INSTI), emtricitabine and tenofovir alafenamide are nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)
Applicant	Gilead Sciences
Formulation(s)	FDC Tablet
Dosing Regimen	bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of HIV-1 infection in adults who are HIV-1 treatment-[redacted] (b) (4) associated with resistance to the individual components of BIKTARVY
Recommendation on Regulatory Action	Approval

The Cross-Discipline Team Leader (CDTL) Review is complete and has been added to the NDA/BLA Multi-disciplinary Review and Evaluation. My recommendation for this application is approval.

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/s/

WENDY W CARTER
01/12/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

Application Number:	NDA 210251
Supporting Documents:	
Product:	GS-9883
Indication:	HIV
Sponsor:	Gilead Sciences, Inc.
Review Division:	DAVP
Reviewer:	John Dubinion, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D., DABT
Division Director:	Debra B. Birnkrant, M.D.
Project Manager:	Suzanne Strayhorn, M.Sc.

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1 Studies Reviewed

Carcinogenicity
Study no. TX-141-2047 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study of GS-9883-01 in 001178-T (Hemizygous) rasH2 Transgenic Mice

2 Carcinogenicity

Study title: 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study of GS-9883-01 in 001178-T (Hemizygous) rasH2 Transgenic Mice

Study no.:	TX-141-2047 (b) (4)
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12/16/15
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GS-9883-01, 15-467-001A (94.5%); vehicle control: 0.5% (w/w) hydroxypropyl methylcellulose (Methocel K100 LV) and 0.1% (w/w) Tween® 20 in reverse osmosis water; positive control: 7.5 mg/mL N-Nitrosomethylurea (NMU) in citrate-buffered saline (pH 4.5)
CAC concurrence:	ECAC met to discuss this protocol on 11/17/15. ECAC's recommended doses: 0, 10, 30, and 300 mg/kg/day for females and doses of 0, 5, 15 and 100 mg/kg/day for males, by oral gavage, with the high doses based on decreased body weight gain at 1000 mg/kg/day (more pronounced in males) and saturation of exposure.

Key Study Findings

- GS-9883 administered by oral gavage to transgenic mice at doses of 0, 10, 30, and 300 mg/kg/day in females; and 0, 5, 15 and 100 mg/kg/day in males for 6 months did not significantly change survival rate or induce tumor development in CByB6F1/Tg rasH2 hemizygous mice.
- The systemic drug exposures ($AUC_{0\text{-}24h}$) at Week 26 was 2340 µg.h/ml in females and 1560 µg.h/ml in males, and were sufficiently higher than the human AUC of 165 ug.h/ml.

Adequacy of Carcinogenicity Study

The doses used for this study were based on the NOAEL and body weight gain deficiency in the 4-week repeat-dose study (TX-141-2042). The study is considered adequate.

Appropriateness of Test Models

Tg.rasH2 (CByB6F1/Tg rasH2 hemizygous) transgenic mice are an appropriate animal model.

Evaluation of Tumor Findings

Neoplastic findings, combined spleen/urinary bladder/uterus/vagina b-hemangioma/m-hemangiosarcoma tumors, reached statistical significance ($P < 0.05$) in females administered 30 mg/kg/day compared with controls; however, the absence of findings at 100 mg/kg/day indicate this finding was not GS-9883-related.

Methods

Doses:	0, 10, 30, and 300 mg/kg/day for females 0, 5, 15 and 100 mg/kg/day for males positive control: single NMU 75 mg/kg/day ip injection
Frequency of dosing:	Once daily
Dose volume:	5 mL/kg/day
Route of administration:	Oral gavage (ip for group 5 NMU positive control)
Formulation/Vehicle:	0.5% (w/w) hydroxypropyl methylcellulose (Methocel K100 LV) and 0.1% (w/w) Tween® 20 in reverse osmosis water
Basis of dose selection:	NOAEL, based on deficiency in body weight gain in a 4-wk tox study (TX-141-2042).
Species/Strain:	CByB6F1-Tg[HRAS]2Jic hemizygous transgenic mice (for TK: CByB6F1-Tg(HRAS)2Jic wild type
Number/Sex/Group:	25 (group 1-4), positive control NMU: 10/group
Age:	8 weeks (dosing)(BW:15.0 – 29.6 g).
Animal housing:	Individually housed
Paradigm for dietary restriction:	Not applicable
Dual control employed:	Yes (Group 1 was vehicle control, Group 5 was positive control, see above)
Interim sacrifice:	No
Satellite groups:	Toxicokinetics (non-transgenic mice 40/sex/group 1-4, 0 for NMU group)
Deviation from study protocol:	Unremarkable

Group	Subgroup	No. of Animals[a]		Dose Level (mg/kg/day)		Dose Concentration[b] (mg/mL)	
		Male	Female	Male	Female	Male	Female
1 (Control)[c]	1 (Carcinogenicity)	25	25	0	0	0	0
	2 (Toxicokinetic)	7	7	0	0	0	0
2 (Low)	1 (Carcinogenicity)	25	25	5	10	1	2
	2 (Toxicokinetic)	40	40	5	10	1	2
3 (Mid)	1 (Carcinogenicity)	25	25	15	30	3	6
	2 (Toxicokinetic)	40	40	15	30	3	6
4 (High)	1 (Carcinogenicity)	25	25	100	300	20	60
	2 (Toxicokinetic)	40	40	100	300	20	60
5 (Positive Control)[d]	1 (Carcinogenicity)	10	10	75	75	7.5	7.5

a Each toxicokinetic group had at least one animal/sex to serve as a possible replacement, if needed.
b Concentrations were corrected for water, salt and solvent content and lot specific purity. A correction factor of 1.13 was used
c Group 1 received vehicle control article only.
d Group 5 was administered one intraperitoneal dose of N-methyl-N-nitrosourea (MNU) on Day 1 of the dosing phase. These animals were included as positive controls to ensure animals supplied appropriately express oncogenes and respond to carcinogenic insult.

Observations and Results

Mortality

No GS-9883-related effect on animal survival was noted on study. Survival ranged from 92 to 100% for vehicle control and GS-9883-treated groups of males and females (see charts below). A few unscheduled deaths (found dead or sacrificed in a moribund condition) were considered incidental and most often undetermined, related to a gavage error, or an incidental occurrence of mesothelioma. The causes of death are presented below. Positive control (NMU, group 5) exhibited expected reduction in survival ($p<0.0001$ in all cases).

Table 1: Adjusted Survival Data- Males

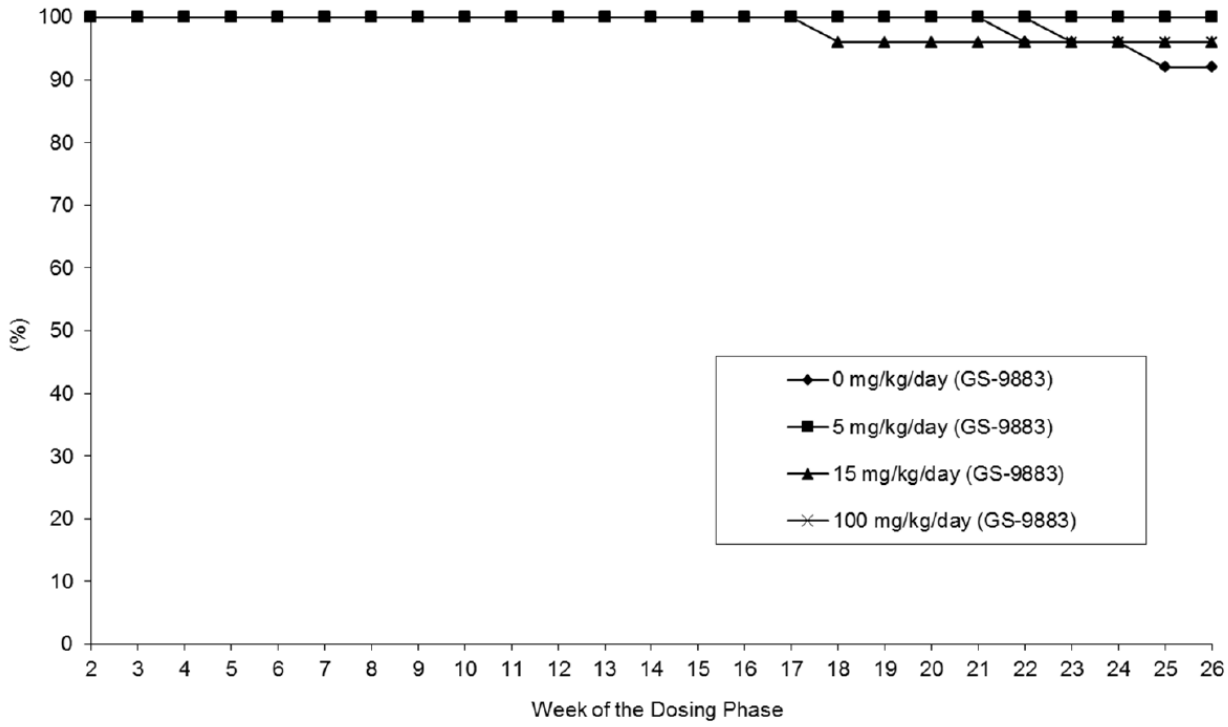


Table 2: Adjusted Survival Data- Females

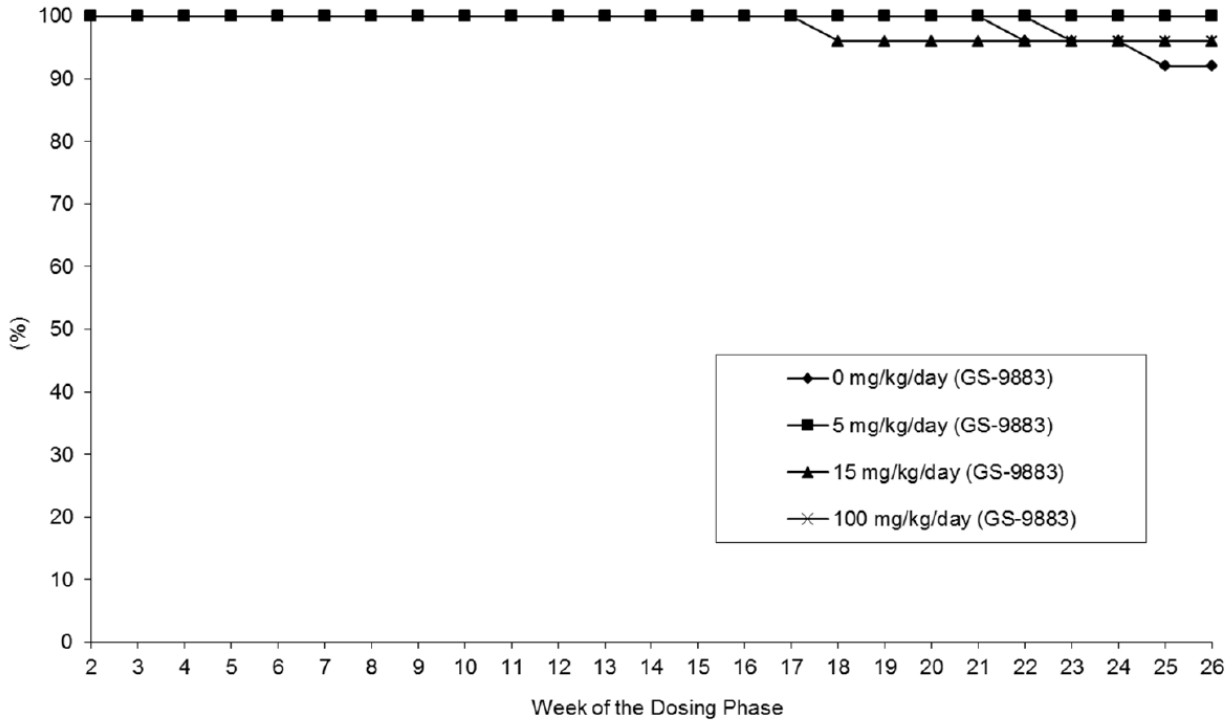


Table 3: Cause of Death/Moribund Condition and Day of Unscheduled Sacrifice/Death

Group	Sex	Animal Number	Dose (mg/kg/day)	Study Day of Death/Sacrifice	Cause of Death/Moribund Condition
1	Male	A38896	0	152	Hematopoietic neoplasm (Malignant lymphoma)
1	Male	A38901	0	174	Gavage-related
3	Male	A39015	15	120	Undetermined
4	Male	A39059	100	155	Undetermined
1	Female	A39146	0	173	Undetermined
2	Female	A39168	10	157	Mesothelioma
3	Female	A39232	30	130	Undetermined
3	Female	A39233	30	144	Undetermined

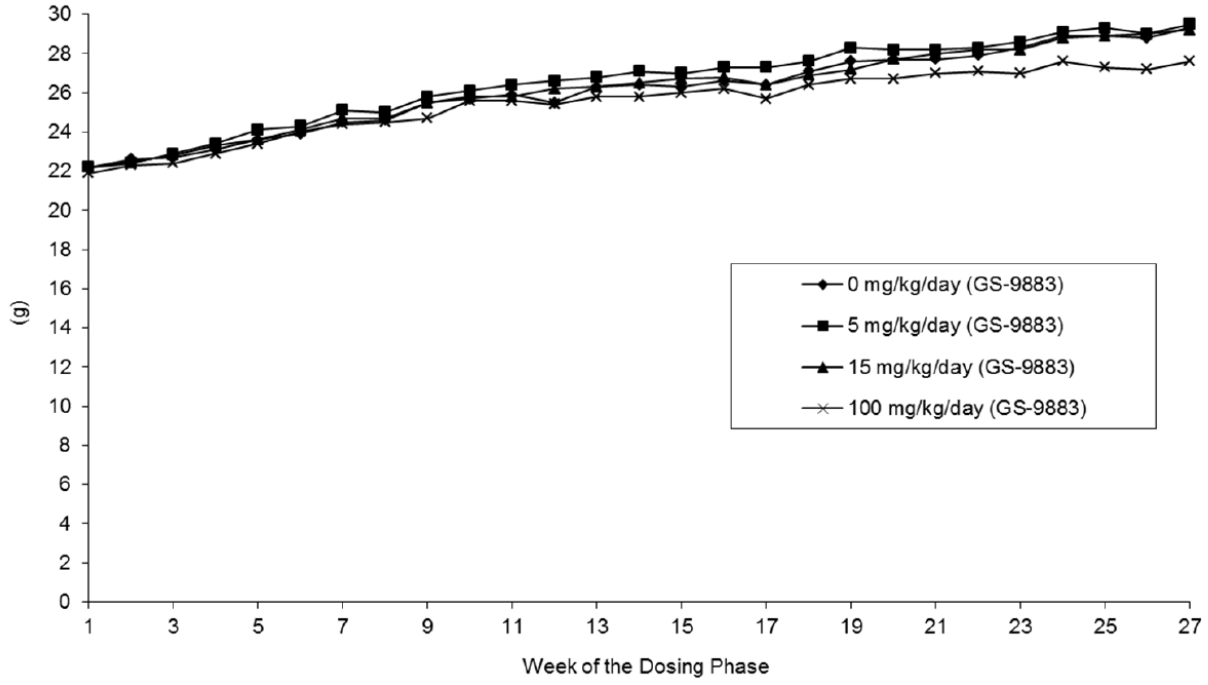
Clinical Signs

No GS-9883-related clinical observations were noted.

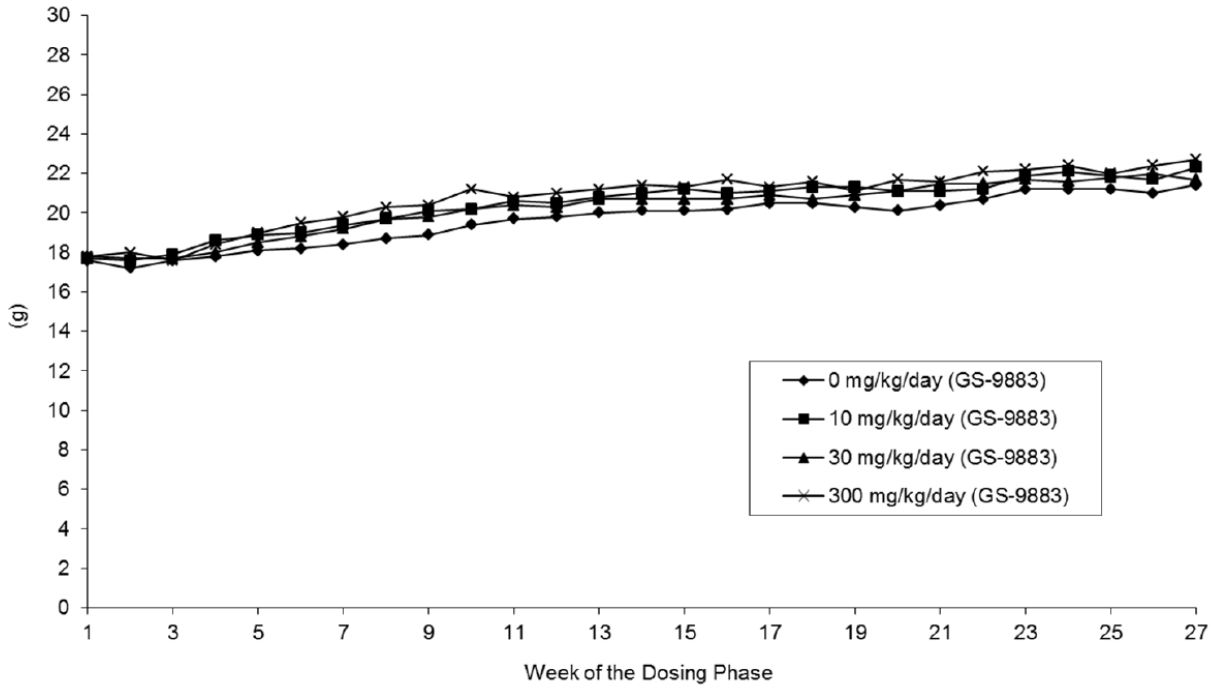
Body Weights

No apparent drug-related effects on body weights were noted due to a lack of dose-dependence and inconsistency in the directional change between the sexes. The following graphs depict body weight change over the duration of the study.

Male:



Female:



Feed Consumption

Minor, nonadverse, changes in food consumption are of uncertain relationship to GS-9883 due to a lack of dose-dependence and inconsistency in the directional change between sexes.

Gross Pathology

Macroscopic findings were sporadic and considered incidental. While a statistically significant increase in the mean liver/gall bladder weight parameters of females administered 300 mg/kg/day (absolute weight and liver/gall bladder to brain weight) was noted, there did not appear to be a microscopic correlate and was considered an incidental finding.

Histopathology

Peer Review
Adequate
Neoplastic
No statistically significant GS-9883-related findings were noted in males. In females administered 30 mg/kg/day, combined spleen/urinary bladder/uterus/vagina b-hemangioma/m-hemangiosarcoma tumors reached statistical significance ($P < 0.05$) compared with controls; however, the absence

of statistical significance in females administered 100 mg/kg/day indicates this does not represent a GS-9883-related effect. (See sponsor's table of incidence below). For these tumors, the FDA statistical review showed only pair-test to be significant. Both statistical reviews employed Poly-K methods. FDA's secondary reviews confirmed that these findings did not show any statistically significant dose-response relationship in incidence in all tumor types tested in the mice.

Table 4: Primary Neoplastic Findings in Groups 1 through 4 – Scheduled and Unscheduled Sacrifices and Deaths

Tissue/finding Sex	Males				Females			
GS-9883 Dose (mg/kg/day)	0	5	15	100	0	10	30	300
Number of Animals	25	25	25	25	25	25	25	25
Vascular neoplasms								
B-Hemangioma	0	0	1	3	0	1	3*	0
M-Hemangiosarcoma	1	2	3	0	1	2	4*	2
Hemolympho-reticular neoplasms								
M-Lymphoma	1	0	0	0	0	0	0	0
Lung								
B- Adenoma, Bronchiolo-alveolar	2	1	3	4	1	1	0	1
M- Carcinoma, Bronchiolo-alveolar	0	0	0	0	1	1	0	0
M-Mesothelioma	0	0	0	0	0	1	0	0
Thymus								
B-Thymoma	0	0	0	0	2	2	1	5
M-Thymoma	0	0	0	0	2	0	0	1
Harderian gland								
B-Adenoma	1	0	0	0	0	0	1	0
M-Carcinoma	0	1	0	0	0	0	0	0
Mammary Gland								
M-Adenocarcinoma	0	0	0	0	0	0	0	1
Prostate								
M-Carcinoma	1	0	0	0	NA	NA	NA	NA
Uterus								
B-Polyp, endometrial stromal	NA	NA	NA	NA	1	0	0	0

B- = Benign; M- = Malignant; NA = Not applicable

* = Based on statistical analysis of group means, values (B-Hemangioma and M-Hemangiosarcoma combined) are significantly different from control at $p \leq 0.05$. Refer to the Statistical Analysis Report for actual significance levels and tests used.

In summary, no statistically significant increases in incidence rates for all hyperplastic and/or neoplastic findings among the vehicle and drug-treated groups (trend or group comparisons).

Toxicokinetics

Systemic exposures $AUC_{0\text{-}24h}$ measured on week 26 increased with doses from 5 to 100 mg/kg/day in males and from 10 to 300 mg/kg/day in females. Systemic exposures $AUC_{0\text{-}24h}$ on week 26 were higher than in Week 4, suggesting accumulation. Accumulation of GS-9883 after multiple doses in mice was approximately 4-fold in

males and 2-fold in females. The sponsor's table below provides the toxicokinetic parameters across doses from day 1 to week 26.

Table 5: Toxicokinetic Parameters for GS-9883 in Mouse Plasma: Day 1 and Week 26

Interval	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)
Day 1	2	5	M	7540	46600
		10	F	13800	150000
	3	15	M	15900	147000
		30	F	28000	382000
	4	100	M	42000	383000
		300	F	89100	1240000
Week 26	2	5	M	18200	190000
		10	F	25800	341000
	3	15	M	42300	526000
		30	F	69200	861000
	4	100	M	104000	1560000
		300	F	143000	2340000

Dosing Solution Analysis

Unremarkable.

Conclusion

In conclusion, GS-9883 did not significantly induce tumor development carcinogenic in CByB6F1/Tg rasH2 hemizygous mice following daily oral administration for 6 months at doses up to 100 mg/kg/day for males (Week 26 AUC_{0-24h} =1560 µg.h/ml) and up to 300 mg/kg/day for females (Week 26 AUC_{0-24h} =2340 µg.h/ml).

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/s/

JOHN H DUBINION
11/16/2017

HANAN N GHANTOUS
11/16/2017

Application Type	NDA
Application Number(s)	210251
Priority or Standard	Priority
Submit Date(s)	June 10, 2017
Received Date(s)	June 12, 2017
PDUFA Goal Date	February 12, 2018
Division/Office	DAVP/OAP
Review Completion Date	November 9, 2017
Reviewer	Wen Zeng, Ph.D.
Concurring Reviewer	Thamban Valappil, Ph.D.
Established Name	Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) Fixed-Dose Combination
(Proposed) Trade Name	BIKTARVY™
Pharmacologic Class	Bictegravir is an integrase strand-transfer inhibitor (INSTI), emtricitabine and tenofovir alafenamide are nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)
Applicant	Gilead Sciences
Formulation(s)	FDC Tablet
Dosing Regimen	bictegravir 50 mg/emtricitabine 200 mg/TAF 25 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of HIV-1 infection in adults who are HIV-1 treatment-(b) (4) associated with resistance to the individual components of BIKTARVY
Recommendation on Regulatory Action	Approval

Summary:

This memo closes the NDA assignment in DARRTS for the statistics team. The statistical review is complete and has been added to the NDA/BLA Multi-disciplinary Review and Evaluation. The statistical analysis of the efficacy findings supports approval. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

WEN ZENG
11/09/2017

THAMBAN I VALAPPIL
11/09/2017

Office of Clinical Pharmacology Review

NDA #	210251
Link to EDR	NDA 210251 EDR Link
Submission Date	June 12, 2017
Submission Type; Type of Review	New Molecular Entity; Priority Review
Brand Name	BIKTARVY™
Generic Name	Bictegravir (BIC), Emtricitabine (F), Tenofovir Alafenamide (TAF)
Dosage Form and Strength	Tablets: 50 mg BIC, 200 mg F, 25 mg TAF
Route of Administration	Oral
Proposed Indication	Treatment of HIV-1 Infection in Adults who are HIV-1 treatment (b) (4) (b) (4) associated with resistance to the individual components of BIKTARVY™
Applicant	Gilead Sciences Inc.
Associated IND	125589
OCP Review Team	Vikram Arya, Ph.D., FCP Luning (Ada) Zhuang, Ph.D. Kevin Krudys, Ph.D. Islam R. Younis, Ph.D.
OCP Final Signatory	John Lazor, Pharm.D. Director, Division of Clinical Pharmacology IV

Note:

For responses to clinical pharmacology related questions, please refer to BIKTARVY™ multidisciplinary review and evaluation document. This combined clinical pharmacology review consists of the individual reviews of in vivo trials conducted to characterize the clinical pharmacology of either BIC or BIC/F/TAF, pharmacometrics review and individual reviews of in vitro studies.

Please note that throughout this review, "GS-9883" and "BIC" are used interchangeably and refer to Bictegravir and "F" and "FTC" are used interchangeably and refer to Emtricitabine. TAF refers to Tenofovir Alafenamide and TFV refers to tenofovir.

INDIVIDUAL REVIEW OF IN VIVO TRIALS

Link to Individual Trial Reviews	Title	EDR Link to Trial Report
GS-US-380-4270	A Phase 1, Open Label, Fixed-Sequence Study Evaluating the Drug Interaction Potential of Bictegravir (BIC) on Midazolam	EDR Link
GS-US-311-1790	A Phase 1, Randomized, Open Label, Drug Interaction Study Evaluating the Effect of Emtricitabine (F)/Tenofovir Alafenamide (TAF) Fixed-Dose Combination Tablet or GS-9883 (BIC) on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol	EDR Link
GS-US-380-1761	A Phase 1 Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between Bictegravir/Emtricitabine/Tenofovir Alafenamide Fumarate (BIC/F/TAF) and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) tablets	EDR Link
GS-US-380-1999	A Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Bictegravir/Emtricitabine/Tenofovir Alafenamide Fumarate (BIC/F/TAF) and Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX) Fixed-Dose Combination (FDC) tablets	EDR Link
GS-US-141-1479	A Phase 1, Open Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of Bictegravir (BIC) in Subjects with Normal and Impaired Renal Function	EDR Link
GS-US-141-1478	A Phase 1, Open Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of Bictegravir (BIC) in Subjects with Normal and Impaired Hepatic Function	EDR Link
GS-US-141-1233	A Phase 1, Open-Label, Two-Cohort, Multiple-Period, Fixed-Sequence, Crossover Study to Evaluate 1) the Relative Bioavailability of Two BIC/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets Versus BIC (75 mg) Tablet and F/TAF (200/25 mg) FDC Tablet Administered Simultaneously and 2) the Effect of Food on the Pharmacokinetics of BIC, F and TAF when administered as BIC/F/TAF (75/200/25 mg and 50/200/25 mg) FDC Tablets	EDR Link
GS-US-141-1481	A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism, and Excretion of Bictegravir (BIC) in Healthy Subjects	EDR Link
GS-US-380-1991	A Phase 1, Single Dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/F/TAF) Fixed Dose Combination (FDC) Tablets in Healthy Japanese and Caucasian Subjects	EDR Link
GS-US-141-1218	A Phase 1, Double Blind, Randomized, Placebo-Controlled, First-in-Human, Single- and Multiple-Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Oral Bictegravir (BIC) in Healthy Subjects and a Randomized, Open-Label, 2-Cohort, 3-Period, Crossover, Pharmacokinetic Study Evaluating the Drug Interaction Potential between Emtricitabine/Tenofovir Alafenamide (F/TAF) Fixed Dose Combination Tablet and BIC in Healthy Subjects	EDR Link
GS-US-141-1487	A Randomized, Blinded, Placebo Controlled Phase 1 Study Evaluating the Effect of BIC on Renal Function as Assessed by Markers of Glomerular Filtration Rate (GFR)	EDR Link
GS-US-380-3908	A Phase 1, Blinded, Placebo-Controlled, Two Period Crossover, Drug Interaction Study to Assess the Effect of Bictegravir/Emtricitabine/Tenofovir Alafenamide Fumarate (BIC/F/TAF) on Metformin Pharmacokinetics in Healthy Subjects	EDR Link
GS-US-141-1485	A Phase 1 Adaptive Study to Evaluate Transporter, Cytochrome (CYP) 450-Mediated and UGT1A1 Drug-Drug Interactions between Bictegravir (BIC) and Probe Drugs	EDR Link
GS-US-380-3909	A Phase 1, Open Label, Multiple-Cohort, Multiple-Period, Fixed-Sequence, Drug Interaction Study to Evaluate the Effect of Antacid and Mineral Supplements on Bictregravir (BIC) Pharmacokinetics	EDR Link

Study #	GS-US-380-4270	**Study Period:** January 4, 2017– January 30, 2017
Title	A Phase 1, Open Label, Fixed-Sequence Study Evaluating the Drug Interaction Potential of Bictegravir (BIC) on Midazolam	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: Evaluate the effect of BIC when administered as BIC/F/TAF on the PK of the CYP3A probe midazolam.
Secondary: Evaluate the safety and tolerability of BIC/F/TAF and MDZ administered alone and in combination.

Rationale:
The applicant conducted this trial to gain further insights into the pharmacokinetics (PK) and drug interaction potential of BIC. Of note, F or TAF is not anticipated to affect CYP3A enzymes *in vivo*, hence, the effect (if any) of B/F/TAF on midazolam can be attributed solely to BIC.

In vitro findings in hepatocytes did not rule out the potential for weak cytochrome P450 enzyme 3A (CYP3A) induction *in vivo* by BIC. To address this concern, the applicant conducted the trial to evaluate the effect of BIC, when administered as the BIC/F/TAF FDC, on the PK of the CYP3A probe midazolam (MDZ).

Dose Selection:

BIC/F/TAF (50/200/25 mg) FDC was selected for use in the current study because it is the FDC formulation evaluated in Phase 3 trials and proposed for marketing.

MDZ (2 mg oral syrup): The 2 mg dose of MDZ is commonly used in DDI trials and the exposures of MDZ after reference (period 3) and test (period 1) treatment were anticipated to be significantly lower than the maximum recommended oral MDZ dose of 20 mg.

Design and PK Assessments:

Open label, fixed-sequence, single- and multiple-dose, single center study.

Table 1: Trial Design

	Period 1	Period 2	Period 3
Day	1	3 - 11	12
Treatment	A	B	C
n = 14	MDZ Single Dose	B/F/TAF QD	B/F/TAF Single Dose + MDZ Single Dose

QD = once-daily

Source: Clinical Study Report, Page 21

Days 1 and 12: Single dose of MDZ administered within 5 minutes of completing a standard moderate-fat meal (approximately 600 kcal, and approximately 27% fat).

Days 3 through 11: BIC/F/TAF administered within 5 minutes of completing a standard moderate-fat meal (approximately 600 kcal, and approximately 27% fat).

On days 1 and 12, MDZ was to be dosed at approximately the same time. On day 12, MDZ was administered under fed conditions, 5 hours after a single dose of BIC/F/TAF under fed conditions.

PK Sampling and Assessments:

Blood samples were collected on Days 1 and 12 at pre-dose (< 5 min), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose, relative to the morning dose of MDZ. The plasma pharmacokinetic (PK) parameters of MDZ were calculated as applicable with and without BIC/F/TAF treatment.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations
BIC/F/TAF (50/200/25 mg tablets; batch # EN1503B2, Expiration date August 2017), MDZ 2 mg oral syrup from Roxanne Laboratories.

RESULTS

Enrolled	14	Completed	14	Discontinued Due to AE	0	PK Population	14	Safety Population	14

Protocol Deviations
No important protocol deviations were reported in the trial.

Demographics
An equal number of male and female subjects were enrolled in this study. Median age was 36 years (range: 24 to 45 years), median (Q1, Q3) $eGFR_{CG}$ was 117.7 (104.9, 123.0) mL/min and median (Q1, Q3) BMI was 25.9 (24.5, 26.6) kg/m^2.

Results:

Table 2: Plasma PK parameters of MDZ following single dose administration of MDZ alone and following co-administration of multiple doses of B/F/TAF and single dose of MDZ

MDZ PK Parameter	Treatment A MDZ (N = 14)	Treatment C (B/F/TAF + MDZ) (N = 14)
C_{max} (ng/mL)[a]	6.0 (39.1)	6.2 (32.3)
T_{max} (h)[b]	1.00 (0.50, 2.00)	1.00 (0.50, 1.50)
AUC_{last} (h*ng/mL)[a]	31.5 (43.8)	36.6 (38.6)
AUC_{inf} (h*ng/mL)[a]	33.3 (45.4)	38.4 (40.0)
$t_{1/2}$ (h)[b]	4.73 (2.91, 5.13)	4.46 (2.70, 5.31)
CL/F (mL/h)[a]	67,247.1 (29.6)	60,377.4 (43.2)
V_z/F (mL)[a]	394,059.5 (30.4)	346,344.2 (34.1)

Treatment A = Single dose of MDZ 2 mg oral syrup; Treatment C = Single dose of MDZ 2 mg oral syrup 5 hours after a single dose of B/F/TAF (1 × 50/200/25 mg tablet)
a Mean (%CV)
b Median (Q1, Q3)
Source: final clinical study report, page 42

Table 3: Statistical comparison of the mean PK parameters of midazolam between test and reference treatments

MDZ PK Parameter Mean (%CV)	Mean (%CV) Test Treatment C (B/F/TAF + MDZ) (N = 14)	Reference Treatment A MDZ (N = 14)	% GLSM Ratio (90% CI)
AUC_{inf} (h*ng/mL)	38.4 (40.0)	33.3 (45.4)	114.52 (99.79, 131.42)
AUC_{last} (h*ng/mL)	36.6 (38.6)	31.5 (43.8)	115.47 (99.67, 133.78)
C_{max} (ng/mL)	6.2 (32.3)	6.0 (39.1)	103.44 (87.23, 122.68)
$t_{1/2}$ (h)[a]	4.46 (2.70, 5.31)	4.73 (2.91, 5.13)	—

Treatment A = Single dose of MDZ 2 mg oral syrup; Treatment C = Single dose of MDZ 2 mg oral syrup 5 hours after a single dose of B/F/TAF (1 × 50/200/25 mg tablet)
a Median (Q1, Q3)
Means presented are unadjusted arithmetic means

Source: final clinical study report, page 42

Safety:
No Grade 3 or 4 AEs, serious adverse events (SAEs), AEs leading to study discontinuation, or deaths were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Note: The applicant mentions that renal function was determined by "$eGFR_{CG}$", however, estimated CrCL [denoted as $CrCL_{CG}$] (instead of eGFR) is a better descriptor because the applicant used Cockcroft-Gault equation which would provide an estimate of estimate creatinine clearance (and not an estimate of GFR).

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

The applicant conducted the trial to evaluate whether BIC is a CYP3A inducer *in vivo* (as suggested by *in vitro* assessments), however, the results of the *in vivo* DDI trial did not show a decrease in MDZ concentrations. The applicant evaluated the potential of BIC to induce CYP3A enzymes in two separate *in vitro* studies; study AD-141-2292 evaluated whether BIC can activate pregnane X receptor (PXR) which controls the expression of genes encoding proteins involved in drug disposition such as CYP3A4 and study AD-141-2305 evaluated the potential for BIC to induce CYP3A by evaluating changes in mRNA expression and activity. Of note, study AD-141-2292 was conducted using hepatoma derived cell lines and study AD-141-2305 was conducted using sandwich culture human hepatocytes from three donors (as recommended in the 2012 FDA Drug-Drug Interaction Guidance). Results from study AD-141-2292 suggest that BIC does not have the potential to induce CYP3A enzymes *in vivo* (at a concentration of 15 µM, there was < 17% activation of PXR; the maximum plasma concentration (C_{max}, total) in humans is ~14 µM). Results from AD-141-2305 suggested that BIC is a weak inducer of CYP3A (geometric unbound EC_{50} of 19.1 µM for CYP3A4 mRNA), however it is important to note that the hepatocyte incubation media was serum-free. Considering that BIC is highly bound to plasma proteins (% f_u is 0.25%), the maximum free concentration (C_{max}, free) of BIC available *in vivo* (0.035 µM) to enter the cell membrane and activate the PXR receptor is expected to be significantly lower compared with geometric unbound EC_{50} determined in AD-141-2305. Hence, the experimental conditions of study AD-141-2305 may explain, in part, the differences between *in vitro* prediction of weak induction by BIC and the results from the DDI trial with midazolam which showed that BIC/F/TAF did not significantly alter MDZ exposures.

Conclusion:

- BIC/F/TAF did not significantly alter the concentration of midazolam.
- Because midazolam is a sensitive substrate of CYP3A, the results of the trial also suggest that BIC/F/TAF is not anticipated to significantly alter the concentrations of other CYP3A substrates.

Proposed Labeling Recommendation:
Applicant's proposal to include midazolam in Section 7.5 (Drugs without Clinically Significant Interactions with [TRADENAME]) is acceptable.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-380-4270\report-body.pdf

Clinical Site: Seaview Jacksonville, LLC. 7898 Baymeadows Way, Jacksonville, FL.

Bioanalytical Report:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-380-4270\basar (b) (4) 60-16131.pdf

Bioanalytical Site: (b) (4)

Study #	GS-US-311-1790	**Study Period:** April 14, 2015-September 29, 2015
Title	A Phase 1, Randomized, Open Label, Drug Interaction Study Evaluating the Effect of Emtricitabine (F)/Tenofovir Alafenamide (TAF) Fixed-Dose Combination Tablet or GS-9883 (BIC) on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol **Note: Results pertaining to F/TAF were reviewed as part of NDA 208464. The review outlined below only focuses on assessments conducted with BIC (Cohort 2).**	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: To determine the effect of FTC and TAF administered as the F/TAF 200/25 mg FDC tablet or BIC 75 mg on the PK of a representative hormonal contraceptive medication, norgestimate (NGM)/ethinyl estradiol (EE) (Ortho Tri-Cyclen® Lo).

Secondary: To evaluate the safety and tolerability of administration of F/TAF FDC or BIC when given with a representative hormonal contraceptive medication, NGM/EE (Ortho Tri-Cyclen® Lo).

Rationale:

Oral contraceptives containing a combination of an EE and a progestin are among the most frequently used methods of birth control. The applicant conducted the trial to gain quantitative information regarding the safe and effective use of BIC/F/TAF and oral contraceptives.

Dose Selection:

BIC (75 mg): The 75 mg dose was selected because this was the dose of BIC used in the Phase 2 efficacy and safety study of BIC co-administered with F/TAF (200/25 mg) in study GS-US-141-1475). Of note, although the applicant used BIC 75 mg in the trial, the results can be extrapolated to BIC/F/TAF (50/200/25 mg) because the mean systemic exposures of BIC after administration of BIC 75 mg under moderate fat conditions are expected to be higher than mean systemic exposures of BIC after administration of BIC/F/TAF 50/200/25 mg under fed (high fat and moderate fat) conditions. Hence, the results from this trial are expected to provide a conservative estimate of the effect of BIC/F/TAF on NGM/EE.

Ortho-Tricyclene® Lo (NGM 0.18 mg/0.215 mg/0.25 mg/EE 0.025 mg): Approved Combined Oral Contraceptive (COC)

Design and PK Assessments (Note: GS-9883 in the various tables refers to BIC):

Table 1: Study Schema for Cohort 2

	Part A	Part B		
	Lead-in	Cycle 1	Cycle 2	
Study Day	L1-L28	1-28	29-42	43-56
Cycle Day	1-28	1-28	1-14	15-28
OC [a]	X	X	X	X
GS-9883 75 mg[a]			X	

[a] Administered once daily in the morning with food

Source: Clinical Study Report, Page 22

All study treatments were administered at approximately the same time each day in the morning with food.

PK Sampling and Assessments:

Serial PK blood samples were collected on Study Days 14 and 42 at the following time points relative to dosing: pre-dose (≤ 5 minutes prior to dosing), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose. The plasma PK parameters were calculated for NGM (if possible), NGMN, NG, EE, FTC, TAF, TFV, and BIC. Of note, norgestimate is a pro-drug and is rapidly and completely metabolized by first pass (intestinal and/or hepatic) metabolism to metabolites norelgestromin (17-desacetyl norgestimate; NGMN) and norgestrel (NG). Therefore, the applicant assessed the plasma concentration of NGM, NGMN, and NG.

PD Sampling:

Blood samples for LH and FSH were collected pre-dose on Study Days 14 and 42. Blood samples for progesterone were collected pre-dose on Study Days 21 and 49.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations
BIC (75 mg tablets; lot # 1504B1, expiration date February 2016), Ortho-Tricyclene® Lo (Lot # 15BM311, expiration date January 2017).

RESULTS

Enrolled	16	Completed	15*	Discontinued Due to AE	0	PK Population	15	Safety Population	16

*One subject (subject # 3648-1014) withdrew consent; the last dose of the subject was on study day 29. The subject did not complete cycle 2.

Protocol Deviations
No important protocol deviations were reported in the trial.

Demographics
Sixteen female subjects were enrolled in Cohort 2 of the study. Median age was 36 years (range: 26 to 45 years), median (Q1, Q3) estimated CrCL at baseline was 125.56 (123.06, 134.19 mL/min) and median (min, max) BMI was 25.9 (22, 29.7) kg/m^2.

Results:

Pharmacokinetic Evaluation:

NGM: The majority of NGM concentrations were below the limit of quantification; therefore, no PK assessments were conducted.

NGMN:

Table 2: Mean pharmacokinetic parameters of NGMN after administration of OC only and after co-administration of OC + BIC

Norelgestromin PK parameter	GS-9883+OC (Test) (N = 15)	OC Only (Reference) (N = 16)
AUC_{last} (pg•h/mL)	16,237.5 (18.1)	14,979.9 (19.3)
AUC_{tau} (pg•h/mL)	16,237.5 (18.1)	14,979.9 (19.3)
C_{max} (pg/mL)	1697.3 (21.2)	1370.0 (16.4)
C_{tau} (pg/mL)	476.3 (30.1)	427.7 (27.4)
T_{max} (h) [a]	2.00 (1.50, 3.00)	2.00 (2.00, 2.75)
$T_{1/2}$ (h) [a]	33.47 (28.85, 50.61)	31.16 (25.13, 41.37)
T_{last} (h) [a]	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)
CL_{ss}/F (L/h)	13.6 (17.7)	14.8 (18.4)

Data presented as mean (%CV) unless otherwise noted.
a median (Q1, Q3)
Source: Clinical Study Report, Page 58

Table 3: Statistical comparison of the mean pharmacokinetic parameters of NGMN after administration of OC only and after co-administration of OC + BIC

Norelgestromin PK Parameter	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	GS-9883+OC (Test) (N = 15)	OC only (Reference) (N = 16)		
AUC_{tau} (h•pg/mL)	15,836.76	14,729.43	107.52	104.74, 110.37
C_{max} (pg/mL)	1663.62	1352.86	122.97	114.35, 132.25
C_{tau} (pg/mL)	455.80	414.39	109.99	104.82, 115.42

GLSM = Geometric Least-Squares Mean
ANOVA model including treatment as a fixed effect was used for the comparison
Source: Clinical Study Report, Page 59

NG:

Table 4: Mean pharmacokinetic parameters of norgestrel after administration of OC only and after co-administration of OC + BIC

Norgestrel PK parameter	GS-9883+OC (Test) (N = 15)	OC Only (Reference) (N = 16)
AUC_{last} (pg•h/mL)	68,487.7 (86.4)	56,964.7 (75.8)
AUC_{tau} (pg•h/mL)	68,487.7 (86.4)	56,964.7 (75.8)
C_{max} (pg/mL)	3430.7 (71.9)	2850.0 (64.6)
C_{tau} (pg/mL)	2709.3 (93.1)	2237.3 (83.8)
T_{max} (h)[a]	2.00 (2.00, 4.00)	3.00 (2.00, 3.50)
$T_{1/2}$ (h)[a]	75.64 (66.39, 102.39)[c]	100.93 (85.97, 138.03)[b]
T_{last} (h)[a]	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)
CL_{ss}/F (L/h)	4.3 (43.6)	4.8 (40.4)

Data presented as mean (%CV) unless otherwise noted.
a median (Q1, Q3)
b N = 15
c N = 14
Source: Clinical Study Report, Page 62

Table 5: Statistical comparison of the mean pharmacokinetic parameters of NG after administration of OC only and after co-administration of OC + BIC

Norgestrel PK Parameter	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	GS-9883+OC (Test) (N = 15)	OC only (Reference) (N = 16)		
AUC_{tau} (h•pg/mL)	55,328.21	49,004.59	112.90	106.81, 119.35
C_{max} (pg/mL)	2933.27	2544.08	115.30	109.50, 121.40
C_{tau} (pg/mL)	2135.48	1877.04	113.77	106.39, 121.66

GLSM = Geometric Least-Squares Mean
ANOVA model including treatment as a fixed effect was used for the comparison
Source: Clinical Study Report, Page 63

EE:

Table 6: Mean pharmacokinetic parameters of EE after administration of OC only and after co-administration of OC + BIC

Ethinyl Estradiol PK parameter	GS-9883+OC (Test) (N = 15)	OC Only (Reference) (N = 16)
AUC_{last} (pg•h/mL)	840.5 (32.1)	799.3 (34.1)
AUC_{tau} (pg•h/mL)	840.5 (32.1)	799.3 (34.1)
C_{max} (pg/mL)	87.4 (31.6)	75.1 (29.0)
C_{tau} (pg/mL)	18.9 (41.9)	18.1 (45.8)
T_{max} (h)[a]	2.00 (2.00, 3.00)	2.00 (2.00, 2.75)
$T_{1/2}$ (h)[a]	18.64 (15.28, 27.45)	16.45 (15.28, 22.85)
T_{last} (h)[a]	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)
CL_{ss}/F (L/h)	32.8 (33.3)	34.9 (34.5)

Data presented as mean (%CV) unless otherwise noted.
a median (Q1, Q3)
Source: Clinical Study Report, Page 66

Table 7: Statistical comparison of the mean pharmacokinetic parameters of EE after administration of OC only and after co-administration of OC + BIC

Ethinyl Estradiol PK Parameter	GLSMs by Treatment		GLSM Ratio Test/Reference (%)	90% CI
	GS-9883+OC (Test) (N = 15)	OC only (Reference) (N = 16)		
AUC_{tau} (h•pg/mL)	788.95	757.15	104.20	98.74, 109.96
C_{max} (pg/mL)	82.83	72.33	114.51	103.10, 127.17
C_{tau} (pg/mL)	17.17	16.42	104.54	95.49, 114.44

GLSM = Geometric Least-Squares Mean
ANOVA model including treatment as a fixed effect was used for the comparison
Source: Clinical Study Report, Page 67

BIC:

Table 8: Mean pharmacokinetic parameters of BIC after administration of OC + BIC

GS-9883 PK parameter	GS-9883+OC (N = 15)
AUC_{last} (ng•h/mL)	172,190.5 (15.1)
AUC_{tau} (ng•h/mL)	172,190.5 (15.1)
C_{max} (ng/mL)	11,880.0 (8.7)
C_{tau} (ng/mL)	4554.0 (19.5)
T_{max} (h)[a]	2.50 (2.00, 3.00)
$T_{1/2}$ (h)[a]	19.47 (18.21, 22.33)
T_{last} (h)[a]	24.00 (24.00, 24.00)
CL_{ss}/F (L/h)	0.4 (15.8)

Data presented as mean (%CV) unless otherwise noted.
a median (Q1, Q3)
Source: final clinical study report, page 72

Because all subjects were taking NGM/EE prior to administration of BIC 75 mg, there was no data available from "BIC only" administration to conduct a statistical analysis.

Pharmacodynamic Evaluation:

Table 9: Summary of progesterone, LH, and FSH concentrations following administration of NGM/EE alone and with BIC

PD parameter	GS-9883+OC (Cycle 2) (Test) (N = 16)	OC only (Cycle 1) (Reference) (N = 16)
Progesterone (ng/mL)	0.4 (0.4, 0.6)	0.4 (0.4, 0.6)
LH (mIU/mL)	4.4 (2.5, 9.4)	4.5 (1.4, 7.8)
FSH (mIU/mL)	4.3 (1.6, 6.3)	2.7 (1.8, 5.4)

Data presented as median (Q1, Q3).
Source: final clinical study report, page 73

Safety:
No Grade 3 or 4 AEs, serious adverse events (SAEs), or AEs leading to study discontinuation, or deaths were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct
- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results
The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

NGMN is a substrate of CYP3A. Co-administration of NGM/EE with BIC did not significantly change the mean AUC of NGMN, thereby suggesting that BIC is not an inhibitor or inducer of CYP3A and further confirming the results of trial GS-US-380-4270 (DDI trial of BIC with midazolam) in which BIC did not have a significant impact on midazolam exposures and *in vitro* study AD-141-2293 which did not suggest the potential for BIC to affect CYP3A enzymes *in vivo*. The increase in mean C_{max} of NGMN by approximately 23% after co-administration of NGM/EE with BIC may be due to other mechanisms considering that the mean C_{max} of NGMN increased by approximately 17% after co-administration of NGM/EE with F/TAF (both F and TAF do not inhibit CYP enzymes *in vivo*).

The increase in mean C_{max} of EE (approximately 15%) is not expected to be clinically relevant.

Proposed Labeling Recommendation:

Applicant's proposal to include norgestimate and ethinyl estradiol in Section 7.5 (Drugs without Clinically Significant Interactions with [TRADENAME]) is acceptable.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

\\cdsesub1\evsprod\nda208464\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-311-1790\report-body.pdf

Clinical Site: Seaview Research Inc. 3898 NW 7th Street, Miami, FL.

Bioanalytical Reports:

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Bioanalytical Site: (b) (4)

Study #	GS-US-380-1761	**Study Period:** July 20, 2015- September 10, 2015
Title	A Phase 1 Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between Bictegravir/Emtricitabine/Tenofovir Alafenamide Fumarate (BIC/F/TAF) and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) tablets	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary Objectives:
To evaluate the steady-state PK of BIC, F, and TAF upon co-administration of BIC/F/TAF and LDV/SOF FDC and to evaluate the steady-state PK of SOF, GS-566500 and GS-331007 (metabolites of SOF), and LDV upon co-administration of BIC/F/TAF and LDV/SOF FDC.

Secondary Objectives:
To evaluate the steady-state PK of tenofovir (TFV) upon co-administration of BIC/F/TAF FDC with LDV/SOF FDC and to evaluate the safety and tolerability of administration of BIC/F/TAF FDC or LDV/SOF FDC alone or in combination.

Rationale:
The trial was conducted to obtain quantitative drug-drug interaction information for the safe and effective use of BIC/F/TAF with LDV/SOF.
Dose Selection:
LDV/SOF (90/400): Approved doses of LDV and SOF as part of LDV/SOF combination (Harvoni®).
BIC/F/TAF (75/200/25): For F and TAF, the applicant used the approved doses in F/TAF FDC. For BIC, the applicant is seeking approval of BIC/F/TAF 50/200/25 mg FDC; however, the trial was conducted using BIC/F/TAF 75/200/25 mg FDC. Despite the differences in the dose of BIC, the results from the trial can be extrapolated to BIC/F/TAF 50/200/25 mg considering that the mean systemic exposures of BIC after administration of BIC/F/TAF 75/200/25 mg under fed (high fat) conditions are expected to be higher than mean systemic exposures of BIC after administration of BIC/F/TAF 50/200/25 mg under fed (high fat and moderate fat) conditions. Hence, the results from this trial are expected to provide a conservative estimate of the effect of BIC/F/TAF on LDV/SOF. Of note, the applicant did not evaluate the effect of a moderate fat meal on the pharmacokinetics of BIC, F, or TAF after administration of BIC/F/TAF 75/200/25 mg in the food effect trial (GS-US-141-1233).

Design and PK Assessments:

Treatment A: LDV/SOF 1 X 90/400 mg tablet once daily for 10 days (day 1 through 10)
Treatment B: BIC/F/TAF 75/200/25 mg tablet once daily for 10 days (days 11-20)
Treatment C: LDV/SOF 1X90/400 mg tablet once daily + BIC/F/TAF 75/200/25 mg tablet once daily for 10 days (days 21-30)

All study treatments were to be administered orally following an overnight fast (no food or liquids, except water) for at least 8 hours and within 5 minutes of completing a standard moderate-fat breakfast (approximately 600 calories and 27% fat). Serial blood samples were collected on Days 10, 20, and 30 at pre-dose (≤ 5 min) and up to 24 hours post-dose. As appropriate for each analyte, the plasma PK parameters were calculated for BIC, FTC, TAF, TFV, SOF, GS-566500, GS-331007, and LDV were calculated.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations
LDV/SOF (90/400 mg tablets; lot # DK1303B1; expiration date April 2017), BIC/F/TAF (75/200/25 mg; lot # EN1501B1, expiration date April 2016)

RESULTS									
Enrolled	30	Completed	30	Discontinued Due to AE	0	PK Population	30	Safety Population	30

Protocol Deviations

No protocol deviations were reported in the trial.

Demographics

The trial enrolled 20 male subjects and 10 female subjects. The median age was 33 years (range: 20 to 45 years) and median BMI was 25.6 kg/m^2 (range 20.3 to 29.6 kg/m^2). The median estimated creatinine clearance (calculated using Cockcroft-Gault formula) was 116.4 mL/min (range 90.4-188 mL/min).

Results:

Table 1: Mean plasma pharmacokinetic parameters of BIC following multiple-dose administration of BIC/F/TAF or LDV/SOF +BIC/F/TAF

	Mean (%CV)	
GS-9883 PK Parameter	**GS-9883/F/TAF (75/200/25mg) (N = 30)**	**LDV/SOF (90/400mg) + GS-9883/F/TAF (75/200/25mg) (N = 30)**
AUC_{tau} (h•ng/mL)	188,231.7 (19.3)	188,882.4 (20.8)
C_{max} (ng/mL)	13,570.0 (16.6)	13,306.3 (15.2)
C_{tau} (ng/mL)	4992.3 (29.9)	5188.0 (29.2)
T_{max} (h)[a]	3.00 (3.00, 4.00)	3.00 (2.00, 4.00)
CL_{ss}/F (mL/h)	411.7 (17.7)	412.0 (18.6)

a Median (Q1, Q3)

Source: final clinical study report, page 50

Table 2: Mean plasma pharmacokinetic parameters of FTC following multiple-dose administration of BIC/F/TAF or LDV/SOF +BIC/F/TAF

	Mean (%CV)	
FTC PK Parameter	**GS-9883/F/TAF (75/200/25mg) (N = 30)**	**LDV/SOF (90/400mg) + GS-9883/F/TAF (75/200/25 mg) (N = 30)**
AUC_{tau} (h•ng/mL)	11,505.7 (20.4)	11,309.1 (15.0)
C_{max} (ng/mL)	2013.3 (15.2)	2036.3 (26.6)
C_{tau} (ng/mL)	73.4 (21.6)	74.9 (19.2)
T_{max} (h)[a]	2.00 (2.00, 3.00)	2.50 (2.00, 3.00)
$t_{1/2}$ (h)[a]	6.23 (4.87, 7.76)	6.42 (5.69, 7.80)
CL_{ss}/F (mL/h)	17,892.5 (14.8)	18,024.4 (13.1)

a Median (Q1, Q3)

Source: final clinical study report, page 52

Table 3: Mean plasma pharmacokinetic parameters of TAF following multiple-dose administration of BIC/F/TAF or LDV/SOF +BIC/F/TAF

TAF PK Parameter	Mean (%CV)	
	GS-9883/F/TAF (75/200/25mg) (N = 30)	LDV/SOF (90/400mg) + GS-9883/F/TAF (75/200/25mg) (N = 30)
AUC_{last} (h•ng/mL)	342.6 (33.6)	430.0 (29.3)
C_{max} (ng/mL)	261.6 (49.7)	304.8 (46.0)
T_{max} (h)[a]	1.50 (1.00, 2.00)	1.75 (1.50, 2.00)
$t_{1/2}$ (h)[a]	0.40 (0.32, 0.44)	0.42 (0.36, 0.48)
CL_{ss}/F (mL/h)	80,178.6 (30.9)	63,107.5 (32.4)
V_Z/F (mL)	45,958.0 (34.5)	40,360.6 (37.5)

a Median (Q1, Q3)

Source: final clinical study report, page 54

Table 4: Mean plasma pharmacokinetic parameters of TFV following multiple-dose administration of BIC/F/TAF or LDV/SOF +BIC/F/TAF

TFV PK Parameter	Mean (%CV)	
	GS-9883/F/TAF (75/200/25mg) (N = 30)	LDV/SOF (90/400mg) + GS-9883/F/TAF (75/200/25mg) (N = 30)
AUC_{tau} (h•ng/mL)	284.1 (21.0)	474.7 (20.8)
C_{max} (ng/mL)	18.3 (19.5)	26.2 (19.6)
C_{tau} (ng/mL)	9.3 (21.2)	16.9 (23.8)
T_{max} (h)[a]	3.00 (3.00, 4.00)	3.50 (3.00, 4.00)

a Median (Q1, Q3)

Source: final clinical study report, page 56

Table 5: Mean plasma pharmacokinetic parameters of SOF following multiple-dose administration of BIC/F/TAF or LDV/SOF +BIC/F/TAF

SOF PK Parameter	Mean (%CV)	
	LDV/SOF (90/400mg) (N = 30)	LDV/SOF (90/400mg) + GS-9883/F/TAF (75/200/25mg) (N = 30)
AUC_{tau} (h•ng/mL)	2967.2 (24.6)	3166.6 (24.3)
C_{max} (ng/mL)	1697.1 (38.2)	1914.2 (37.4)
T_{max} (h)[a]	2.00 (2.00, 3.00)	2.00 (1.50, 3.00)
$t_{1/2}$ (h)[a]	0.47 (0.39, 0.54)	0.51 (0.44, 0.58)
CL_{ss}/F (mL/h)	141,730.4 (21.5)	133,098.8 (23.0)

a Median (Q1, Q3)

Source: final clinical study report, page 58

Table 6: Mean plasma pharmacokinetic parameters of GS-566500 following multiple-dose administration of BIC/F/TAF or LDV/SOF +BIC/F/TAF

GS-566500 PK Parameter	Mean (%CV)	
	LDV/SOF (90/400mg) (N = 30)	LDV/SOF (90/400mg) + GS-9883/F/TAF (75/200/25mg) (N = 30)
AUC_{tau} (h•ng/mL)	2727.1 (15.4)	2685.4 (17.1)
C_{max} (ng/mL)	616.7 (18.8)	611.4 (19.1)
T_{max} (h)[a]	3.00 (3.00, 4.00)	3.00 (2.00, 4.00)
C_{last} (ng/mL)	27.2 (54.7)	16.1 (44.7)
T_{last} (h)[a]	12.00 (12.00, 18.00)	18.00 (18.00, 18.00)
$t_{1/2}$ (h)[a]	2.22 (2.08, 2.49)	2.57 (2.33, 2.74)

a Median (Q1, Q3)

Source: final clinical study report, page 60

Table 7: Mean plasma pharmacokinetic parameters of GS-331007 following multiple-dose administration of BIC/F/TAF or LDV/SOF +BIC/F/TAF

GS-331007 PK Parameter	Mean (%CV)	
	LDV/SOF (90/400mg) (N = 30)	LDV/SOF (90/400mg) + GS-9883/F/TAF (75/200/25mg) (N = 30)
AUC_{tau} (h•ng/mL)	10,370.7 (14.9)	11,552.3 (17.2)
C_{max} (ng/mL)	822.1 (17.7)	903.9 (18.2)
C_{tau} (ng/mL)	308.0 (18.4)	315.7 (20.6)
T_{max} (h)[a]	4.00 (4.00, 4.50)	4.50 (3.00, 4.50)

a Median (Q1, Q3)

Source: final clinical study report, page 62

Table 8: Mean plasma pharmacokinetic parameters of LDV following multiple-dose administration of BIC/F/TAF or LDV/SOF +BIC/F/TAF

LDV PK Parameter	Mean (%CV)	
	LDV/SOF (90/400mg) (N = 30)	LDV/SOF (90/400mg) + GS-9883/F/TAF (75/200/25mg) (N = 30)
AUC_{tau} (h•ng/mL)	11,500.0 (28.6)	10,175.1 (35.0)
C_{max} (ng/mL)	656.4 (25.3)	567.0 (31.1)
C_{tau} (ng/mL)	400.9 (34.3)	364.5 (38.8)
AUC_{last} (h•ng/mL)	11,474.5 (28.6)	10,175.6 (35.0)
T_{max} (h)[a]	4.75 (4.50, 5.00)	5.00 (4.50, 6.00)
CL_{ss}/F (mL/h)	8462.4 (29.2)	9762.8 (29.6)

a Median (Q1, Q3)

Source: final clinical study report, page 64

Table 9: Mean PK parameters, geometric least squares mean ratio (GLSM) and 90% confidence interval (CI) of BIC, F, TAF, and TFV after administration of LDV/SOF and co-administration of LDV/SOF with BIC/F/TAF

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	LDV/SOF+GS-9883/F/TAF (Test) (N = 30)	GS-9883/F/TAF (Reference) (N = 30)	
GS-9883			
AUC_{tau} (h•ng/mL)	188,882.4 (20.8)	188,231.7 (19.3)	100.11 (97.17, 103.14)
C_{max} (ng/mL)	13,306.3 (15.2)	13,570.0 (16.6)	98.25 (94.04, 102.66)
C_{tau} (ng/mL)	5188.0 (29.2)	4992.3 (29.9)	103.99 (99.44, 108.74)
FTC			
AUC_{tau} (h•ng/mL)	11,309.1 (15.0)	11,505.7 (20.4)	98.89 (95.47, 102.43)
C_{max} (ng/mL)	2036.3 (26.6)	2013.3 (15.2)	99.19 (93.51, 105.20)
C_{tau} (ng/mL)	74.9 (19.2)	73.4 (21.6)	102.62 (98.85, 106.54)
TAF			
AUC_{last} (h•ng/mL)	430.0 (29.3)	342.6 (33.6)	126.65 (119.26, 134.49)
C_{max} (ng/mL)	304.8 (46.0)	261.6 (49.7)	117.23 (99.53, 138.08)
TFV			
AUC_{tau} (h•ng/mL)	474.7 (20.8)	284.1 (21.0)	166.97 (160.09, 174.14)
C_{max} (ng/mL)	26.2 (19.6)	18.3 (19.5)	143.36 (137.21, 149.80)
C_{tau} (ng/mL)	16.9 (23.8)	9.3 (21.2)	180.95 (172.75, 189.54)

Source: final clinical study report, page 6
Note: GS-9883= BIC

Table 10: Mean PK parameters, geometric least squares mean ratio (GLSM) and 90% confidence interval (CI) of SOF, GS-566500, GS-331007 and LDV after administration of LDV/SOF and co-administration of LDV/SOF with BIC/F/TAF

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	LDV/SOF+GS-9883/F/TAF (Test) (N = 30)	LDV/SOF (Reference) (N = 30)	
SOF			
AUC_{tau} (h•ng/mL)	3166.6 (24.3)	2967.2 (24.6)	106.67 (101.07, 112.58)
C_{max} (ng/mL)	1914.2 (37.4)	1697.1 (38.2)	111.41 (100.45, 123.57)
GS-566500			
AUC_{tau} (h•ng/mL)	2685.4 (17.1)	2727.1 (15.4)	98.19 (94.43, 102.11)
C_{max} (ng/mL)	611.4 (19.1)	616.7 (18.8)	98.96 (95.14, 102.93)
GS-331007			
AUC_{tau} (h•ng/mL)	11,552.3 (17.2)	10,370.7 (14.9)	110.98 (107.94, 114.10)
C_{max} (ng/mL)	903.9 (18.2)	822.1 (17.7)	109.90 (106.78, 113.12)
C_{tau} (ng/mL)	315.7 (20.6)	308.0 (18.4)	102.01 (98.53, 105.61)
LDV			
AUC_{tau} (h•ng/mL)	10,175.1 (35.0)	11,500.0 (28.6)	87.32 (82.61, 92.29)
C_{max} (ng/mL)	567.0 (31.1)	656.4 (25.3)	85.40 (80.74, 90.33)
C_{tau} (ng/mL)	364.5 (38.8)	400.9 (34.3)	89.92 (84.24, 95.99)

Source: final clinical study report, page 5

Safety

No Grade 3 or 4 AEs, AEs related to study drug, deaths, SAEs, or discontinuations of study drug due to an AE were reported.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

Co-administration of LDV/SOF and BIC/F/TAF increased the mean C_{max} and AUC of TAF by 17% and 27%, respectively. Considering that the half-life of TAF was not changed, the increase in TAF seems to be driven by intestinal inhibition of P-gp transporters by LDV. The increase in mean C_{max} and AUC of TAF is not expected to be clinically relevant as concomitant administration of F/TAF (Descovy®) with other protease inhibitors has shown a higher magnitude of increase in the mean C_{max} and AUC of TAF (with atazanavir/ritonavir, the mean

increase in C_{max} and AUC of TAF is 77% and 89%, respectively, and with lopinavir/ritonavir, the mean increase in C_{max} and AUC of TAF is 119% and 45%, respectively; information taken from clinical pharmacology review of Descovy® available at Drugs@FDA). Per the prescribing information of Descovy®, atazanavir/ritonavir or lopinavir/ritonavir can be co-administered with Descovy® without any need for dose adjustments. The mean C_{max} and AUC of TFV increased by 43% and 67% respectively, which may be due to the increased bioavailability of TAF. The increase in mean TFV exposures observed in this trial is not expected to be clinically relevant as concomitant administration of F/TAF (Descovy®) with other protease inhibitors have shown a higher magnitude of increase in the mean C_{max} and AUC of TFV (with atazanavir/ritonavir, the mean increase in C_{max} and AUC of TFV is 112% and 161%, respectively, and with lopinavir/ritonavir, the mean increase in C_{max} and AUC of TFV is 274% and 316%, respectively; information taken from clinical pharmacology review of Descovy® available at Drugs@FDA). Per the prescribing information of Descovy®, atazanavir/ritonavir or lopinavir/ritonavir can be co-administered with Descovy®, without any need for dose adjustments.

Proposed Labeling Recommendation:

Applicant's proposal to include LDV/SOF in Section 7.5 (Drugs without Clinically Significant Interactions with [TRADENAME]) is acceptable.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

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Clinical Site: Seaview Jacksonville, LLC. 7898 Baymeadows Way, Jacksonville, FL.

Bioanalytical Reports:

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Bioanalytical Site: (b) (4)

Study #	GS-US-380-1999	**Study Period:** Jan 28, 2016 – March 19, 2016
Title	A Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Bictegravir/Emtricitabine/Tenofovir Alafenamide Fumarate (BIC/F/TAF) and Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX) Fixed-Dose Combination (FDC) tablets	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

The primary objectives were to evaluate the steady-state pharmacokinetics of BIC, F, TAF and TFV upon administration of BIC/F/TAF alone or co-administration with SOF/VEL/VOX (+ an additional 100 mg VOX) and to evaluate the steady-state PK of SOF (and its metabolites GS-566500 and GS-331007), VEL and VOX after administration of SOF/VEL/VOX (+an additional 100 mg VOX) and upon co-administration of SOF/VEL/VOX (+an additional 100 mg VOX) and B/F/TAF FDC. The secondary objective was to evaluate the safety and tolerability of B/F/TAF FDC or SOF/VEL/VOX (+ an additional 100 mg VOX) alone or when co-administered.

Rationale:

The trial was conducted to obtain quantitative drug-drug interaction information for the safe and effective use of BIC/F/TAF with SOF/VEL/VOX (+ an additional 100 mg VOX).

Dose Selection:

SOF/VEL/VOX (400/100/100 mg): Doses of SOF, VEL and VOX in the approved FDC (Vosevi®). An additional 100 mg VOX was given to account for the higher VOX exposure observed in HCV-infected patients as compared to the VOX exposure observed in healthy subjects.

BIC/F/TAF (50/200/25 mg): Doses of BIC, F and TAF used in Phase 3 trials (as FDC) and proposed by the applicant for registration.

Design and PK Assessments:

Treatment A: BIC/F/TAF 50/200/25 mg tablet once daily for 10 days (days 1-10) administered under fed conditions.

Treatment B: BIC/F/TAF 50/200/25 mg tablet once daily + SOF/VEL/VOX 400/100/100 mg once daily + VOX 100 mg for 10 days (days 11-20) administered under fed conditions.

Treatment C: SOF/VEL/VOX 400/100/100 mg tablet once daily for 10 days (days 21-30) + VOX 100 mg administered under fed conditions.

Subjects were assigned to one of the six treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA) and received the three study treatments with the first treatment starting on day 1. All study treatments were administered orally at approximately the same time each day with 240 mL of water and following a standard moderate-fat breakfast. Serial blood samples were collected on Days 10, 20, and 30 at the following time points relative to study drug administration: pre-dose and up to 24 hours post-dose. Plasma concentration of BIC, F, TAF, TFV, SOF, GS-566500, GS-331007, VEL, and VOX were determined and the pharmacokinetic parameters were computed using non-compartmental methods.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations

SOF/VEL/VOX (400/100/100 mg tablets; batch # ER 1501B2, expiration date January 2017), BIC/F/TAF (50/200/25 mg tablets; lot # EN1503B1, expiration date August 2016), VOX (100 mg tablets, batch # DY1502B1, expiration date September 2016).

RESULTS									
Enrolled	30	Completed	30	Discontinued Due to AE	0	PK Population	30	Safety Population	30

Protocol Deviations

No protocol deviations were reported in the trial.

Demographics

Out of the 30 subjects enrolled in the trial, 19 subjects were male and 11 subjects were female. Median age was 36 years (range: 21 to 43), and median BMI was 26.6 (range 20.3 to 30) kg/m^2.

Results:

Table 1: Mean (%CV) pharmacokinetic parameters of BIC after administration of BIC/F/TAF FDC and co-administration of BIC/F/TAF FDC and SOF/VEL/VOX + VOX

BIC PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	B/F/TAF (N = 30)
AUC_{tau} (hr•ng/mL)	128,196.2 (20.1)	120,187.3 (19.5)
C_{max} (ng/mL)	8265.3 (14.7)	8525.0 (20.0)
C_{tau} (ng/mL)	3572.0 (30.5)	3224.0 (29.7)
T_{max} (hr)[a]	4.00 (3.00, 4.00)	3.00 (2.00, 3.00)
CL_{ss}/F (mL/hr)	404.3 (19.2)	431.0 (19.7)

a Median (Q1, Q3)

Source: final clinical study report, page 50

Table 2: Mean (%CV) pharmacokinetic parameters of FTC after administration of BIC/F/TAF FDC and co-administration of BIC/F/TAF FDC and SOF/VEL/VOX + VOX

FTC PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	B/F/TAF (N = 30)
AUC_{tau} (hr•ng/mL)	9444.8 (14.3)	9919.9 (12.1)
C_{max} (ng/mL)	1630.0 (25.6)	1829.7 (21.6)
C_{tau} (ng/mL)	70.5 (22.2)	63.9 (20.5)
T_{max} (hr)[a]	2.00 (2.00, 3.00)	2.00 (1.53, 2.02)
$t_{1/2}$ (hr)[a]	7.33 (6.10, 9.18)	7.23 (4.88, 8.35)
CL_{ss}/F (mL/hr)	21,579.7 (13.7)	20,432.1 (11.5)
V_z/F (mL)	235,198.7 (33.4)	201,934.3 (28.6)

a Median (Q1, Q3)

Source: final clinical study report, page 51

Table 3: Mean (%CV) pharmacokinetic parameters of TAF after administration of BIC/F/TAF FDC and co-administration of BIC/F/TAF FDC and SOF/VEL/VOX + VOX

TAF PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	B/F/TAF (N = 30)
AUC_{tau} (hr•ng/mL)	443.4 (38.2)	281.6 (35.5)
AUC_{last} (hr•ng/mL)	441.5 (38.3)	279.7 (36.0)
C_{max} (ng/mL)	280.4 (61.0)	217.2 (47.8)
T_{max} (hr)[a]	1.50 (1.50, 2.00)	1.50 (1.00, 1.50)
$t_{1/2}$ (hr)[a]	0.50 (0.45, 0.53)	0.39 (0.37, 0.45)
CL_{ss}/F (mL/hr)	64,801.1 (39.1)	102,684.9 (43.3)
V_z/F (mL)	47,048.7 (35.7)	66,940.6 (75.2)

a Median (Q1, Q3)

Source: final clinical study report, page 53

Table 4: Mean (%CV) pharmacokinetic parameters of TFV after administration of BIC/F/TAF FDC and co-administration of BIC/F/TAF FDC and SOF/VEL/VOX + VOX

TFV PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	B/F/TAF (N = 30)
AUC_{tau} (hr•ng/mL)	480.1 (20.0)	286.8 (20.2)
C_{max} (ng/mL)	26.9 (20.8)	17.8 (21.8)
C_{tau} (ng/mL)	16.7 (22.1)	9.6 (22.6)
T_{max} (hr)[a]	3.00 (3.00, 4.97)	3.00 (2.00, 3.03)

a Median (Q1, Q3).

Source: final clinical study report, page 55

Table 5: Mean (%CV) pharmacokinetic parameters of SOF after administration of SOF/VEL/VOX + VOX and co-administration of SOF/VEL/VOX + VOX + BIC/F/TAF FDC

SOF PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	SOF/VEL/VOX+VOX (N = 30)
AUC_{tau} (hr•ng/mL)	3450.1 (27.8)	3129.2 (22.6)
C_{max} (ng/mL)	1867.2 (48.0)	1574.3 (33.0)
T_{max} (hr)[a]	1.50 (1.50, 2.00)	1.90 (1.50, 2.00)
$t_{1/2}$ (hr)[a]	0.56 (0.50, 0.62)	0.54 (0.48, 0.59)
CL_{ss}/F (mL/hr)	125,547.8 (30.2)	134,196.4 (22.3)
V_z/F (mL)	105,647.8 (34.4)	109,446.4 (37.5)

a Median (Q1, Q3)

Source: final clinical study report, page 57

Table 6: Mean (%CV) pharmacokinetic parameters of GS-566500 after administration of SOF/VEL/VOX + VOX and co-administration of SOF/VEL/VOX + VOX + BIC/F/TAF FDC

GS-566500 PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	SOF/VEL/VOX+VOX (N = 30)
AUC_{tau} (hr•ng/mL)	2978.5 (22.8)	3056.2 (22.5)
C_{max} (ng/mL)	612.0 (25.1)	629.0 (23.3)
T_{max} (hr)[a]	2.50 (2.00, 3.00)	3.00 (2.00, 4.00)
$t_{1/2}$ (hr)[a]	2.80 (2.58, 3.06)	2.52 (2.41, 2.70)

a Median (Q1, Q3)

Source: final clinical study report, page 59

Table 7: Mean (%CV) pharmacokinetic parameters of GS-331007 after administration of SOF/VEL/VOX + VOX and co-administration of SOF/VEL/VOX + VOX + BIC/F/TAF FDC

GS-331007 PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	SOF/VEL/VOX+VOX (N = 30)
AUC_{tau} (hr•ng/mL)	11,157.2 (16.3)	10,843.3 (17.0)
C_{max} (ng/mL)	851.7 (15.7)	831.5 (17.1)
C_{tau} (ng/mL)	308.3 (21.3)	303.3 (19.7)
T_{max} (hr)[a]	4.00 (3.00, 4.00)	4.00 (3.00, 5.00)
$t_{1/2}$ (hr)[a]	15.49 (13.26, 21.80)	14.98 (12.02, 17.12)

a Median (Q1, Q3)

Source: final clinical study report, page 61

Table 8: Mean (%CV) pharmacokinetic parameters of VEL after administration of SOF/VEL/VOX + VOX and co-administration of SOF/VEL/VOX + VOX + BIC/F/TAF FDC

VEL PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	SOF/VEL/VOX+VOX (N = 30)
AUC_{tau} (hr•ng/mL)	7708.9 (36.4)	8048.1 (33.9)
C_{max} (ng/mL)	897.6 (31.6)	937.3 (29.9)
C_{tau} (ng/mL)	137.6 (52.9)	144.1 (47.2)
T_{max} (hr)[a]	3.00 (3.00, 4.00)	4.00 (3.00, 4.97)
$t_{1/2}$ (hr)[a]	11.59 (9.83, 13.91)	10.22 (8.74, 11.62)
CL_{ss}/F (mL/hr)	14,527.7 (32.8)	14,060.0 (40.0)
V_z/F (mL)	241,984.1 (34.1)	214,425.8 (40.4)

a Median (Q1, Q3)

Source: final clinical study report, page 63

Table 9: Mean (%CV) pharmacokinetic parameters of VOX after administration of SOF/VEL/VOX + VOX and co-administration of SOF/VEL/VOX + VOX + BIC/F/TAF FDC

VOX PK Parameter	Mean (%CV)	
	B/F/TAF + SOF/VEL/VOX+VOX (N = 30)	SOF/VEL/VOX+VOX (N = 30)
AUC_{tau} (hr•ng/mL)	4460.3 (66.1)	4818.6 (61.3)
C_{max} (ng/mL)	879.8 (69.1)	929.3 (55.6)
C_{tau} (ng/mL)	27.8 (71.4)	27.6 (56.5)
T_{max} (hr)[a]	5.00 (4.00, 5.00)	5.00 (4.00, 5.00)
$t_{1/2}$ (hr)[a]	6.96 (5.82, 8.26)	7.10 (5.54, 8.16)
CL_{ss}/F (mL/hr)	64,359.9 (62.4)	57,438.6 (57.5)
V_z/F (mL)	704,006.6 (77.7)	647,636.4 (74.8)

a Median (Q1, Q3)

Source: final clinical study report, page 65

Table 10: Mean PK parameters, geometric least squares mean ratio (GLSM) and 90% confidence interval (CI) of SOF, GS-566500, GS-331007, VEL and VOX after administration of SOF/VEL/VOX +VOX and co-administration of SOF/VEL/VOX +VOX and BIC/F/TAF

	Mean (%CV)		
	B/F/TAF + SOF/VEL/VOX+VOX (Test) (N = 30)	SOF/VEL/VOX+VOX (Reference) (N = 30)	%GLSM Ratio (90% CI) (Test/Reference)
SOF PK Parameter			
AUC_{tau} (hr•ng/mL)	3450.1 (27.8)	3129.2 (22.6)	108.69 (102.41, 115.35)
C_{max} (ng/mL)	1867.2 (48.0)	1574.3 (33.0)	114.07 (104.02, 125.09)
GS-566500 PK Parameter			
AUC_{tau} (hr•ng/mL)	2978.5 (22.8)	3056.2 (22.5)	97.50 (95.33, 99.71)
C_{max} (ng/mL)	612.0 (25.1)	629.0 (23.3)	97.15 (92.61, 101.92)
GS-331007 PK Parameter			
AUC_{tau} (hr•ng/mL)	11,157.2 (16.3)	10,843.3 (17.0)	102.95 (100.44, 105.52)
C_{max} (ng/mL)	851.7 (15.7)	831.5 (17.1)	102.66 (99.45, 105.97)
C_{tau} (ng/mL)	308.3 (21.3)	303.3 (19.7)	101.28 (98.10, 104.56)
VEL PK Parameter			
AUC_{tau} (hr•ng/mL)	7708.9 (36.4)	8048.1 (33.9)	95.77 (90.21, 101.67)
C_{max} (ng/mL)	897.6 (31.6)	937.3 (29.9)	96.00 (91.24, 101.00)
C_{tau} (ng/mL)	137.6 (52.9)	144.1 (47.2)	94.42 (88.02, 101.28)
VOX PK Parameter			
AUC_{tau} (hr•ng/mL)	4460.3 (66.1)	4818.6 (61.3)	91.01 (80.04, 103.49)
C_{max} (ng/mL)	879.8 (69.1)	929.3 (55.6)	89.84 (76.36, 105.69)
C_{tau} (ng/mL)	27.8 (71.4)	27.6 (56.5)	96.74 (88.31, 105.97)

Source: final clinical study report, page 7

Table 11: Mean PK parameters, geometric least squares mean ratio (GLSM) and 90% confidence interval (CI) of BIC, F, TAF, and TFV after administration of BIC/F/TAF and co-administration of SOF/VEL/VOX+VOX with BIC/F/TAF

	Mean (%CV)		
	B/F/TAF + SOF/VEL/VOX+VOX (Test) (N = 30)	B/F/TAF (Reference) (N = 30)	%GLSM Ratio (90% CI) (Test/Reference)
BIC PK Parameter			
AUC_{tau} (hr•ng/mL)	128,196.2 (20.1)	120,187.3 (19.5)	106.60 (103.34, 109.96)
C_{max} (ng/mL)	8265.3 (14.7)	8525.0 (20.0)	97.69 (94.39, 101.10)
C_{tau} (ng/mL)	3572.0 (30.5)	3224.0 (29.7)	110.46 (104.61, 116.63)
FTC PK Parameter			
AUC_{tau} (hr•ng/mL)	9444.8 (14.3)	9919.9 (12.1)	94.94 (93.05, 96.87)
C_{max} (ng/mL)	1630.0 (25.6)	1829.7 (21.6)	88.55 (83.11, 94.34)
C_{tau} (ng/mL)	70.5 (22.2)	63.9 (20.5)	110.22 (104.80, 115.91)
TAF PK Parameter			
AUC_{tau} (hr•ng/mL)	443.4 (38.2)	281.6 (35.5)	157.25 (144.20, 171.48)
AUC_{last} (hr•ng/mL)	441.5 (38.3)	279.7 (36.0)	158.02 (144.68, 172.58)
C_{max} (ng/mL)	280.4 (61.0)	217.2 (47.8)	128.05 (108.90, 150.56)
TFV PK Parameter			
AUC_{tau} (hr•ng/mL)	480.1 (20.0)	286.8 (20.2)	167.36 (161.55, 173.38)
C_{max} (ng/mL)	26.9 (20.8)	17.8 (21.8)	151.41 (144.85, 158.27)
C_{tau} (ng/mL)	16.7 (22.1)	9.6 (22.6)	173.55 (167.77, 179.53)

Source: final clinical study report, page 6

Safety

No Grade 3 or 4 AEs, SAEs, or AEs leading to premature discontinuations of the study drug or death was reported in the trial.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

Co-administration of SOF/VEL/VOX increased the mean C_{max} and AUC of TAF by 28% and 57%, respectively. Considering that the mean half-life of TAF was not changed (data not shown), the increase in TAF seems to be driven by intestinal inhibition of P-gp transporters by VEL and VOX. The increase in mean C_{max} and AUC of TAF is not expected to be clinically relevant for the same reason as outlined in the discussion

of trial GS-US-380-1761. The mean C_{max} and AUC of TFV increased by 51% and 67% respectively, which may be due to the increased bioavailability of TAF. The increase in mean TFV exposures observed in this trial is not expected to be clinically relevant for the same reason as outlined in the discussion of trial GS-US-380-1761.

Proposed Labeling Recommendation:

Applicant's proposal to include SOF/VEL/VOX in Section 7.5 (Drugs without Clinically Significant Interactions with [TRADENAME]) is acceptable.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-380-1999\report-body.pdf

Clinical Site: Seaview Jacksonville, LLC. 7898 Baymeadows Way, Jacksonville, FL.

Bioanalytical Reports:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-380-1999\basar (b) (4) 60-1609a.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-380-1999\basar (b) (4) 60-1609b.pdf

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Bioanalytical Sites: (b) (4)

Study #	GS-US-141-1479	**Study Period:** April 17, 2015 through July 13, 2015
Title	A Phase 1, Open Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of Bictegravir (BIC) in Subjects with Normal and Impaired Renal Function	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: Evaluate the PK profile of BIC in subjects with impaired renal function relative to matched, healthy controls with normal renal function.
Secondary: Evaluate the safety and tolerability of BIC in subjects with normal and impaired renal function.

Rationale:
The applicant conducted this trial to assess if there are differences in the systemic exposure of BIC due to differences in renal function (as determined by estimated creatinine clearance using Cockcroft-Gault equation) so that dosing recommendations of BIC/F/TAF in subjects with different degree of renal function can be determined. Of note, approved prescribing information of F/TAF (Descovy®) indicates that no dose adjustment of Descovy® is recommended for patients with estimated creatinine clearance greater than or equal to 30 mL/min and Descovy® is not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL/min).

Dose Selection:

BIC (75 mg): The 75mg dose was selected because this was the dose of BIC used in the Phase 2 efficacy and safety study of BIC co-administered with F/TAF (200/25 mg) in study GS-US-141-1475). Further, results from trial GS-US-141-1218 do not suggest a potential for drug-drug interaction between BIC and F/TAF.

Design and PK Assessments:

Phase 1, open-label, parallel-group, adaptive, single-dose study to evaluate the PK of BIC in subjects with impaired renal function. The renal function was determined using the Cockcroft-Gault (C-G) equation.

The study was designed to enroll subjects with normal renal function ($CrCL_{CG} \geq 90$ mL/min). and the following adaptive cohorts: Cohort 1 (Severe Renal Impairment; $CrCL_{CG}$ of 15-29 mL/min; n=10 subjects), Cohort 2 (Moderate Renal Impairment; $CrCL_{CG}$ of 30-59 mL/min; n=10 subjects), and Cohort 3 (Mild Renal Impairment; $CrCL_{CG}$ of 60-89 mL/min; n=10 subjects). Adaptive cohorts were to be enrolled only if supported by preliminary safety data and if substantial changes in BIC exposure were observed in subjects with renal impairment in the previous cohort. **Based on results from the severe renal impairment group, the applicant did not enroll any subjects in the moderate renal impairment group and the mild renal impairment group.** Each subject with normal renal function was matched for age (± 10 years), sex, and BMI (± 20, $18 \leq$ BMI ≤ 40 [kg/m2]) with a subject in the impaired renal function group.

PK Sampling and Assessments:

Serial blood samples were collected on day 1 at the following time points relative to study drug administration: Pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, and 144 hours post-dose. The plasma PK parameters of BIC were calculated. Urine samples were collected over the following collection intervals relative to study drug administration on day 1: pre-dose (within the 12 hour period prior to day 1 dose) and 0-12, 12-24, 24-48, 48-72, 72-96, 96-120 and 120-144 hours post-dose. he following urine PK parameters were calculated for BIC: A_e, F_e, and CL_r.
Plasma protein binding of BIC was assessed 2 hours post-dose by equilibrium dialysis method using a multi

equilibrium dialyzer system and 5000 molecular weight cut off dialysis membranes. The dialysis time was 4 hours, which was determined in a time-to-equilibrium experiment. Equilibrium dialysis was carried out using a plasma volume of 0.75-0.9 mL, which was first spiked with [^{14}C]GS-9883 at concentration of 0.5 µg/mL (approximately 0.06 µCi/mL), and dialyzed against an equal volume of 0.133M potassium phosphate buffer (pH 7.4). Radioactivity in post-dialysis plasma and buffer samples was determined by LSC and was used for the percent unbound calculation.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations
BIC 75 tablets, batch # EC1504B1, Expiration date February 2016)

RESULTS

Enrolled	19	Completed	18*	Discontinued	1	PK Population	18	Safety Population	18

*: 10 subjects with severe renal impairment ($CrCL_{CG}$ 15-29 mL/min) and 8 matched control subjects with normal renal function ($CrCL_{CG} \geq 90$ mL/min).
**: Subject was enrolled in the several renal impairment, was not dosed, and discontinued the study after consent withdrawal.

Protocol Deviations
No important protocol deviations were reported in the trial.

Demographics
There were 10 subjects in the severe renal impairment group (7 males and 3 females) and 8 subjects in the normal renal function group (6 males and 2 females). Median age was 68 years (range: 22 to 75 years) in the severe renal impairment group and 61 years (range 22 to 67 years) in the normal renal function group. The median BMI was 26.5 kg/m^2 in the severe renal impairment group and 27.8 kg/m^2 in the normal renal function group. The median (Q1, Q3) $CrCL_{CG}$ was 23.7 (22.5, 25.6) mL/min and 106.1 (94.3, 117.1) mL/min in the severe renal impairment group and the normal renal function group, respectively.

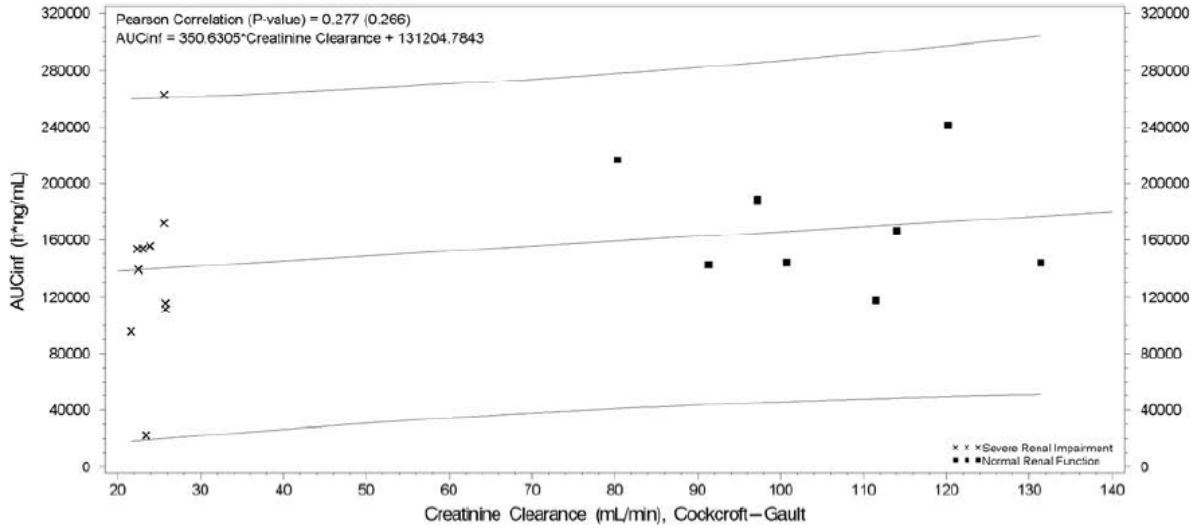
Results:

Table 1: Plasma PK parameters of BIC following single dose administration of BIC 75 mg to subjects with severe renal impairment and subjects with normal renal function

GS-9883 PK Parameter	Mean (%CV)	
	Severe Renal Impairment (N = 10)	Normal Renal Function (N = 8)
AUC_{inf} (h•ng/mL)	138,169.7 (44.4)	170,105.6 (24.8)
AUC_{last} (h•ng/mL)	136,956.4 (44.2)	168,876.8 (24.7)
C_{max} (ng/mL)	5977.0 (34.8)	7227.5 (29.5)
AUC_{exp} (%)	0.98 (84.91)	0.70 (53.90)
C_{last} (ng/mL)	44.07 (65.40)	41.83 (56.85)
T_{max} (h)[a]	3.50 (2.05, 6.00)	3.50 (2.00, 4.00)
T_{last} (h)[a]	144.00 (96.00, 144.00)	144.00 (144.00, 144.00)
$t_{1/2}$ (h)[a]	17.68 (12.14, 21.93)	19.19 (18.02, 21.16)
CL/F (mL/h)	815.9 (109.7)	464.0 (23.4)
V_z/F (mL)	16,270.4 (58.5)	12,976.4 (25.5)

a Median (Q1, Q3)
Source: final clinical study report, page 54

Fig 1: Regression analysis of BIC AUC_{inf} as a function of $CrCL_{CG}$ following single dose administration of BIC 75 mg to subjects with severe renal impairment and subjects with normal renal function



The p-value was based on the Pearson correlation between creatinine clearance and AUC_{inf}.
Values for $eGFR_{CG}$ were those used in study entry criteria, measured during screening prior to the baseline (Day −1) visit.
Note: The middle line represents the regression line and the top and the bottom lines represent the 95 % confidence interval (details on page 153 of final clinical study report).
Source of figure: final clinical study report, page 57

Linear regression analyses of BIC AUC_{inf} versus screening $CrCL_{CG}$ indicated no trend between systemic exposure of BIC and renal function. Similar results indicated no trend between AUC_{last} versus $CrCL_{CG}$ and C_{max} versus $CrCL_{CG}$ (graphs not shown).

Table 2: Plasma protein binding, free C_{max}, AUC_{last}, and AUC_{inf} of BIC following single dose administration of BIC 75 mg to subjects with severe renal impairment and subjects with normal renal function

	Mean (%CV)	
GS-9883 PK Parameter	**Severe Renal Impairment (N = 10)**	**Normal Renal Function (N = 8)**
Unbound Plasma GS-9883 at 2 h (%)	0.75 (72.03)	0.49 (9.32)
Free AUC_{inf} (h•ng/mL)[a]	830.6 (32.1)	824.5 (24.7)
Free AUC_{last} (h•ng/mL)[a]	822.5 (32.0)	818.6 (24.6)
Free C_{max} (ng/mL)[a]	37.7 (21.6)	35.0 (28.4)

a Free AUC_{last}, free AUC_{inf}, and free C_{max} were calculated based on unbound plasma GS-9883 (PK parameter × percentage unbound GS-9883 ÷ 100 for each subject).
Source: final clinical study report, page 55

In individual subjects (includes all subjects with the exception of subject # 7588-1003), unbound plasma BIC ranged from 0.43% to 0.63%, except for 1 subject (subject # 7588-1003) in the severe renal impairment group who had a significantly higher percentage of unbound plasma BIC (2.28%). This subject also had lower plasma BIC exposure. After exclusion of this subject, the mean % of unbound plasma BIC in the severe renal impairment group was 0.58%.

Table 3: Statistical comparison of the mean PK parameters of BIC following single dose administration of BIC 75 mg to subjects with severe renal impairment and subjects with normal renal function

(including data from subject 7588-103)

GS-9883 PK Parameter	GLSM		GLSM Ratio, % (90% CI)
	Severe Renal Impairment (Test) (N = 10)	Normal Renal Function (Reference) (N = 8)	
Total AUC_{inf} (h•ng/mL)	120,378.98	165,738.64	72.63 (48.80, 108.10)
Total AUC_{last} (h•ng/mL)	119,198.88	164,570.16	72.43 (48.54, 108.07)
Total C_{max} (ng/mL)	5582.27	6950.43	80.32 (59.56, 108.30)
Free AUC_{inf} (h•ng/mL)[a]	797.32	802.98	99.29 (79.49, 124.04)
Free AUC_{last} (h•ng/mL)[a]	789.50	797.32	99.02 (79.24, 123.74)
Free C_{max} (ng/mL)[a]	36.97	33.67	109.80 (87.46, 137.85)

a Free AUC_{last}, free AUC_{inf}, and free C_{max} were calculated based on unbound plasma GS-9883 (PK parameter × percentage unbound GS-9883 ÷ 100 for each subject).

Source: final clinical study report, page 55

Table 4: Statistical comparison of the mean PK parameters of BIC following single dose administration of BIC 75 mg to subjects with severe renal impairment and subjects with normal renal function (after excluding subject 7588-103)

GS-9883 PK Parameter	GLSM		GLSM Ratio, % (90% CI)
	Severe Renal Impairment (Test) (N = 9)	Normal Renal Function (Reference) (N = 8)	
Total AUC_{inf} (h•ng/mL)	145,031.12	165,738.64	87.51 (69.65, 109.94)
Total AUC_{last} (h•ng/mL)	143,902.82	164,570.16	87.44 (69.70, 109.70)
Total C_{max} (ng/mL)	6263.64	6950.43	90.12 (71.45, 113.67)
Free AUC_{inf} (h•ng/mL)[a]	837.32	802.98	104.28 (83.88, 129.63)
Free AUC_{last} (h•ng/mL)[a]	830.81	797.32	104.20 (83.93, 129.37)
Free C_{max} (ng/mL)[a]	36.16	33.67	107.39 (85.34, 135.13)

a Free AUC_{last}, free AUC_{inf}, and free C_{max} were calculated based on unbound plasma GS-9883 (PK parameter × percentage unbound GS-9883 ÷ 100 for each subject).

Data from Subject 7588-1003 were excluded from the analyses due to unusually low GS-9883 concentrations.

Source: final clinical study report, page 56

Table 5: Mean (%CV) pharmacokinetic parameters of BIC following single dose administration of BIC 75 mg to subjects with severe renal impairment and subjects with normal renal function

GS-9883 PK Parameter	Mean (%CV)	
	Severe Renal Impairment (N = 10)	Normal Renal Function (N = 8)
A_e from 0 to 144 h (ng)	707,225.12 (29.67)	805,900.59 (52.00)
F_e from 0 to 144 h	0.009 (29.670)	0.011 (51.999)
CL_r (mL/h)	7.25 (103.98)	4.56 (34.59)

Source: final clinical study report, page 57

The fraction of the BIC dose and the amount of unchanged BIC excreted in the urine were similar between subjects with severe renal impairment and subjects with normal renal function.

Safety:
No Grade 3 or 4 AEs, serious adverse events (SAEs), AEs leading to study discontinuation, or deaths were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Of note, the applicant mentions that "renal function was based on estimated glomerular filtration rate calculated using Cockcroft-Gault equation ($eGFR_{CG}$)", however, estimated CrCL [denoted as $CrCL_{CG}$] (instead of $eGFR_{CG}$) is an accurate descriptor because the applicant used C-G equation which would provide $CrCL_{CG}$ (and not $eGFR_{CG}$).

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

The results of the trial demonstrate that severe renal impairment (estimated $CrCL_{CG}$ 15-29 mL/min) did not significantly alter the pharmacokinetics of BIC. It should be noted that although the results of the trial suggest no significant change in BIC exposures in subjects with severe renal impairment and TAF (when given alone) can be given to subjects with estimated CrCL ≥ 15 mL/min, BIC/F/TAF is not recommended for use in subjects with severe renal impairment (estimated CrCL 15-29 mL/min) because BIC/F/TAF is a fixed dose combination (FDC) product and F/TAF is not approved for use in subjects with estimated CrCl< 30 mL/min. Therefore, the recommendation for use of BIC/F/TAF in subjects with renal impairment is guided by the most conservative dosing recommendation for affected components in the setting of renal impairment (i.e., F).

The applicant evaluated the PK of BIC in subjects with severe renal impairment (estimated $CrCL_{CG}$ 15-29 mL/min) in this trial and based on the results, did not evaluate the PK of BIC in subjects with moderate renal impairment (estimated $CrCL_{CG}$ 30-59 mL/min) and mild renal impairment (estimated $CrCL_{CG}$ 60-89 mL/min). The applicant's approach is acceptable considering that the severe renal impairment group did not show a significant change in the PK of BIC and hence, the PK of BIC is not anticipated to be significantly altered in subjects with moderate renal impairment (estimated $CrCL_{CG}$ 30-59 mL/min) and mild renal impairment (estimated $CrCL_{CG}$ 60-89 mL/min).

The following pieces of information also support the applicant's proposed recommendation:

1) The results from the mass balance trial shows that only 1.3% of the orally administered BIC is excreted unchanged through the renal route.
2) Trial GS-US-380-1490 (one of the Phase 3 trials) enrolled subjects with estimated CrCL ≥ 30 mL/min and no relationship between BIC exposures and efficacy was observed.

Proposed Labeling Recommendation:

Applicant's proposal of [redacted] **is acceptable.**

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

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Clinical Sites: Clinical Pharmacology of Miami, Inc. Miami, FL (enrolled 4 subjects); Orlando Clinical Research Center, Orlando, FL (enrolled 4 subjects); Prism Research, St. Paul, Minnesota (enrolled 3 subjects); New Orleans Center for Clinical Research (enrolled 5 subjects), and Christchurch Clinical Studies Trust (enrolled 3 subjects).

Bioanalytical Reports:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-141-1479\basar [redacted] 60-1522a.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-141-1479\basar [redacted] 60-1522b.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-141-1479\basar [redacted] 60n-1525.pdf

Bioanalytical Site: [redacted]

Study #	GS-US-141-1478	**Study Period:** February 10, 2016 through May 9, 2016
Title	A Phase 1, Open Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of Bictegravir (BIC) in Subjects with Normal and Impaired Hepatic Function	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: Evaluate the PK profile of BIC in subjects with impaired hepatic function relative to matched, healthy controls with normal hepatic function.
Secondary: Evaluate the safety and tolerability of BIC in subjects with normal and impaired hepatic function.

Rationale:

Nonclinical and human absorption, distribution, metabolism, and excretion (ADME) studies indicated that BIC was mainly eliminated through hepatic metabolism mediated by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and cytochrome P450 enzyme 3A (CYP3A4). Hence, hepatic impairment may alter the disposition of BIC.

The applicant conducted this trial to assess if there are differences in the systemic exposure of BIC due to differences in hepatic function (as determined by Child-Pugh-Turcotte [CPT] score) so that dosing recommendations of BIC/F/TAF in subjects with different degrees of hepatic impairment can be determined. Of note, approved prescribing information of F/TAF (Descovy®) indicates that no dose adjustment of Descovy® is recommended for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Descovy® has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Dose Selection:
BIC (75 mg): The 75 mg dose was selected because this was the dose of BIC used in the Phase 2 efficacy and safety study of BIC co-administered with F/TAF (200/25 mg) in study GS-US-141-1475). Further, results from trial GS-US-141-1218 do not suggest a potential for drug-drug interaction between BIC and F/TAF.

Design and PK Assessments:
The trial planned to enroll up to 40 subjects using an adaptive study design that included up to 2 cohorts of subjects with hepatic impairment (20 subjects in Cohort 1 [10 subjects with moderate hepatic impairment and 10 subjects with normal hepatic function] and 20 subjects in cohort 2 [10 subjects with mild hepatic impairment and 10 subjects with normal hepatic function]). Subjects in Cohort 1 received a single oral dose of BIC in the morning under fed conditions (Day 1). Subjects remained confined to the study center until the completion of assessments on Day 7. Dosing of the matched subjects with normal hepatic function occurred after the subject with moderate impaired hepatic function had completed all PK assessments. Enrollment of Cohort 2 (mild hepatic impairment) was determined by the applicant based on review of preliminary safety and PK data from Cohort 1.

PK Sampling and Assessments:

Serial blood samples were collected on day 1 at the following time points relative to study drug administration: pre-dose and up to 144 hours post-dose. The PK parameters of BIC were calculated.

Additional blood samples were collected at 2 and 8 hours post-dose for determination of plasma protein binding. Plasma protein binding was determined by equilibrium dialysis method using a multi equilibrium dialyzer system and 5000 molecular weight cut off dialysis membranes. The dialysis time was 4 hours, which

was determined in a time-to-equilibrium experiment. Equilibrium dialysis was carried out using a plasma volume of 0.7-1 mL, which was first spiked with [^{14}C]GS-9883 at concentration of 0.5 µg/mL (approximately 0.06 µCi/mL), and dialyzed against an equal volume of 0.133M potassium phosphate buffer (pH 7.4). Radioactivity in post-dialysis plasma and buffer samples was determined by LSC and was used for the percent unbound calculation.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations
BIC 75 tablet, batch # EC1504B2, Expiration date August 2016

RESULTS

Enrolled	10	Completed	10	Discontinued	0	PK Population	10	Safety Population	10

Note: Based on the results from cohort 1, the applicant decided not to enroll any subjects in the mild hepatic impairment group.

Protocol Deviations
No protocol deviations were reported in the trial.

Demographics
Ten subjects with moderate hepatic impairment (7 males and 3 females) and 10 healthy control subjects (7 males and 3 females) were enrolled in Cohort 1. Median age was 56 years (range: 48 to 64 years) in the moderate hepatic impairment group and 56 years (range 43 to 68 years) in the healthy control group. The median BMI was 29.3 kg/m^2 (range 18.2 to 33.8 kg/m^2) in the moderate hepatic impairment group and 28.3 kg/m^2 (range 22 to 34 kg/m^2) in the healthy control group. In the moderate hepatic impairment group, there were 4 subjects with Child-Pugh score of 7, 4 subjects with Child-Pugh score of 8, and 2 subjects with Child-Pugh score of 9. Aside from hepatic insufficiency, the subjects were sufficiently healthy for study participation based upon medical history, physical examination, vital signs, and screening laboratory evaluations.

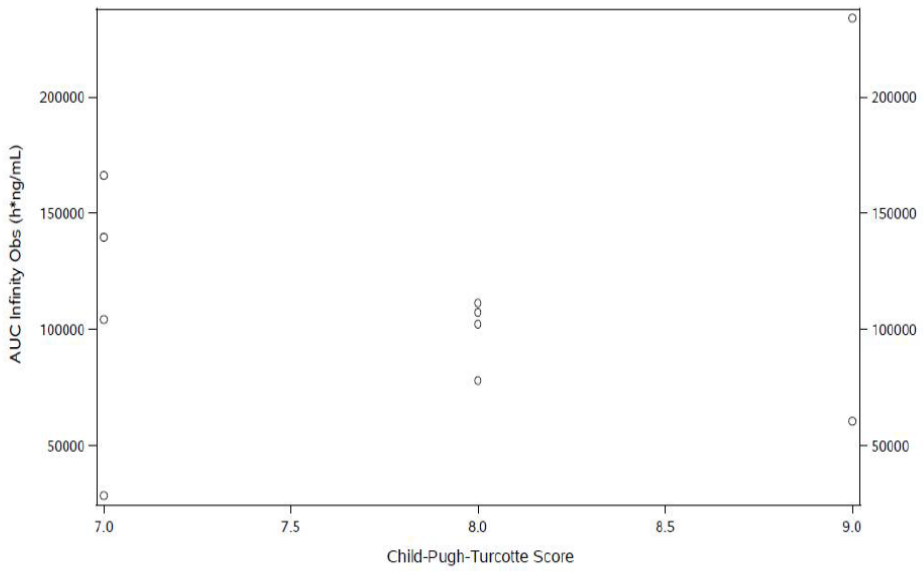
Results:

Table 1: Mean (%CV) plasma PK parameters of BIC following single dose administration of BIC 75 mg to subjects with moderate hepatic impairment group and subjects in healthy control group

BIC PK Parameter	Moderate Hepatic Impairment (N = 10)	Healthy Control (N = 10)
AUC_{inf} (h•ng/mL)	113,086.2 (50.7)	172,883.6 (23.4)
C_{max} (ng/mL)	5013.0 (29.1)	7849.0 (27.8)
C_{24} (ng/mL)	1643.6 (47.5)	2666.0 (24.9)
T_{max} (h)	3.50 (3.00, 4.00)	3.00 (2.00, 3.00)
$t_{1/2}$ (h)	17.44 (15.75, 18.94)	18.95 (17.96, 19.55)
AUC_{last} (h•ng/mL)	111,584.1 (49.9)	171,566.3 (23.4)
$\%AUC_{exp}$ (%)	1.1 (80.3)	0.8 (64.8)
CL/F (mL/h)	900.0 (74.2)	454.9 (22.7)
V_z/F (mL)	18067.8 (34.4)	12,893.3 (31.2)

Data are presented as mean (%CV), except for T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3).
Source: final clinical study report, page 51

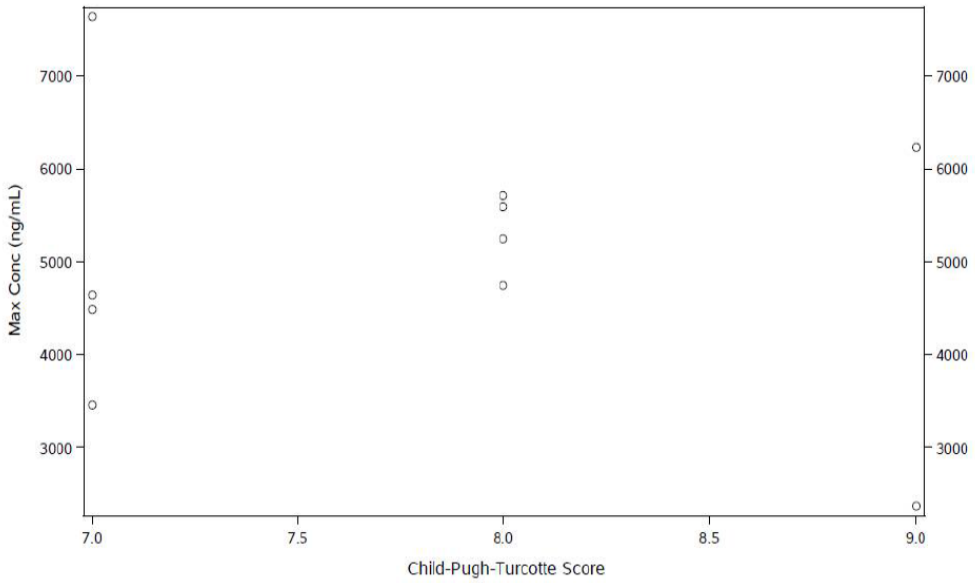
Fig 1: Scatter plot between AUC_{inf} and Child-Pugh scores at baseline in subjects with moderate hepatic impairment



Moderate hepatic impairment: Spearman R square = -0.013 95% CI = (-0.637, 0.622)

Source: final clinical study report, page 53

Fig 2: Scatter plot between C_{max} and Child-Pugh scores at baseline in subjects with moderate hepatic impairment



Conc = concentration

Moderate hepatic impairment: Spearman R square = 0.017, 95% CI = (-0.554, 0.695)

Source: final clinical study report, page 54

BIC AUC_{inf} or C_{max} vs Child-Pugh scores did not indicate any trend (albeit based on a limited number of subjects) between systemic exposure of BIC and hepatic function.

Table 2: Plasma protein binding, free C_{max}, and free AUC_{inf} of BIC following single dose administration of BIC 75 mg to subjects with moderate hepatic impairment and subjects in healthy control group.

BIC PK Parameter	Mean (%CV)	
	Moderate Hepatic Impairment (N = 10)	Healthy Control (N = 10)
Mean Unbound Plasma Fraction BIC	0.809 (21.4)	0.610 (6.2)
Free AUC_{inf} (h•ng/mL)	880.9 (55.7)	1054.2 (22.7)
Free C_{max} (ng/mL)	39.6 (27.7)	48.1 (28.2)

Free PK parameter is calculated as: Mean unbound fraction (%) * PK Parameter /100 for a single subject.
Source: final clinical study report, page 51

Table 3: Statistical comparison of the mean PK parameters of BIC following single dose administration of BIC 75 mg to subjects with moderate hepatic impairment and subjects in healthy control group

BIC PK Parameter	GLSM		%GLSM Ratio (90% CI)
	Moderate Hepatic Impairment (Test) (N = 10)	Healthy Control (Reference) (N = 10)	
AUC_{inf} (h•ng/mL)	99085.41	168779.84	58.71 (41.28, 83.50)
C_{max} (ng/mL)	4798.52	7557.17	63.50 (49.80, 80.96)
C_{24} (ng/mL)	1336.05	2591.06	51.56 (30.96, 85.87)
Free AUC_{inf} (h•ng/mL)	786.84	1028.05	76.54 (56.48, 103.71)
Free C_{max} (ng/mL)	38.11	46.03	82.78 (64.98, 105.45)

GLSM = geometric least-squares mean
Free PK parameter is calculated as: Mean unbound fraction (%) * PK Parameter /100 for a single subject.
Source: final clinical study report, page 52

Safety:
No Grade 3 or 4 AEs, serious adverse events (SAEs), AEs leading to study discontinuation, or deaths were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct
- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results
The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:
The mean total (protein bound + unbound) BIC exposure (AUC_{inf}) was approximately 41% lower in subjects with moderate hepatic impairment as compared with normal matched control subjects. Based on comparison of unbound BIC exposures, the mean BIC exposure decreased by approximately 23% lower in subjects with moderate hepatic impairment as compared with normal matched control subjects. The difference between the magnitude of decrease in total and free BIC exposures (total mean BIC exposures decrease by approximately 41 % and free mean BIC exposures decrease by approximately 23%) appears to be driven by the increase in free fraction of BIC in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function. The results of *in vitro* study AD-141-2289 suggests that based on the predicted extraction ratio

(13%), BIC is a low extraction ratio drug, hence, changes in protein binding would be expected to alter the hepatic clearance of BIC as was observed in this trial. Of note, BIC AUC_{inf} or C_{max} vs Child-Pugh scores did not indicate any trend between systemic exposure of BIC and hepatic function. Overall, the decrease in BIC exposure is not expected to be clinically relevant.

Proposed Labeling Recommendation:

Applicant has proposed the following recommendation: "No dose adjustment of [TRADENAME] is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. [TRADENAME] has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). The applicant's proposal is acceptable.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

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Clinical Sites: Orlando Clinical Research Center, Orlando, FL (enrolled 6 subjects); New Orleans Center for Clinical Research, Knoxville, TN (enrolled 5 subjects), American Research Corporation at The Texas Liver Institute (enrolled 3 subjects), and Clinical Pharmacology of Miami, Inc., Miami, FL (enrolled 6 subjects).

Bioanalytical Reports:

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Bioanalytical Site: (b) (4)

Study #	GS-US-141-1233	**Study Period:** June 8, 2015 through November 9, 2015
Title	A Phase 1, Open-Label, Two-Cohort, Multiple-Period, Fixed-Sequence, Crossover Study to Evaluate 1) the Relative Bioavailability of Two BIC/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets Versus BIC (75 mg) Tablet and F/TAF (200/25 mg) FDC Tablet Administered Simultaneously and 2) the Effect of Food on the Pharmacokinetics of BIC, F and TAF when administered as BIC/F/TAF (75/200/25 mg and 50/200/25 mg) FDC Tablets.	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary:

Evaluate the relative bioavailability of 2 BIC/F/TAF FDC tablets (75/200/25 mg and 50/200/25 mg) compared to BIC 75 mg tablets + F/TAF 200/25 mg tablets administered simultaneously under fasted conditions.

Secondary:

a) Assess the effect of food on the pharmacokinetics of BIC, F, and TAF when administered as BIC/F/TAF FDC tablets (75/200/25 mg and 50/200/25 mg).
b) Evaluate the safety and tolerability of single doses of BIC/F/TAF FDC tablets (75/200/25 mg and 50/200/25 mg) compared with BIC 75 mg + F/TAF 200/25 mg tablets.

Rationale:

The applicant conducted trial GS-US-141-1475 (Phase 2 safety and efficacy trial) using BIC (75 mg) tablets + F/TAF (200/25 mg) tablets. The results of trial GS-US-141-1475 showed maintenance of virologic suppression with BIC +F/TAF. The applicant conducted trial GS-US-141-1233 to assist with dose selection of BIC (either 75 mg or 50 mg to be administered as BIC/F/TAF FDC) and dosing instructions for BIC/F/TAF relative to food for the Phase 3 trials.

Design and PK Assessments:

Open label, 2-cohort, fixed-sequence, single-dose, single-center, Phase 1 study. Following completion of screening and day -1 assessments, eligible subjects received the study treatment beginning on day 1 as follows:

Table 1: Trial design for cohort 1

	Cohort 1					
	Period 1		Period 2		Period 3	
Study Day(s)	Day 1	Days 2-8	Day 9	Days 10-16	Day 17	Day 21
Treatment	A	Washout	B	Washout	C	Discharge

Treatment A = single-dose F/TAF (200/25 mg) FDC tablet and single dose BIC tablet (75 mg) administered simultaneously, orally under fasted conditions
Treatment B = single-dose B/F/TAF (75/200/25 mg) FDC tablet administered orally under fasted conditions
Treatment C = single-dose B/F/TAF (75/200/25 mg) FDC tablet administered orally under fed conditions with a high-fat meal

Source: Trial synopsis of GS-US-141-1233, page 3

Table 2: Trial design for cohort 2

	Cohort 2							
	Period 1		Period 2		Period 3		Period 4	
Study Day(s)	Day 1	Days 2-8	Day 9	Days 10-16	Day 17	Days 18-24	Day 25	Day 29
Treatment	A	Washout	D	Washout	E	Washout	F	Discharge

Treatment A = single-dose F/TAF (200/25 mg) FDC tablet and single dose BIC tablet (75 mg) administered simultaneously, orally under fasted conditions
Treatment D = single-dose B/F/TAF (50/200/25 mg) FDC tablet administered orally under fasted conditions
Treatment E = single-dose B/F/TAF (50/200/25 mg) FDC tablet administered orally under fed conditions with a high-fat meal
Treatment F = single-dose B/F/TAF (50/200/25 mg) FDC tablet administered orally under fed conditions with a moderate-fat meal
Source: Trial synopsis of GS-US-141-1233, page 3

Composition of meals used in the trial:

High fat breakfast: 800 calories with approximately 50% calories from fat
Moderate fat breakfast: 600 calories with approximately 27% calories from fat

PK Sampling and Assessments:

Serial blood samples were collected on days 1, 9, and 17 in both Cohorts 1 and 2 and on day 25 in Cohort 2 at the following times relative to drug administration: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 hours post-dose. Plasma concentrations of BIC, F and TAF were determined and the following single-dose plasma PK parameters of BIC, FTC, and TAF were calculated, as applicable: AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, C_{last}, T_{max}, T_{last}, CL/F, V_z/F, and $t_{1/2}$.

Table 3: Various comparisons in cohort 1 and cohort 2

Cohort	Comparison		Boundary
	Test	Reference	
Cohort 1	Treatment B	Treatment A	80% – 125%[a]
	Treatment C	Treatment B	80% – 125%
Cohort 2	Treatment D	Treatment A	70% – 143%
	Treatment E	Treatment D	80% – 125%
	Treatment F	Treatment D	80% – 125%

a Due to the high variability of TAF C_{max}, a wider equivalence boundary (70% – 143%) was used compared with other parameters/analytes.

Source: Trial synopsis of GS-US-141-1233, page 5

Population: ☑ Healthy Volunteers ☐ Patients	Administration: ☑ Fasted ☑ Fed (depending on the cohort and period)

Formulations
BIC/F/TAF 75/200/25 mg, lot # EN1501B1, expiration date April 2016;
BIC/F/TAF 50/200/25 mg, lot # EN1503B1, expiration date August 2016
BIC 75 mg, lot #s EC1504B1 and EC1504B2, expiration date August 2016
F/TAF 200/25 mg, lot # CR1408B1, expiration date December 2016

RESULTS

Enrolled	56[1]	Completed	55[2]	Discontinued	1[3]	PK Population	55	Safety Population	56

1: 28 subjects enrolled in cohort 1 and 28 subjects enrolled in cohort 2.

2: 28 subjects completed the study in cohort 1 and 27 subjects completed the study in cohort 2.
3: 1 subject (subject # 02687-2026) in Cohort 2 discontinued study drug due to withdrawal of consent after receiving treatments A and D

Protocol Deviations

No protocol deviations were reported in the trial.

Demographics

Cohort 1 enrolled 18 males and 10 females. Median age was 30 years (range: 21 to 43) and median body mass index (BMI) was 24.5 kg/m^2 (range 19.1 to 29.3 kg/m^2).
Cohort 2 enrolled 17 males and 11 females. Median age was 32 years (range: 23 to 45) and median body mass index (BMI) was 27.3 kg/m^2 (range 20.1 to 29.7 kg/m^2).

Pharmacokinetics:

Cohort 1:

Table 4: BIC plasma pharmacokinetic parameters (Cohort 1)

	BIC 75 mg + F/TAF	75-mg B/F/TAF FDC	
BIC PK Parameter[a]	Fasted (N = 28)	Fasted (N = 28)	High Fat (N = 28)
C_{max} (ng/mL)	5593.9 (31.0)	7123.9 (21.6)	8941.1 (16.9)
AUC_{last} (hr•ng/mL)	119,619.4 (26.6)	151,844.0 (26.9)	216,733.1 (23.4)
AUC_{inf} (hr•ng/mL)	123,174.0 (26.6)	156,637.5 (27.5)	226,142.1 (24.9)
T_{max} (hr)	1.50 (1.00, 3.00)	2.00 (1.50, 3.00)	3.00 (3.00, 4.00)
$t_{1/2}$ (hr)	18.41 (16.71, 20.39)	18.88 (17.49, 20.32)	19.59 (18.32, 21.55)
CL/F (mL/hr)	653.6 (28.0)	518.0 (31.7)	349.4 (21.8)
V_z/F (mL)	17,446.5 (30.0)	13,957.1 (31.0)	9919.6 (15.6)

a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).

Source: final clinical study report, page 57

Table 5: FTC plasma pharmacokinetic parameters (Cohort 1)

	BIC 75 mg + F/TAF	75-mg B/F/TAF FDC	
FTC PK Parameter[a]	Fasted (N = 28)	Fasted (N = 28)	High Fat (N = 28)
C_{max} (ng/mL)	2153.6 (21.5)	2264.3 (22.7)	1872.5 (20.1)
AUC_{last} (hr•ng/mL)	11,199.3 (13.7)	11,412.3 (13.5)	11,483.0 (15.7)
AUC_{inf} (hr•ng/mL)	11,436.4 (13.2)	11,642.8 (13.2)	11,706.5 (15.6)
T_{max} (hr)	1.50 (1.00, 2.00)	1.00 (1.00, 1.50)	2.50 (2.00, 3.00)
$t_{1/2}$ (hr)	20.99 (17.64, 23.57)	23.46 (19.53, 26.94)	22.95 (18.56, 25.52)
CL/F (mL/hr)	17,770.5 (12.6)	17,468.3 (13.3)	17,477.1 (15.3)
V_z/F (mL)	548,289.2 (32.6)	582,473.7 (24.1)	545,154.3 (19.5)

a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).

Source: final clinical study report, page 63

Table 6: TAF plasma pharmacokinetic parameters (Cohort 1)

TAF PK Parameter[a]	BIC 75 mg + F/TAF	75-mg B/F/TAF FDC	
	Fasted (N = 28)	Fasted (N = 28)	High Fat (N = 28)
C_{max} (ng/mL)	276.7 (51.7)	253.3 (44.2)	212.2 (49.4)
AUC_{last} (hr•ng/mL)	223.6 (45.2)	205.5 (45.5)	315.3 (44.0)
AUC_{inf} (hr•ng/mL)	225.1 (45.0)	206.8 (45.2)	319.7 (43.1)
T_{max} (hr)	0.50 (0.50, 0.75)	0.50 (0.50, 0.75)	2.00 (1.50, 2.00)
$t_{1/2}$ (hr)	0.38 (0.30, 0.43)	0.41 (0.30, 0.46)	0.48 (0.39, 0.58)
CL/F (mL/hr)	135,079.2 (47.9)	147,822.0 (47.0)	90,346.0 (36.7)
V_z/F (mL)	70,868.1 (39.7)	78,196.2 (35.0)	66,202.5 (63.3)

a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).

Source: final clinical study report, page 69

Cohort 2:

Table 7: BIC plasma pharmacokinetic parameters (Cohort 2)

BIC PK Parameter[a]	BIC 75 mg + F/TAF	50-mg B/F/TAF FDC		
	Fasted (N = 28)	Fasted (N = 27)	High Fat (N = 27)	Moderate Fat (N = 27)
C_{max} (ng/mL)	6791.1 (26.4)	5228.1 (16.9)	5936.3 (18.3)	6279.6 (18.3)
AUC_{last} (hr•ng/mL)	142,396.6 (30.5)	109,061.4 (21.0)	135,117.3 (21.1)	135,217.3 (22.9)
AUC_{inf} (hr•ng/mL)	146,931.6 (31.1)	112,619.6 (21.9)	140,032.4 (21.8)	140,197.7 (23.6)
T_{max} (hr)	2.00 (1.00, 3.00)	2.00 (1.00, 3.03)	4.00 (2.00, 6.00)	3.00 (2.00, 4.00)
$t_{1/2}$ (hr)	18.84 (16.47, 20.80)	18.94 (15.98, 20.17)	19.13 (17.05, 21.45)	19.34 (17.25, 20.51)
CL/F (mL/hr)	568.4 (37.8)	468.4 (26.0)	376.3 (25.8)	378.7 (26.8)
V_z/F (mL)	14,791.5 (29.8)	12,294.7 (17.8)	10,174.3 (17.1)	10,252.8 (19.7)

a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).

Source: final clinical study report, page 60

Table 8: FTC plasma pharmacokinetic parameters (Cohort 2)

FTC PK Parameter[a]	BIC 75 mg + F/TAF	50-mg B/F/TAF FDC		
	Fasted (N = 28)	Fasted (N = 27)	High Fat (N = 27)	Moderate Fat (N = 27)
C_{max} (ng/mL)	2166.4 (27.0)	2220.4 (30.1)	1881.1 (24.2)	1998.9 (18.4)
AUC_{last} (hr•ng/mL)	11,035.5 (14.4)	10,652.9 (13.6)	10,213.0 (12.0)	10,738.3 (9.8)
AUC_{inf} (hr•ng/mL)	11,234.6 (14.2)	10,873.9 (13.6)	10,467.0 (11.9)	10,973.3 (9.5)
T_{max} (hr)	1.50 (1.00, 1.50)	1.50 (1.00, 1.52)	2.00 (1.50, 4.00)	2.00 (2.00, 3.00)
$t_{1/2}$ (hr)	19.24 (13.48, 21.09)	19.12 (16.21, 23.98)	22.60 (18.58, 27.96)	19.49 (17.28, 25.91)
CL/F (mL/hr)	18,151.8 (14.5)	18,704.1 (13.0)	19,374.5 (12.1)	18,391.5 (10.0)
V_z/F (mL)	475,734.6 (32.5)	543,212.4 (29.6)	633,121.5 (34.1)	569,563.7 (26.8)

a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).

Source: final clinical study report, page 66

Table 9: TAF plasma pharmacokinetic parameters (Cohort 2)

TAF PK Parameter[a]	BIC 75 mg + F/TAF	50-mg B/F/TAF FDC		
	Fasted (N = 28)	Fasted (N = 28)	High Fat (N = 27)	Moderate Fat (N = 27)
C_{max} (ng/mL)	291.9 (55.4)	249.2 (51.6)	236.6 (65.1)	251.1 (66.7)
AUC_{last} (hr•ng/mL)	236.7 (45.3)	207.1 (46.5)	310.3 (34.9)	290.6 (41.3)
AUC_{inf} (hr•ng/mL)	238.3 (45.0)	208.8 (46.3)	318.4 (32.8)	293.1 (40.9)
T_{max} (hr)	0.50 (0.50, 0.75)	0.50 (0.50, 1.00)	2.00 (1.00, 3.00)	1.50 (1.00, 2.00)
$t_{1/2}$ (hr)	0.38 (0.33, 0.39)	0.33 (0.31, 0.45)	0.56 (0.44, 0.75)	0.40 (0.34, 0.53)
CL/F (mL/hr)	130,228.3 (59.1)	160,246.3 (76.3)	86,343.3 (31.1)	100,787.1 (43.2)
V_z/F (mL)	67,478.8 (51.4)	80,358.2 (66.7)	82,772.4 (70.0)	60,482.4 (44.0)

a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).

Source: final clinical study report, page 72

Assessment of Relative Bioavailability:

Table 10: Relative bioavailability assessment (Cohort 1 & Cohort 2)

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Test	Reference	
B/F/TAF (75/200/25 mg), fasted (Test) (N = 28) vs BIC 75 mg + F/TAF (200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	151,844.0 (26.9)	119,619.4 (26.6)	126.76 (117.82,136.37)
AUC_{inf} (hr•ng/mL)	156,637.5 (27.5)	123,174.0 (26.6)	126.82 (117.87,136.45)
C_{max} (ng/mL)	7123.9 (21.6)	5593.9 (31.0)	130.72 (119.95,142.45)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	11,412.3 (13.5)	11,199.3 (13.7)	101.89 (99.50, 104.33)
AUC_{inf} (hr•ng/mL)	11,642.8 (13.2)	11,436.4 (13.2)	101.78 (99.45, 104.16)
C_{max} (ng/mL)	2264.3 (22.7)	2153.6 (21.5)	104.86 (97.73, 112.50)
TAF PK Parameter			
AUC_{last} (hr•ng/mL)	205.5 (45.5)	223.6 (45.2)	91.62 (82.13, 102.21)
AUC_{inf} (hr•ng/mL)	206.8 (45.2)	225.1 (45.0)	91.56 (82.27, 101.91)
C_{max} (ng/mL)	253.3 (44.2)	276.7 (51.7)	95.47 (79.88, 114.10)
B/F/TAF (50/200/25 mg), fasted (Test) (N = 27) vs BIC 75 mg + F/TAF (200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	109,061.4 (21.0)	142,396.6 (30.5)	78.46 (73.38, 83.89)
AUC_{inf} (hr•ng/mL)	112,619.6 (21.9)	146,931.6 (31.1)	78.56 (73.44, 84.04)
C_{max} (ng/mL)	5228.1 (16.9)	6791.1 (26.4)	78.07 (73.41, 83.01)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,652.9 (13.6)	11,035.5 (14.4)	96.52 (93.95, 99.15)
AUC_{inf} (hr•ng/mL)	10,873.9 (13.6)	11,234.6 (14.2)	96.76 (94.22, 99.37)
C_{max} (ng/mL)	2220.4 (30.1)	2166.4 (27.0)	102.36 (93.85, 111.64)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	207.1 (46.5)	236.7 (45.3)	85.37 (75.24, 96.85)
AUC_{inf} (hr•ng/mL)	208.8 (46.3)	238.3 (45.0)	85.48 (75.33, 97.00)
C_{max} (ng/mL)	249.2 (51.6)	291.9 (55.4)	84.17 (67.59, 104.81)

a N = 28 for both the Test and Reference groups

Source: Trial synopsis of GS-US-141-1233, page 6

Assessment of Food Effect:

Table 11: Food effect assessment (Cohort 1 & Cohort 2)

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Test	Reference	
B/F/TAF (75/200/25 mg), high fat (Test) (N = 28) vs B/F/TAF (75/200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	216,733.1 (23.4)	151,844.0 (26.9)	144.45 (134.26, 155.40)
AUC_{inf} (hr•ng/mL)	226,142.1 (24.9)	156,637.5 (27.5)	145.88 (135.58, 156.95)
C_{max} (ng/mL)	8941.1 (16.9)	7123.9 (21.6)	126.74 (116.30, 138.12)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	11,483.0 (15.7)	11,412.3 (13.5)	100.34 (97.99, 102.75)
AUC_{inf} (hr•ng/mL)	11,706.5 (15.6)	11,642.8 (13.2)	100.24 (97.95, 102.59)
C_{max} (ng/mL)	1872.5 (20.1)	2264.3 (22.7)	83.18 (77.53, 89.25)
TAF PK Parameter			
AUC_{last} (hr•ng/mL)	315.3 (44.0)	205.5 (45.5)	156.81 (140.57, 174.94)
AUC_{inf} (hr•ng/mL)	319.7 (43.1)	206.8 (45.2)	158.20 (142.14, 176.08)
C_{max} (ng/mL)	212.2 (49.4)	253.3 (44.2)	83.22 (69.63, 99.46)
B/F/TAF (50/200/25 mg), high fat (Test) (N = 27) vs B/F/TAF (50/200/25 mg), fasted (Reference) (N = 27)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	135,117.3 (21.1)	109,061.4 (21.0)	123.96 (115.91, 132.57)
AUC_{inf} (hr•ng/mL)	140,032.4 (21.8)	112,619.6 (21.9)	124.41 (116.27, 133.11)
C_{max} (ng/mL)	5936.3 (18.3)	5228.1 (16.9)	113.23 (106.45, 120.43)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,213.0 (12.0)	10,652.9 (13.6)	96.02 (93.47, 98.65)
AUC_{inf} (hr•ng/mL)	10,467.0 (11.9)	10,873.9 (13.6)	96.41 (93.88, 99.02)
C_{max} (ng/mL)	1881.1 (24.2)	2220.4 (30.1)	85.52 (78.37, 93.31)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	310.3 (34.9)	207.1 (46.5)	162.62 (143.10, 184.80)
AUC_{inf} (hr•ng/mL)	318.4 (32.8)	208.8 (46.3)	166.55 (146.54, 189.29)
C_{max} (ng/mL)	236.6 (65.1)	249.2 (51.6)	91.71 (73.46, 114.49)
B/F/TAF (50/200/25 mg), moderate fat (Test) (N = 27) vs B/F/TAF (50/200/25 mg), fasted (Reference) (N = 27)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	135,217.3 (22.9)	109,061.4 (21.0)	123.56 (115.53, 132.14)
AUC_{inf} (hr•ng/mL)	140,197.7 (23.6)	112,619.6 (21.9)	124.06 (115.95, 132.74)
C_{max} (ng/mL)	6279.6 (18.3)	5228.1 (16.9)	119.90 (112.72, 127.53)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,738.3 (9.8)	10,652.9 (13.6)	101.17 (98.48, 103.94)
AUC_{inf} (hr•ng/mL)	10,973.3 (9.5)	10,873.9 (13.6)	101.33 (98.66, 104.06)
C_{max} (ng/mL)	1998.9 (18.4)	2220.4 (30.1)	91.84 (84.17, 100.21)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	290.6 (41.3)	207.1 (46.5)	148.20 (130.41, 168.41)
AUC_{inf} (hr•ng/mL)	293.1 (40.9)	208.8 (46.3)	148.23 (130.42, 168.47)
C_{max} (ng/mL)	251.1 (66.7)	249.2 (51.6)	99.04 (79.33, 123.65)

a N = 28 for the Reference group

Source: Trial synopsis of GS-US-141-1233, page 8

Safety:

No Grade 3 or 4 AEs, serious adverse events (SAEs), AEs leading to study discontinuation, or deaths were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

1) Relative to administration of BIC (75 mg) + F/TAF (200/25 mg) under fasting conditions, administration of BIC/F/TAF (50/200/25 mg) under fasting conditions showed a decrease in the mean systemic exposure of BIC and TAF. The decrease in the mean systemic exposure of BIC and TAF is not expected to be clinically relevant because the efficacy data in the Phase 3 trials was collected using BIC/F/TAF (50/200/25 mg) FDC tablets. Of note, the efficacy of BIC/F/TAF (50/200/25 mg) FDC tablets is approximately 90% across the various trials.
2) Relative to administration of BIC/F/TAF (50/200/25 mg) under fasting conditions, administration of BIC/F/TAF (50/200/25 mg) with a moderate-fat meal and high-fat meal increased the mean systemic exposure (AUC_{inf}) of BIC (by approximately 25% with moderate-fat meal and high-fat meal) and TAF (by approximately 48% with a moderate fat meal and 67% with a high-fat meal). The increase in the mean systemic exposure BIC and TAF is not expected to be clinically relevant because:
   i) BIC/F/TAF was administered without regard to food in the Phase 3 trials and the exposure-response analysis suggests lack of association between BIC and TAF exposures and adverse events.
   ii) The increase in mean TAF exposures with a moderate fat meal and a high fat meal is similar to the increase in mean TAF exposures after administration of Descovy® with a high fat meal (C_{max} [90% CI] is 0.85 [0.75-0.95] and AUC [90% CI] is 1.75 [1.64-1.88]. The prescribing information of Descovy® recommends administration without regards to food.

Applicant's Proposed Labeling Recommendation:

The applicant has proposed that BIC/F/TAF can be administered with or without food. Further the applicant has incorporated the results pertaining to the effect of food on the pharmacokinetics of BIC, F, and TAF (after administration of BIC/F/TAF 50/200/25 mg tablets) in Section 12.3 of the proposed prescribing information. The applicant's proposal is acceptable.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

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Clinical Site: SeaView Jacksonville, LLC. 7898 Baymeadows Way, Jacksonville, FL.

Bioanalytical Reports:

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Bioanalytical Site: (b) (4)

Study #	GS-US-141-1481	**Study Period:** April 10, 2015 through May 26, 2015
Title	A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism, and Excretion of Bictegravir (BIC) in Healthy Subjects	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: Determine the mass balance of BIC following single, oral dose of [^{14}C] BIC.

Secondary:

c) Evaluate the PK of BIC and its metabolite(s), where possible.

d) Determine the metabolic profile of BIC in humans following administration of a single, oral dose of radiolabeled [^{14}C] BIC.

e) Assess safety and tolerability of [^{14}C] BIC.

Rationale:

The applicant conducted this trial to assess the mass balance, absorption, distribution, metabolism, and excretion (ADME), metabolite profile, route of elimination, and pharmacokinetics (PK) of BIC in humans following administration of a single, oral dose of [^{14}C] BIC.

Dose Selection:

BIC: 100 mg BIC (99 mg of nonradiolabeled BIC) plus approximately 100 μCi [1 mg] radiolabeled [^{14}C] BIC) administered orally as an approximately 40-mL ethanolic solution (4:6 [v/v] water:ethanol, pH adjusted with HCl). Results from the first-in-human trial (GS-US-141-1218) showed that accumulation ratio of BIC following multiple once-daily doses was approximately 1.6. Hence, for the mass balance trial, the applicant selected 100 mg BIC to cover the clinically relevant exposures of BIC. Of note, BIC 75 mg dose was used in the Phase 2 efficacy and safety trial (trial GS-US-141-1475) which evaluated BIC + F/TAF (200/25 mg).

Design and PK Assessments:

Eight subjects were enrolled in the study and on the morning of day 1, subjects were administered a single, oral dose of 100 mg BIC (approximately 100 μCi radiolabeled [^{14}C] BIC [equivalent to approximately 1 mg BIC] and approximately 99 mg of non-radiolabeled BIC within 5 minutes of completing a moderate-fat breakfast.

PK Sampling and Assessments:

Whole blood and plasma samples were collected for total radioactivity, PK analysis and metabolite profiling/identification at the following time points: 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 hrs post dose. After the 120 hr post-dose time point, additional blood samples for whole blood and/or plasma samples were collected at 24 hr intervals up to the morning of day 22 (504 hours post-dose) or until one of the following two conditions were met: 1) LSC indicated that the radioactivity levels in samples from 2 consecutive 24-hour collection intervals had decreased to levels below BLQ or 2) both urine and stool collection was discontinued. Urine and stool samples were collected pre-dose (defined as within a 12-hour period prior to day 1 dose for urine sampling and within a 24-hour period prior to day 1 dose for stool sampling) and in the following collection intervals: 0-12 hrs, 12-24 hrs, 24-48 hrs, 48-72 hrs, 72-96 hrs, 96-120 hrs. After the 120-hr post-dose time point, urine and stool samples were collected over successive 24-hr collection intervals up to the morning of day 22 (504 hr post-dose) or until LSC indicated that the radioactivity levels in samples from 2 consecutive 24 hr collection intervals were ≤ 1% of the administered dose and the cumulative [^{14}C]-radioactivity recovered in urine plus stool was ≥ 90% of the administered dose.

Population: ☑ Healthy Volunteers ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations
BIC 100 mg lot # EC1505A; expiration date May 2015.
Lot #s GS017-023-0583-X-20150324-CLI (where X refers to B, C, D, and E); lots were obtained after aliquoting GS017-023-0583-A-20150324-CLI into vials as sublots B, C, D, and E.

RESULTS

Enrolled	8	Completed	8	Discontinued	0	PK Population	8	Safety Population	8

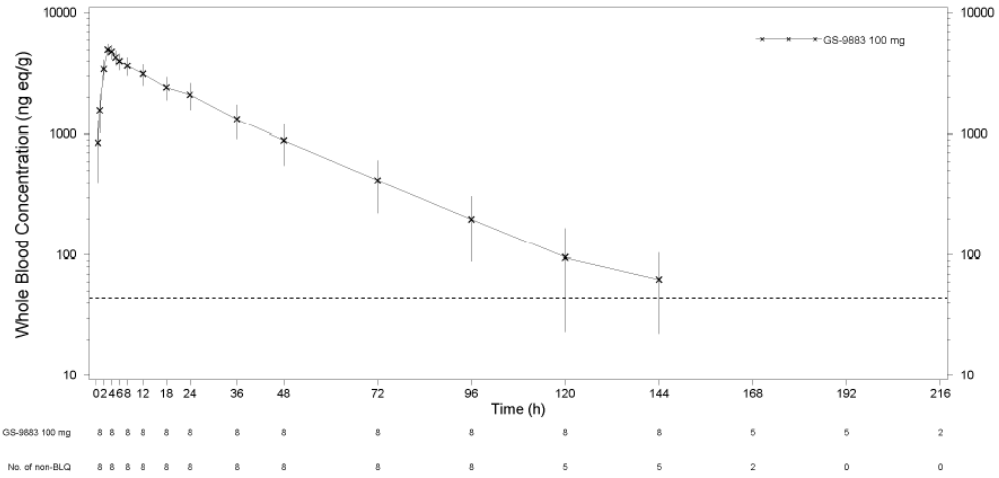
Protocol Deviations
No protocol deviations were reported in the trial.

Demographics
The trial enrolled only male subjects. Median age was 37 years (range: 20 to 43 years) and median BMI was 27.5 kg/m^2 (range: 19.7 to 30 kg/m^2).

Results:

Plasma:

Fig 1 shows the mean (standard deviation) whole blood concentration of total [^{14}C] radioactivity versus time



Values BLQ were treated as 0 at predose and one-half of the LLOQ at postdose time points for the analysis. Lower limit of quantitation was defined as 44.4 ng eq/g for whole blood concentration of total [^{14}C]-radioactivity. Values where no sample was available were treated as missing for the analysis. Concentration values that were ≤ LLOQ are not displayed on the figure. Reference line indicates the LLOQ.

Source: final clinical study report, page 47

In most subjects, quantifiable levels of total radioactivity were observed for up to 144 hours following administration of [^{14}C] BIC.

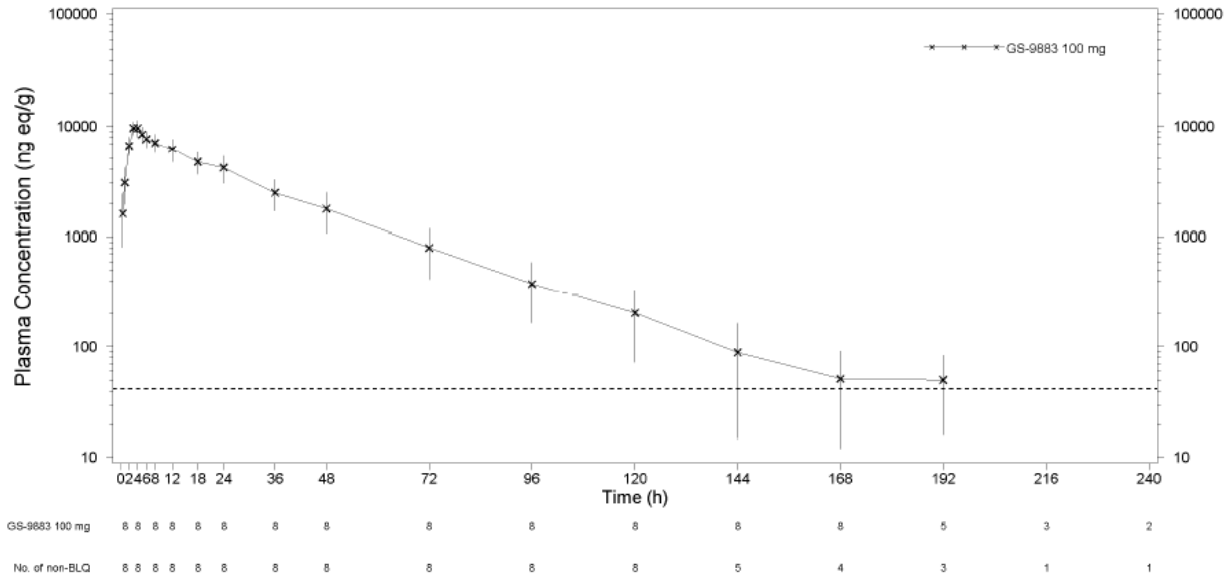
Table 1: Pharmacokinetic parameters for total [^{14}C] radioactivity in whole blood

PK Parameter[a]	GS-9883 100 mg (N = 8)
AUC_{last} (h•[ng eq/g])	135,315.7 (25.0)
AUC_{inf} (h•[ng eq/g])	137,866.8 (24.8)
AUC_{exp} (%)	1.90 (24.69)
C_{max} (ng eq/g)	5038.8 (11.4)
C_{last} (ng eq/g)	80.71 (22.21)
T_{max} (h)	3.00 (3.00, 3.51)
T_{last} (h)	144.00 (96.02, 156.00)
$t_{1/2}$ (h)	22.85 (17.84, 25.77)

a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).

Source: final clinical study report, page 48

Fig 2: Mean (standard deviation) plasma concentration of total radioactivity versus time



Values BLQ were treated as 0 at predose and one-half of the LLOQ at postdose time points for the analysis. Lower limit of quantitation was defined as 42.1 ng eq/g for plasma concentration of total [^{14}C]-radioactivity. Values where no sample was available were treated as missing for the analysis. Concentration values that were ≤ LLOQ are not displayed on the figure. Reference line indicates the LLOQ.

Source: final clinical study report, page 49

Table 2: Pharmacokinetic parameters for total [^{14}C] radioactivity in plasma

PK Parameter[a]	GS-9883 100 mg (N = 8)
AUC_{last} (h•[ng eq/g])	264,299.7 (27.4)
AUC_{inf} (h•[ng eq/g])	266,300.2 (27.1)
AUC_{exp} (%)	0.82 (41.41)
C_{max} (ng eq/g)	9893.8 (14.5)
C_{last} (ng eq/g)	64.51 (26.41)
T_{max} (h)	3.51 (3.00, 4.00)
T_{last} (h)	156.00 (120.01, 192.00)
$t_{1/2}$ (h)	21.28 (19.13, 24.67)

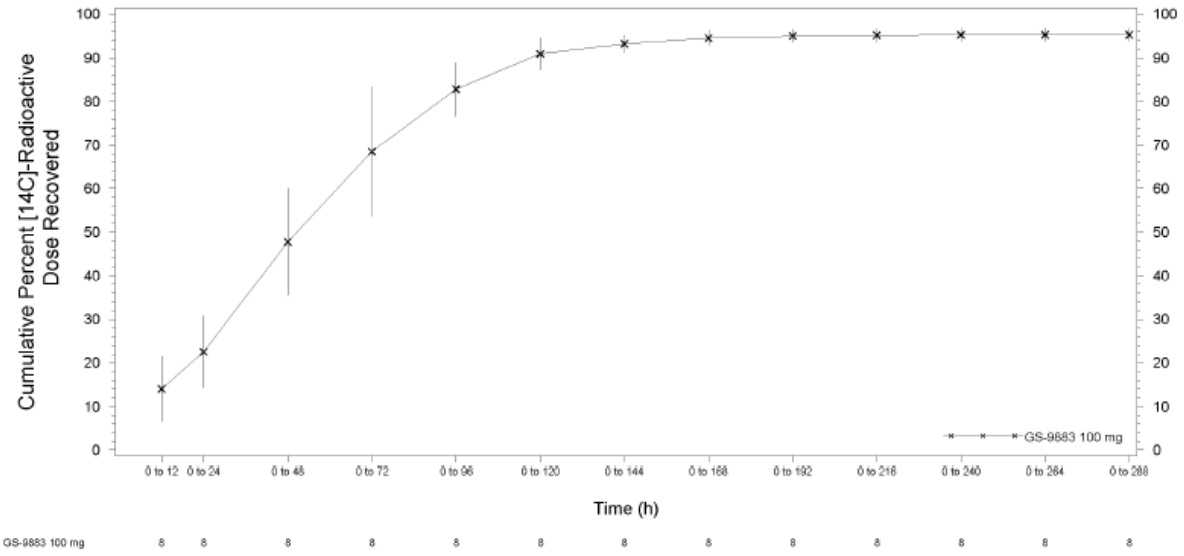
a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).

Source: final clinical study report, page 50

Mean blood-to-plasma ratio of total [^{14}C] radioactivity (determined at each protocol specific sampling time) was approximately 0.5 to 0.55 through 120 hours post-dose indicating that BIC is not preferentially distributed in the red blood cells relative to plasma.

Urine and Feces:

Fig 3: Mean (SD) cumulative combined urinary and fecal recovery of total [^{14}C] radioactivity (% of radioactive dose excreted) versus time



Values BLQ were treated as 0 for the analysis. Values where no sample was available were treated as missing for the analysis.

Source: final clinical study report, page 55

Following a single oral dose of 100 mg BIC, mean (SD) cumulative combined urinary and fecal recovery of [^{14}C] BIC was 95.3% (1.5%). Majority (90.9%) of the administered radioactivity was recovered in the first 120 hours post-dose. The mean (SD) fecal recovery of the administered radioactive dose was 60.3% (5.5%) and the mean (SD) urinary recovery of the administered radioactive dose was 35.0% (4.95%).

Pharmacokinetic Parameters of BIC in Plasma and Urine:

Table 3: Pharmacokinetic parameters of BIC in plasma

PK Parameter[a]	GS-9883 100 mg (N = 8)
AUC_{last} (h•ng/mL)	227,309.8 (29.5)
AUC_{inf} (h•ng/mL)	229,409.4 (29.7)
AUC_{exp} (%)	0.89 (50.22)
C_{max} (ng/mL)	9495.0 (15.2)
C_{last} (ng/mL)	77.25 (52.39)
T_{max} (h)	3.50 (3.00, 4.00)
T_{last} (h)	144.00 (96.00, 144.00)
CL/F (mL/h)	476.0 (33.5)
V_z/F (mL)	11,801.7 (20.0)
$t_{1/2}$ (h)	17.26 (14.80, 20.68)

a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).

Source: final clinical study report, page 57

Table 4: Pharmacokinetic parameters of BIC in urine

PK Parameter[a]	GS-9883 100 mg (N = 8)
A_e (mg)	1.305 (32.764)
%Dose Recovered	1.305 (32.798)
CL_r (mL/h)	6.160 (41.167)

a Data are presented as mean (%CV).

Source: final clinical study report, page 58

Through 144 hours post-dose, about 1.3% (1.30 mg) of the administered BIC dose (100 mg) was recovered unchanged in the urine, indicating minimal urinary elimination of BIC.

Metabolite Profiling of BIC in Plasma, Urine, and Feces:

Metabolite profiling and quantitation in **plasma** was performed with samples pooled for individual subjects between 0 to 144 hours post-dose. BIC and 13 metabolites were identified in human plasma. [^{14}C] BIC was the major circulatory radioactive component and M20 (hydroxy-BIC-sulfate) and M15 (BIC-glucuronide) were the major metabolites in plasma, accounting for 67.9%, 20.1%, and 8.6%, respectively, of the plasma $AUC_{0\text{-}72h}$ of total radioactivity.

Table 5: Quantification of BIC and metabolites in plasma pooled from all subjects between 0 and 144 hours post dose

Metabolite ID[a]	M15	M21	M23 M51	M52	M20	GS-9883	Total Radioactivity Concentration (ng Eq/g)[b]
$[M+H]^+$ (m/z)	626	466	466/448	448	546	450	
Time point (h)							
1	281.396	47.962	BLQ	BLQ	212.185	2495.831	3036
4	520.255	93.801	80.262	BLQ	760.075	8216.735	9670
8	391.845	107.899	39.043	63.888	1419.729	5076.951	7099
12	340.899	93.871	33.966	55.581	1235.141	4416.865	6176
24	668.912	58.094	BLQ	119.923	638.205	2664.445	4150
48	67.456	63.897	BLQ	BLQ	593.224	1055.094	1780
72	63.268	50.195	BLQ	BLQ	407.852	285.755	807
144	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	99
AUC_{0-t} (h•ng/mL)	21,097	4788	505	1420	49,264	166,104	277,441
T_{last} (h)	72	72	12	24	72	72	144
% Total radioactivity $AUC_{0-72\ h}$	**8.6**	**2.0**	**0.2**	**0.6**	**20.1**	**67.9**	

BLQ = below the limit of quantitation (15 dpm peak height, which was up to 1.5% of the run for the pooled plasma samples injected)

a Additional metabolites were detected by LC/MS/MS method in plasma, but their levels were too low to be quantified using a radioquantitation method, including the following: M56, M9, M37, M16, M57, M59, and M12.

b Data were provided by Gilead Sciences, Inc.

Source: final clinical study report, page 59

Metabolite profiling and quantitation in **urine** was performed with samples pooled for individual subjects within the period of 0 to 96 hours post-dose. Approximately 33.5% of the radioactive dose was recovered in the urine. BIC and 20 metabolites were identified in human urine and M15 (co-eluted with M58, both glucuronides of BIC) was the major radioactive component in the urine.

Table 6: Quantification of BIC and metabolites in urine pooled per individual subject

Metabolite ID [a]	$[M+H]^+$ (m/z)	Subject Number								Mean
		3001	3002	3003	3004	3005	3006	3007	3008	
U1		0.93	0.57	0.53	BLQ	0.38	0.26	0.58	BLQ	**0.40**
M9	567	0.46	0.43	0.96	0.48	0.68	0.56	0.73	0.66	**0.62**
M45	642	0.67	1.0	0.64	1.36	0.26	1.54	0.50	1.67	**0.95**
M12/M59	642	1.04	0.62	0.67	0.79	0.12	1.03	0.31	0.63	**0.65**
M35	642	0.53	0.60	0.66	0.99	0.40	1.44	0.47	0.53	**0.70**
M15/M58	626	13.84	21.28	14.73	33.44	29.27	15.13	18.73	24.69	**21.39**
M21/M22	466/448	2.56	1.13	1.98	1.27	0.74	2.16	3.03	4.17	**2.13**
M23/M51	466/488	0.72	1.38	1.24	0.67	0.58	1.22	0.81	1.73	**1.05**
M52	448	0.36	0.26	0.28	BLQ	BLQ	0.60	0.98	0.22	**0.34**
GS-9883	450	4.65	3.77	7.87	2.92	1.47	3.59	1.95	2.34	**3.57**
U2		1.97	0.53	1.46	1.26	1.23	3.47	0.67	1.33	**1.49**
Radioactivity recovery in urine within 0 to 96 hours (% dose)[b]		27.73	31.56	31.00	43.16	35.07	32.61	28.76	38.37	33.53

BLQ = below the limit of quantitation (15 dpm peak height, which was up to 0.78% of the run for the pooled urine samples injected)

a Additional metabolites were detected by LC/MS/MS method in urine, but their levels were too low to be quantified using a radioquantitation method, including the following: M53, M54, M55, M56, M20, M37, M16, and M57.

b Data were provided by Gilead Sciences, Inc.

Source: final clinical study report, page 60

Metabolite profiling and quantitation in **feces** was performed with the feces samples pooled for individual subjects. On average, 58.5% of the administered radioactivity was recovered within 0 to 144 hours post-dose. Unchanged BIC, M9 (desfluoro-hydroxy-BIC-cysteine conjugate), M21/M22 (hydroxy-BIC/desfluoro-hydroxy-BIC co-eluted), and M23 (hydroxy-BIC) accounted on average for 30.6%, 13.0%, 8.1%, and 3.6%, respectively, of the administered dose.

Table 7: Quantification of BIC and metabolites in feces pooled per subject

Metabolite ID[a]	$[M+H]^+$ (m/z)	Subject Number								Mean
		3001	3002	3003	3004	3005	3006	3007	3008	
U1		BLQ	1.11	2.85	BLQ	BLQ	2.33	1.94	BLQ	**1.03**
M9	567	10.14	8.28	21.71	9.57	9.79	18.86	18.24	7.70	**13.04**
U2		1.12	4.87	4.87	1.02	BLQ	3.38	1.89	BLQ	**2.15**
M21/M22	466/448	8.24	10.13	5.17	5.41	7.17	10.70	8.65	9.46	**8.12**
M23	466	3.15	3.66	2.94	2.48	4.12	3.24	6.30	2.84	**3.59**
GS-9883	450	43.44	30.47	21.67	32.27	31.61	23.23	26.24	35.49	**30.55**
Radioactivity recovery in feces within 0 to 144 hours (% dose)[a]		66.09	58.51	59.19	50.76	52.69	61.73	63.25	55.49	**58.46**

BLQ = below the limit of quantitation (15 dpm peak height, which was up to 0.71% of the run for the pooled fecal samples injected)

a Data were provided by Gilead Sciences, Inc.

Source: final clinical study report, page 61

The pooled fecal samples between 0 to 48 hours, 48 to 72 hours, and 72 to 144 hours across all subjects were also characterized for metabolites. Approximately 58.4% of the radioactive dose was recovered in the feces within the period of 0 to 144 hours post-dose.

Table 8: Quantification of BIC and metabolites in feces samples pooled per collection interval

Metabolite ID	U1	M9	U2	M21 M22	M23	GS-9883	Radioactivity Recovery (% Dose)[a]
$[M+H]^+$ (m/z)		567		466 448	466	450	
Time interval							
0-48 h	BLQ	3.84	0.54	1.97	0.82	12.33	19.50
48-72 h	0.32	2.99	0.63	2.03	1.91	9.11	16.98
72-144 h	BLQ	2.68	BLQ	3.05	4.02	12.22	21.96
Cumulative results (% Dose)	**0.32**	**9.50**	**1.17**	**7.05**	**6.75**	**33.65**	58.44

BLQ = below the limit of quantitation (15 dpm peak height, which was up to 0.84% of the run for the pooled fecal samples injected)

a Data were provided by Gilead Sciences, Inc.

Source: final clinical study report, page 62

The applicant used an optimized LC/MS method to separate M21 (hydroxy-BIC) and M22 (desfluoro-hydroxy-BIC) in pooled feces samples because these two metabolites co-eluted during the metabolite profiling process. Under the optimized chromatographic conditions, M22 eluted as a single peak and the radioactivity was quantified, however, M21 co-eluted with M23 and the percent of M21 was calculated by subtraction of M22 from M21/M22 mixture (data for M21/22 shown table 6).

Table 9: Percent of radioactive dose as M21 or M22 in feces samples pooled per individual subject (0-144 hours post-dose)

Final Metabolite Designation	Subject Number								Mean	SD
	3001	3002	3003	3004	3005	3006	3007	3008		
	Percent of Radioactive Dose									
M21/M22[a]	8.24	10.1	5.17	5.41	7.17	10.7	8.65	9.46	8.12	2.06
M22[b]	4.58	4.18	2.15	1.99	2.00	3.40	4.10	4.33	3.34	1.12
M21[c]	3.66	5.95	3.02	3.42	5.17	7.30	4.55	5.13	4.77	1.43

SD = standard deviation

a Values from (b) (4) Report 60N-1521

b Calculated from percent of run after M22 was chromatographically separated from M21.

c Calculated as c = a – b

Source: final clinical study report, page 63

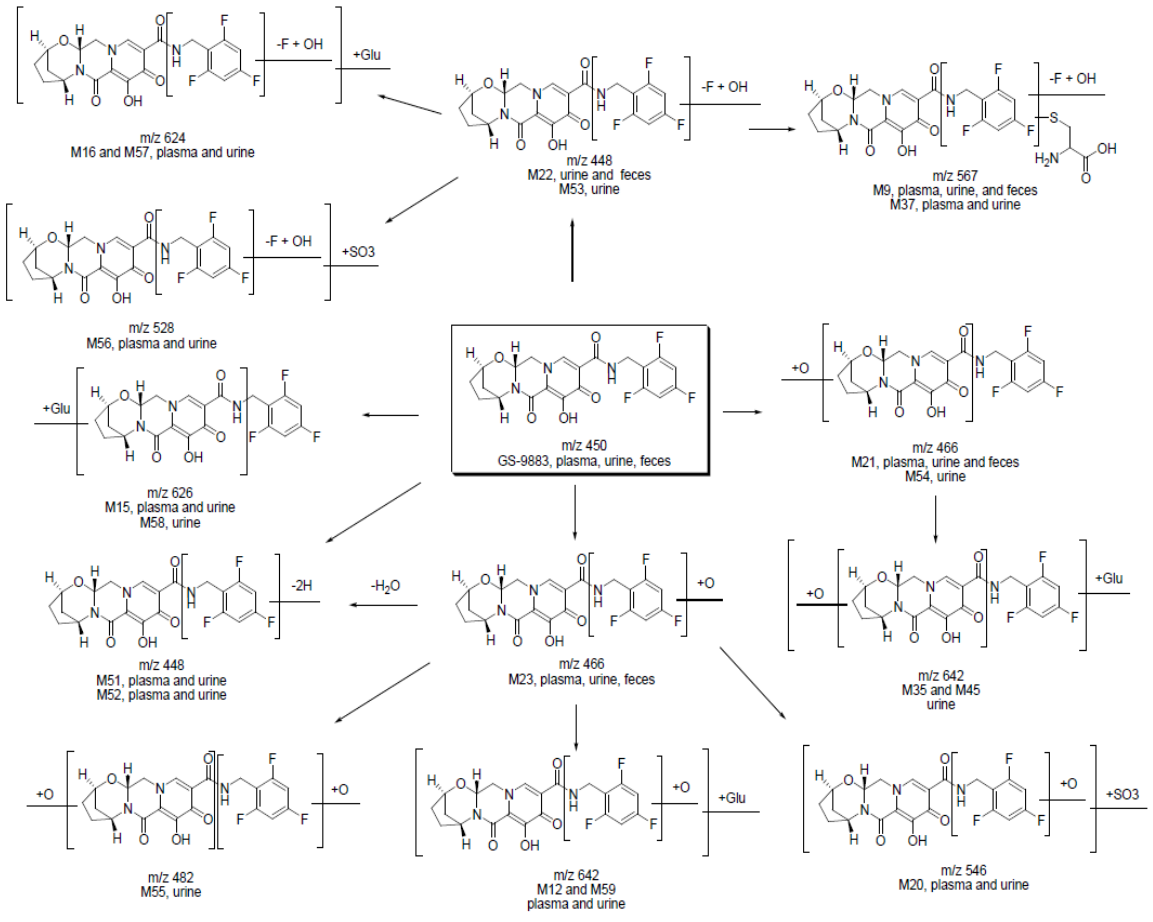
Table 10: Percent of radioactive dose as M21 or M22 in pooled feces samples by collection interval

Final Metabolite Designation	Collection Interval (Hours)			
	0 to 48	48 to 72	72 to 144	Total
	Percent of Dose			
M21/M22[a]	1.97	2.03	3.05	7.05
M22[b]	0.901	1.39	1.83	4.12
M21[c]	1.07	0.637	1.22	2.92

a Values from (b) (4) Report 60N-1521
b Calculated from percent of run after M22 was chromatographically separated from M21.
c Calculated, c = a - b.

Source: final clinical study report, page 63

Fig 4: Biotransformation pathways of BIC in human plasma, urine, and feces following a single 100 µCi/100 mg oral dose of [^{14}C] BIC to healthy male adult subjects



Source: (b) (4) Study # 60N-1521, Page 84
Note: GS-9883=BIC

Safety:

No Grade 3 or 4 AEs, serious adverse events (SAEs), AEs leading to study discontinuation, or deaths were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

- Approximately 91% of the administered radioactivity was recovered in the first 120 hours post-dose, consistent with the $t_{1/2}$ of BIC (approximately 18 hours).
- Renal clearance of unchanged BIC was minimal, with approximately 1.3% of the BIC dose recovered in urine through 144 hours post-dose.
- The non-clinical ADME studies with bile-cannulated animals (which indicated that biliary excretion of unchanged parent is negligible), coupled with the results from this trial suggest that metabolism is the major clearance pathway of BIC in humans.
- Mean blood-to-plasma ratio of total [^{14}C]-radioactivity was approximately 0.50 to 0.55 through 120 hours post-dose, indicating negligible association of radioactivity with blood cells. This finding is consistent with the high plasma protein binding of BIC (> 99%).
- Based on the fraction of the dose eliminated renally (34%) and excreted in the feces as metabolites (25% to 28%), at least 59% of the administered dose was absorbed.

Proposed Labeling Recommendation:

Some of the conclusions from the mass balance trial will be incorporated in section 12.3 of the prescribing information of [TRADENAME].

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-141-1481\report-body.pdf

Clinical Site: Covance Clinical Research Unit, Inc. 3402 Kinsman Blvd. Madison, Wisconsin.

Bioanalytical Reports:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-141-1481\basar (b) (4) 8315912.pdf

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tol-stud-rep\gs-us-141-1481\basar (b) (4) 60-1518b.pdf

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(b) (4)

Study #	GS-US-380-1991	**Study Period:** May 25, 2016-August 18, 2016
Title	A Phase 1, Single Dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/F/TAF) Fixed Dose Combination (FDC) Tablets in Healthy Japanese and Caucasian Subjects.	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: Investigate the single dose PK of BIC, F, and TAF and tenofovir (TFV) when administered as BIC/F/TAF (50/200/25 mg) FDC in healthy Japanese and Caucasian subjects.
Secondary: Assess the safety and tolerability of single dose administration of BIC/F/TAF in healthy Japanese and Caucasian subjects.

Design and PK Assessments:

Open label, single dose, Phase 1 study. Fifty subjects (25 Japanese and 25 Caucasian) were planned to be enrolled in the study. Following completion of screening and day -1 assessments, each subject received a single dose of BIC/F/TAF administered orally under fasted conditions. Japanese subjects were of first generation descent, were born in Japan and had not lived outside Japan > 5 years, and were able to trace maternal and paternal Japanese ancestry of parents and grandparents.

PK Sampling and Assessments:

Blood samples were collected for plasma PK assessments of BIC, F, TAF, and TFV pre-dose and up to 120 hours post-dose and pharmacokinetic parameters were computed.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☑ Fasted ☐Fed

Formulations
BIC/F/TAF 50/200/25 mg (batch # EN1503B2, Expiration date February 2017)

RESULTS

Enrolled	50	Completed	49	Discontinued Due to AE	1	PK Population	50	Safety Population	50

*: One Caucasian subject discontinued the study due to an adverse event.

Protocol Deviations
No protocol deviations were reported in the trial.

Demographics (based on N =50)
The median age (min, max) was 34 years (19, 52) and median (min, max) BMI was 23.2 kg/m^2 (18.4, 29.6). The trial enrolled 26 males and 24 females.

Results:

Table 1: Plasma PK parameters of BIC after single dose administration of BIC/F/TAF (50/200/25 mg) to Caucasian and Japanese subjects

PK Parameter	Mean (%CV)	
	Japanese (N = 25)	Caucasian (N = 25)
AUC_{inf} (h•ng/mL)	114,889.7 (21.2)	103,040.2 (31.3)[a]
AUC_{last} (h•ng/mL)	113,636.7 (20.9)	101,533.4 (30.7)[a]
C_{max} (ng/mL)	6556.0 (17.9)	5224.0 (21.0)
AUC_{exp} (%)	1.04 (64.3)	1.36 (60.4)[a]
T_{max} (h)[b]	1.00 (0.75, 3.00)	3.00 (1.50, 3.00)
$t_{1/2}$ (h)[b]	17.01 (13.95, 19.09)	16.53 (14.87, 19.99)[a]

CV = coefficient of variation
a n = 24; no sample collected past 8 hours for 1 subject
b Median (Q1, Q3)
Source: final clinical study report, page 47

Table 2: Plasma PK parameters of F after single dose administration of BIC/F/TAF (50/200/25 mg) to Caucasian and Japanese subjects

PK Parameter	Mean (%CV)	
	Japanese (test) (N = 25)	Caucasian (reference) (N = 25)
AUC_{inf} (h•ng/mL)	11,166.9 (18.2)	10,613.2 (14.3)[a]
AUC_{last} (h•ng/mL)	10,965.4 (18.6)	10,359.2 (14.3)[a]
C_{max} (ng/mL)	2679.6 (39.9)	2448.4 (21.7)
AUC_{exp} (%)	1.88 (42.4)	2.38 (44.9)[a]
T_{max} (h)[b]	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)
$t_{1/2}$ (h)[b]	18.03 (12.60, 23.23)	24.59 (15.97, 27.42)[a]

CV = coefficient of variation
a n = 24; no sample collected past 8 hours for 1 subject
b Median (Q1, Q3)
Source: final clinical study report, page 50

Table 3: Plasma PK parameters of TAF after single dose administration of BIC/F/TAF (50/200/25 mg) to Caucasian and Japanese subjects

PK Parameter	Mean (%CV)	
	Japanese (test) (N = 25)	Caucasian (reference) (N = 25)
AUC_{inf} (h•ng/mL)	174.8 (51.6)[a]	170.5 (40.8)[b]
AUC_{last} (h•ng/mL)	169.8 (53.1)	167.1 (41.2)[b]
C_{max} (ng/mL)	300.6 (58.3)	262.4 (41.9)
AUC_{exp} (%)	0.95 (83.8)[a]	1.80 (275.2)[b]
T_{max} (h)[c]	0.50 (0.50, 0.50)	0.50 (0.50, 0.75)
$t_{1/2}$ (h)[c]	0.35 (0.27, 0.41)[a]	0.38 (0.31, 0.48)[b]

CV = coefficient of variation
a n = 24; terminal elimination phase could not be reliably estimated for 1 subject
b n = 24; no sample collected past 8 hours for 1 subject
c Median (Q1, Q3)

Source: final clinical study report, page 53

Table 4: Plasma PK parameters of TFV after single dose administration of BIC/F/TAF (50/200/25 mg) to Caucasian and Japanese subjects

PK Parameter	Mean (%CV)	
	Japanese (test) (N = 25)	Caucasian (reference) (N = 25)
AUC_{inf} (h•ng/mL)	325.4 (24.0)	324.2 (24.3)[a]
AUC_{last} (h•ng/mL)	267.1 (24.3)	267.1 (20.4)[a]
C_{max} (ng/mL)	12.0 (30.3)	11.0 (24.4)
AUC_{exp} (%)	17.68 (36.1)	16.76 (40.0)[a]
T_{max} (h)[b]	1.00 (0.75, 1.50)	1.50 (1.00, 1.50)
$t_{1/2}$ (h)[b]	46.21 (41.78, 54.60)	42.98 (40.44, 49.51)[a]

CV = coefficient of variation
a n = 24; no sample collected past 8 hours for 1 subject
b Median (Q1, Q3)

Source: final clinical study report, page 56

Table 5: Statistical analysis of the plasma PK parameters of BIC, F, TAF and TFV after single dose administration of BIC/F/TAF (50/200/25 mg) to Caucasian and Japanese subjects

PK Parameter	Mean (%CV)		GLSM Ratio (%) (90% CI)
	Japanese (test) (N = 25)	Caucasian (reference) (N = 25)	
BIC			
AUC_{inf} (h•ng/mL)	114,889.7 (21.2)	103,040.2 (31.3)[a]	114.33 (100.36, 130.24)
AUC_{last} (h•ng/mL)	113,636.7 (20.9)	101,533.4 (30.7)[a]	114.70 (100.80, 130.51)
C_{max} (ng/mL)	6556.0 (17.9)	5224.0 (21.0)	126.32 (115.05, 138.70)
FTC			
AUC_{inf} (h•ng/mL)	11,166.9 (18.2)	10,613.2 (14.3)[a]	104.54 (96.63, 113.10)
AUC_{last} (h•ng/mL)	10,965.4 (18.6)	10,359.2 (14.3)[a]	105.08 (97.02, 113.81)
C_{max} (ng/mL)	2679.6 (39.9)	2448.4 (21.7)	103.23 (88.23, 120.79)
TAF			
AUC_{inf} (h•ng/mL)	174.8 (51.6)[b]	170.5 (40.8)[a]	97.41 (78.55, 120.80)
AUC_{last} (h•ng/mL)	169.8 (53.1)	167.1 (41.2)[a]	95.92 (77.31, 119.00)
C_{max} (ng/mL)	300.6 (58.3)	262.4 (41.9)	105.59 (85.37, 130.61)
TFV			
AUC_{inf} (h•ng/mL)	325.4 (24.0)	324.2 (24.3)[a]	100.41 (89.54, 112.59)
AUC_{last} (h•ng/mL)	267.1 (24.3)	267.1 (20.4)[a]	99.33 (89.19, 110.62)
C_{max} (ng/mL)	12.0 (30.3)	11.0 (24.4)	107.17 (93.44, 122.92)

CI = confidence interval; CV = coefficient of variation; GLSM = geometric least-squares mean
a n = 24; no sample collected past 8 hours for 1 subject
b n = 24; terminal elimination phase could not be reliably estimated for 1 subject

Source: synopsis of the final clinical study report, page 5

Safety:

No Grade 3 or 4 AEs, serious adverse events (SAEs) or deaths were reported during the study. One Caucasian subject discontinued the study due to event of grade 2 nausea and grade 1 vomiting. Grade 1 vomiting after receiving study drug on Day 1. The nausea and vomiting began after receiving ibuprofen for Grade 2 AEs of neck pain and headache that occurred prior to study drug administration. The nausea and vomiting were considered related to study drug by the investigator. All 4 AEs resolved on Day 3.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Conclusion and Proposed Labeling Recommendation:

The results of the trial suggest that after single dose administration under fasted conditions, the mean pharmacokinetic parameters are similar between Caucasian subjects and Japanese subjects. An increase in the mean C_{max} of BIC by 26% in Japanese subjects relative to Caucasian subjects is observed. Based on the exposure-response (safety) relationship of BIC (and under the assumption that a similar difference in mean C_{max} will be observed if multiple doses of BIC/F/TAF are administered under fed conditions), the increase in BIC exposures is not expected to be clinically relevant.

The applicant has not proposed any labeling recommendation based on the results of the trial.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\gs-us-380-1991\report-body.pdf

Clinical Sites: West Coast Clinical Trials, Inc. Cypress, CA (enrolled 22 subjects) and SNBL Clinical Pharmacology Center, Baltimore, MD (enrolled 28 subjects).

Bioanalytical Reports:

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Bioanalytical Site: (b) (4)

Study #	GS-US-141-1218	**Study Period:** June 11, 2014 through October 19, 2014
Title	A Phase 1, Double Blind, Randomized, Placebo-Controlled, First-in-Human, Single- and Multiple-Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Oral Bictegravir (BIC) in Healthy Subjects and a Randomized, Open-Label, 2-Cohort, 3-Period, Crossover, Pharmacokinetic Study Evaluating the Drug Interaction Potential between Emtricitabine/Tenofovir Alafenamide (F/TAF) Fixed Dose Combination Tablet and BIC in Healthy Subjects	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

The primary objectives of this study were as follows:

- To evaluate the safety and tolerability of single- and multiple-ascending oral doses of BIC compared with placebo in healthy subjects
- To evaluate the PK of BIC following single- and multiple-ascending oral doses of BIC in healthy subjects

The exploratory objectives of this study were as follows:

- To evaluate the effect of food on the PK of BIC
- To evaluate the safety and tolerability of F/TAF and BIC administered separately or together
- To evaluate the effect of F/TAF on the PK of BIC
- To evaluate the effect of BIC on the PK of FTC and TAF and its major metabolite tenofovir (TFV)

Rationale:

First-in-human trial to assess the safety, tolerability, and pharmacokinetics of BIC. The applicant also planned to assess the potential for drug-drug interaction between BIC and F/TAF to support co-administration of BIC and F/TAF in subsequent clinical trials.

Design and PK Assessments:

Four part, first-in-human trial:

Part A: Assessed single ascending dose of BIC in 6 cohorts with 48 unique subjects. 8 subjects in each cohort were randomized 3:1 to receive BIC (n=6) or placebo-to-match (n=2). The following single doses were administered in a sequential manner under fasting conditions: 100 mg (Cohort 1; 1X100 mg tablet); 300 mg (Cohort 2; 3X 100 mg tablet); 600 mg (Cohort 3; 6 X 100 mg tablet); 5 mg (Cohort 4; 1 X 5 mg tablet); 25 mg (Cohort 5; 1 X 25 mg tablet); 50 mg (Cohort 6; 2 X 25 mg tablet). Upon completion of Part A Cohort 1 through Day 14 and in the absence of dose-limiting toxicity and/or meeting pre-specified stopping criteria, additional subjects were enrolled in Cohorts 4 to 6, in which doses lower than the Part A Cohort 1 dose were evaluated concurrently.

Part B: BIC was administered once daily on days 1 through 14 in a blinded manner under fasting conditions. Upon completion of cohorts 2 through 4 in part A, subjects were enrolled in part B. The following doses were administered: 100 mg (Cohort 1; 1X100 mg tablet); 300 mg (Cohort 2; 3X 100 mg tablet); 5 mg (Cohort 3; 1 X 5 mg tablet); 25 mg (Cohort 4; 1 X 25 mg tablet); 50 mg (Cohort 5; 2 X 25 mg tablet).

Part C: Open-label with non-randomized design in which healthy subjects were administered 100 mg GS-9883 in 2 periods with a fixed sequence under fasted and fed (high-fat breakfast; approximately 800 calories, 50% calories from fat) conditions.

Part D: Randomized, open-label, 2-cohort, 3-period, crossover PK study evaluating the drug interaction potential between the F/TAF (F/TAF) FDC tablet and BIC in healthy subjects. All the treatments were under fed (moderate-fat breakfast; approximately 600 calories, 27% calories from fat) conditions.

Cohort 1:

- Period 1: F/TAF (200/25 mg) administered once daily for 7 days
- Period 2: F/TAF (200/25 mg) administered once daily and BIC (100 mg) administered once daily on days 8 through 14
- Period 3: BIC (100 mg) administered once daily on days 15 through 21

Cohort 2:

- Period 1: BIC (100 mg) administered once daily on days 1 through 7
- Period 2: F/TAF (200/25 mg) administered once daily and BIC (100 mg) administered once daily on days 8 through 14
- Period 3: F/TAF (200/25 mg) administered once daily on days 15 through 21

PK and Urine Sampling:

Part A: Blood samples were collected pre-dose and up to 96 hours post-dose. Urine was collected pre-dose and at the following intervals relative to day 1 dosing: 0-6, 6-12, and 12-24 hours post-dose.

Part B: Blood samples were collected pre-dose and up to 24 hours post-dose on days 1 through 7. Pre-dose trough samples were collected on days 4, 5, 6, 10, 11, 12, and 14. Urine was collected pre-dose on days 1 and 7 and at the following intervals relative to days 1 and 7 dosing: 0-6, 6-12, and 12-24 hours post-dose.

Part C: On day 1, blood samples were collected pre-dose and up to 96 hours after administration of BIC in the fasted state. On day 9, subjects were dosed BIC after completion of a high-fat breakfast and blood samples were collected pre-dose and up to 96 hours post-dose. Urine was collected pre-dose on days 1 and 9 and at the following intervals relative to days 1 and 9 dosing: 0-6, 6-12, and 12-24 hours post-dose.

Part D: Blood samples were collected for the analysis of BIC, F, TAF and TFV (as applicable) pre-dose and up to 24 hours post-dose on days 7, 14 and 21. The 24-hour sample was collected pre-dose on dosing days and additional pre-dose samples were collected on days 5, 6, 12, 13, 19, and 20. Urine was collected pre-dose on days 7, 14, and 21 and at the following intervals relative to days 7, 14, and 21 dosing: 0-6, 6-12, and 12-24 hours post-dose.

The PK parameters were estimated using non-compartmental methods.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☑ Fasted ☑ Fed (depending on the cohort and part)

Formulations
BIC 5 mg: Lot # EC1401B1, expiration date April 2015;
BIC 25 mg: Lot # EC1402C1, expiration date May 2015;
BIC 100 mg: Lot # EC1402D1, expiration date May 2015;
F/TAF 200/25 mg: Lot # CR1305B2, expiration date February 2015.

(b) (4)

RESULTS									
Enrolled	130[1]	Completed	128[2]	Discontinued	2[3]	PK Population	55	Safety Population	56

1: 48 subjects randomized in Part A; 40 subjects randomized in Part B, 8 subjects enrolled in Part C, and 34 subjects randomized in Part D.
2: 48 subjects in Part A [including 12 subjects administered placebo]; 39 subjects in Part B [including 9 subjects administered placebo], 8 subjects in Part C, and 33 subjects in Part D
3: 2 subjects (1 subject in Part B and 1 subject in Part D) discontinued due to an adverse event and consent withdrawal, respectively.

Protocol Deviations

No protocol deviations were reported in the trial.

Demographics

Table 1: Demographic characteristics of subjects enrolled in various parts

Part	Median Age (in years) (range)	Gender (M/F)	Median weight (in kg) (range)	Median BMI (kg/m^2) (range)
A (N =48)	35 (20 to 45)	26/22	75 (54 to 99)	27 (19 to 30)
B (N =40)	36 (23 to 45)	22/18	74 (51 to 108)	27 (21 to 30)
C (N =8)	29 (25 to 43)	4/4	69 (61 to 95)	26 (23 to 30)
D (N =34)	37 (19 to 45)	17/17	77 (54 to 99)	27 (22 to 30)

Source: Prepared by the reviewer based on information provided in the final clinical study report.

Pharmacokinetics:

Part A (Pharmacokinetic Assessment after Single Dose):

Table 2: Mean (%CV) plasma pharmacokinetic parameters of BIC after single dose administration of BIC

GS-9883 PK Parameter Mean (%CV)[a]	Single Dose GS-9883					
	5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)	600 mg (N = 6)
AUC_{inf} (hr•ng/mL)	13,059.7 (25.1)	35,718.2 (21.3)	78,399.5 (29.7)	163,028.2 (24.3)	355,917.3 (32.9)	454,446.8 (19.9)
CL/F (mL/hr)	398.8 (19.5)	727.5 (21.4)	675.6 (23.2)	656.2 (32.9)	936.1 (37.0)	1357.2 (16.6)
C_{max} (ng/mL)	691.2 (22.1)	1618.3 (26.7)	3965.0 (40.1)	6998.3 (36.1)	14,605.0 (27.1)	20,050.0 (7.5)
$t_{½}$ (hr)	18.51 (16.81, 19.99)	18.08 (16.63, 19.64)	16.72 (15.77, 17.11)	18.90 (17.96, 20.05)	18.14 (17.86, 20.53)	17.89 (16.38, 19.52)
T_{max} (hr)	1.25 (1.00, 1.50)	2.00 (1.00, 3.00)	3.00 (1.50, 4.00)	2.25 (1.50, 3.00)	3.50 (2.00, 6.00)	3.50 (2.00, 4.00)
V_z/F (mL)	10,312.6 (20.2)	19,038.8 (27.3)	16,701.5 (26.5)	19,834.7 (57.5)	23,228.3 (26.5)	34,770.6 (10.7)

a. Data are presented as mean (%CV), except for T_{max}, and $t_{½}$, which are presented as median (Q1, Q3)

Source: final clinical study report, page 81

Table 3: Statistical comparison of the pharmacokinetic parameters of BIC after single dose administration of BIC (using PK parameters observed after single dose administration of BIC 50 mg as reference)

GS-9883 PK Parameter	%GLSM Ratio (Test/Reference) (90% CI)				
	GS-9883 5 mg (N = 6)	GS-9883 25 mg (N = 6)	GS-9883 100 mg (N = 6)	GS-9883 300 mg (N = 6)	GS-9883 600 mg (N = 6)
Reference GS-9883 50 mg (N = 6)					
AUC_{inf} (hr*ng/mL)	168.11 (130.26, 216.94)	92.22 (71.46, 119.01)	104.08 (80.65, 134.31)	74.23 (57.52, 95.80)	49.12 (38.06, 63.38)
AUC_{last} (hr*ng/mL)	167.65 (129.68, 216.74)	91.93 (71.11, 118.85)	102.22 (79.07, 132.15)	73.90 (57.17, 95.55)	49.01 (37.91, 63.36)
C_{max} (ng/mL)	180.38 (134.63, 241.68)	83.81 (62.56, 112.29)	86.41 (64.50, 115.77)	62.83 (46.89, 84.18)	44.40 (33.14, 59.49)

GLSM = Geometric Least Squares Mean.
Mixed model included dose as a fixed effect.
PK parameters were dose-normalized to GS-9883 50 mg (eg, C_{max} = C_{max} / [dose / 50]).

Source: final clinical study report, page 82

Part B (Pharmacokinetic Assessment after Multiple Dose):

Table 4: Mean (%CV) plasma pharmacokinetic parameters of BIC after multiple dose administration of BIC

	GS-9883 PK Parameter Mean (%CV)[a]	Multiple-Dose GS-9883				
		5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)
Day 1	AUC_{0-24} (hr*ng/mL)	9033.6 (8.2)	27,775.1 (28.3)	58,371.4 (18.9)	79,773.8 (18.9)	180,714.3 (17.6)
	C_{max} (ng/mL)	709.7 (9.5)	2220.0 (35.6)	4648.3 (18.7)	6248.3 (26.8)	13,716.7 (19.1)
	T_{max} (hr)	1.50 (1.50, 1.50)	1.75 (1.00, 3.00)	1.50 (1.00, 2.00)	2.50 (2.00, 3.00)	2.50 (2.00, 4.00)
Day 7	AUC_{tau} (hr*ng/mL)	14,392.0 (16.7)	50,008.2 (26.6)	89,710.1 (22.7)	126,785.8 (23.7)	277,200.2 (16.7)
	C_{max} (ng/mL)	982.5 (7.9)	3455.0 (24.1)	6538.3 (17.6)	9396.7 (20.8)	19,900.0 (21.2)
	C_{tau} (ng/mL)	400.83 (26.9)	1322.00 (27.8)	2241.67 (28.2)	3145.00 (26.1)	6758.33 (21.6)
	T_{max} (hr)	1.50 (1.00, 2.00)	3.00 (2.00, 3.00)	1.75 (1.50, 2.00)	1.75 (1.50, 3.00)	4.00 (2.00, 4.00)
	Accumulation Ratio of AUC (%)	160.5 (19.0)	182.2 (17.1)	154.0 (15.9)	158.5 (12.1)	157.5 (22.6)

a Data are presented as mean (%CV), except for T_{max}, and $t_{½}$, which are presented as median (Q1, Q3)

Source: final clinical study report, page 84

Table 5: Statistical comparison of the pharmacokinetic parameters of BIC after multiple dose administration of BIC (using PK parameters observed after multiple dose administration of BIC 50 mg as reference)

GS-9883 PK Parameter	%GLSM Ratio (Test/Reference) (90% CI)			
	GS-9883 5 mg (N = 6)	GS-9883 25 mg (N = 6)	GS-9883 100 mg (N = 6)	GS-9883 300 mg (N = 6)
Day 1 Reference GS-9883 50 mg (N = 6)				
AUC_{last} (hr*ng/mL)	156.56 (129.91,188.68)	93.76 (77.80, 112.99)	68.22 (56.60, 82.21)	51.69 (42.89,62.30)
C_{max} (ng/mL)	154.10 (122.64,193.63)	92.52 (73.64,116.26)	65.72 (52.30, 82.58)	49.09 (39.07,61.68)
Day 7 Reference GS-9883 50 mg (N = 6)				
AUC_{tau} (hr*ng/mL)	162.30 (130.37, 202.07)	110.58 (88.82, 137.67)	70.44 (56.58, 87.70)	52.02 (41.79, 64.77)
C_{max} (ng/mL)	151.83 (125.10, 184.27)	104.40 (86.02, 126.70)	71.25 (58.71, 86.48)	50.52 (41.62, 61.31)
C_{tau} (ng/mL)	180.65 (137.85, 236.73)	118.03 (90.07, 154.68)	70.43 (53.74, 92.29)	50.89 (38.84, 66.69)

GLSM = Geometric Least Squares Mean
Mixed model included dose as a fixed effect.
PK parameters were dose-normalized to GS-9883 50 mg (eg, Cmax = Cmax / [dose / 50]).

Source: final clinical study report, page 85

After administration of 50 mg once daily, the mean $AUC_{0\text{-}tau}$ of BIC on day 7 was similar to the mean $AUC_{0\text{-}inf}$ of BIC after administration of single dose on day 1, thereby suggesting that steady state was achieved by day 7. The accumulation ratio of BIC at the 50 mg dose was 1.54 and consistent with the estimated accumulation of 1.66 based on a half-life of 18 hours (estimated using 1/(1-exp(-ke*tau)).

Part C (Assessment of Food Effect):

Table 6: Mean (%CV) plasma pharmacokinetic parameters of BIC after single dose administration of BIC under fasted and fed conditions

GS-9883 PK Parameter[a] Mean (%CV)	GS-9883 100 mg Fasted (n=8)	GS-9883 100 mg Fed (n=8)
AUC_{inf} (hr*ng/mL)	117,777.1 (23.3)	214,146.3 (15.9)
C_{max} (ng/mL)	5885.0 (34.9)	11,268.8 (15.1)
$t_{½}$ (hr)	16.04 (15.32, 17.12)	16.87 (16.30, 17.93)
T_{max} (hr)	1.75 (1.25, 3.50)	3.00 (1.75, 3.00)
V_z/F (mL)	21,685.2 (40.3)	11,699.4 (13.3)
CL/F (mL/hr)	891.6 (24.1)	479.4 (18.6)

a Data are presented as mean (%CV), except for T_{max}, and $t_{½}$, which are presented as median (Q1, Q3)

Source: final clinical study report, page 87

Table 7: Statistical comparison of the pharmacokinetic parameters of BIC after single dose

administration of BIC under fasted and fed conditions

GS-9883 PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Test GS-9883 100 mg Fed (n=8)	Reference GS-9883 100 mg Fasted (n=8)	
AUC_{inf} (hr*ng/mL)	214,146.3 (15.9)	117,777.1 (23.3)	183.97 (152.05, 222.59)
AUC_{last} (hr*ng/mL)	209,259.9 (15.1)	115,681.7 (24.0)	183.58 (151.91, 221.86)
C_{max} (ng/mL)	11,268.8 (15.1)	5885.0 (34.9)	200.69 (165.93, 242.74)

GLSM = Geometric Least Squares Mean. CI = Confidence Interval

Source: final clinical study report, page 87

Part D (Assessment of the Potential of DDI between BIC and F/TAF):

BIC:

Table 8: Mean (%CV) plasma pharmacokinetic parameters of BIC after multiple dose administration of BIC alone and multiple dose co-administration of BIC with F/TAF

GS-9883 PK Parameter Mean (%CV)	GS-9883 100 mg (n=34)	GS-9883 100 mg + F/TAF 200/25 mg (n=34)
AUC_{tau} (hr*ng/mL)	213,759.6 (16.9)	217,370.6 (20.3)
CL/F (mL/hr)	481.0 (17.1)	480.4 (22.2)
C_{max} (ng/mL)	14,920.6 (14.9)	14,939.7 (18.4)
C_{tau} (ng/mL)	5687.1 (21.7)	5889.4 (26.3)
T_{max} (hr)	3.00 (1.50, 4.00)	3.00 (2.00, 4.00)

Data are presented as mean (%CV), except for T_{max} and T_{last}, which are presented as median (Q1, Q3).

Source: final clinical study report, page 89

FTC:

Table 9: Mean (%CV) plasma pharmacokinetic parameters of F after multiple dose administration of F/TAF and multiple dose co-administration of F/TAF and BIC

FTC PK Parameter Mean (%CV)	F/TAF (200/25 mg) (n=33)	GS-9883 100 mg + F/TAF (200/25 mg) (n=34)
AUC_{tau} (hr*ng/mL)	9482.2 (14.8)	9680.2 (17.3)
CL/F (mL/hr)	21,502.2 (13.6)	21,239.4 (16.6)
C_{max} (ng/mL)	1796.7 (18.2)	1803.5 (22.6)
C_{tau} (ng/mL)	65.24 (22.2)	69.12 (26.8)
T_{max} (hr)	2.00 (1.50, 3.00)	2.00 (1.50, 3.00)

Data are presented as mean (%CV), except for T_{max} and T_{last}, which are presented as median (Q1, Q3).

Source: final clinical study report, page 91

Note: F= FTC

TAF:

Table 10: Mean (%CV) plasma pharmacokinetic parameters of TAF after multiple dose administration of F/TAF and multiple dose co-administration of F/TAF and BIC

TAF PK Parameter Mean (%CV)	F/TAF (200/25 mg) (n=33)	GS-9883 100 mg + F/TAF (200/25 mg) (n=34)
AUC_{last} (hr*ng/mL)	288.7 (32.0)	366.6 (27.4)
CL/F (mL/hr)	96,116.0 (36.1)	73,650.7 (31.2)
C_{max} (ng/mL)	221.3 (44.4)	299.6 (37.4)
C_{last} (ng/mL)	3.0 (57.7)	1.9 (42.3)
T_{last} (hr)	4.00 (4.00, 5.00)	5.00 (4.00, 5.00)
T_{max} (hr)	1.50 (0.75, 1.67)	1.00 (0.75, 1.50)

Data are presented as mean (%CV), except for T_{max} and T_{last}, which are presented as median (Q1, Q3).
Source: final clinical study report, page 93

TFV:

Table 11: Mean (%CV) plasma pharmacokinetic parameters of TFV after multiple dose administration of F/TAF and multiple dose co-administration of F/TAF and BIC

TFV PK Parameter Mean (%CV)	F/TAF (200/25 mg) (n=33)	GS-9883 100 mg + F/TAF (200/25 mg) (n=34)
AUC_{tau}(hr*ng/mL)	267.5 (19.9)	304.2 (17.9)
CL/F (mL/hr)	96,711.3 (18.0)	84,647.9 (17.3)
C_{max} (ng/mL)	16.5 (26.8)	18.0 (18.7)
C_{tau} (ng/mL)	9.18 (21.7)	10.74 (24.3)
T_{last} (hr)	23.93 (23.93, 24.00)	23.93 (23.93, 23.93)
T_{max} (hr)	3.00 (2.00, 3.00)	3.00 (2.00, 3.00)

Data are presented as mean (%CV), except for T_{max} and T_{last}, which are presented as median (Q1, Q3).
Source: final clinical study report, page 95

Table 12: Statistical comparison of the plasma pharmacokinetic parameters of BIC, F, TAF, and TFV after multiple dose administration of F/TAF and BIC

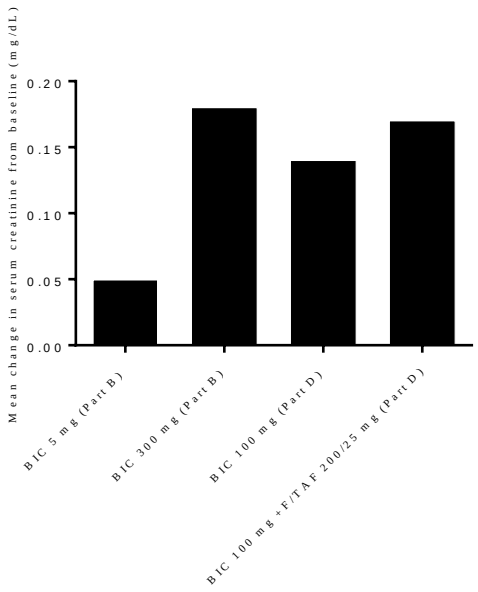
	GLSM		GLSM Ratio (90% CI), %
	Test	Reference	
GS-9883 PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. GS-9883 (Reference) (N = 34)			
AUC_{tau} (hr*ng/mL)	212,852.8	210,816.0	100.97(98.22,103.79
C_{max} (ng/mL)	14,693.24	14,761.70	99.54 (96.41,102.76)
C_{tau} (ng/mL)	5681.53	5553.18	102.31(98.48,106.29)
FTC PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{tau} (hr*ng/mL)	9545.74	9363.40	101.95 (100.13,103.80)
C_{max} (ng/mL)	1759.80	1773.33	99.24 (94.19,104.55)
C_{tau} (ng/mL)	67.04	63.33	105.86 (101.26,110.67)
TAF PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{last}(hr*ng/mL)	352.61	272.28	129.50 (123.67,135.61)
C_{max} (ng/mL)	277.95	203.10	136.86 (116.99,160.09)
TFV PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{tau} (hr*ng/mL)	299.66	263.52	113.72 (110.07,117.49)
C_{max} (ng/mL)	17.66	16.01	110.30 (105.27,115.56)
C_{tau} (ng/mL)	10.46	9.09	115.04 (110.79,119.46)

FTC = emtricitabine; F/TAF = emtricitabine/tenofovir alafenamide (coformulated); GLSM = geometric least-squares mean; TFV = tenofovir

Source: final clinical study report, page 9

Dose dependent changes in serum creatinine were observed in the trial, presumably *via* the inhibition of OCT2 and/or MATE transporters in the kidney known to mediate the efflux of creatinine.

Fig 1: Changes in serum creatinine from baseline in Part B and Part D



Note: In the figure above, for part B, serum creatinine change at Day 14 (compared to pre-dose/baseline) is plotted and for part D, serum creatinine change at Day 7 (compared to pre-dose/baseline) is plotted.

Source: Prepared by reviewer based on information provided in the clinical study report.

Safety:
No Grade 3 or 4 AEs, serious adverse events (SAEs), AEs leading to study discontinuation, or deaths were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

- After single dose administration of BIC, the dose normalized mean C_{max} and AUC decreased with increasing doses of BIC above the 100 mg dose. Considering similarity in half-life of BIC across the dose range (approximately 18 hours), the less than dose proportional increase in BIC exposures with BIC doses above 100 mg seems to be primarily driven by decrease in bioavailability (due to decreased solubility and/or absorption).
- The mean C_{max} and AUC_{inf} of BIC (100 mg single dose) increased by 100% and 84% respectively when administered with food (high fat breakfast) relative to fasting conditions. In trial GS-US-141-1233, the mean C_{max} and AUC_{inf} of BIC (single dose of BIC/F/TAF 50/200/25 mg) increased by 13% and 24%, respectively. Although BIC shows less than dose proportional increase in exposure (probably due to lower solubility and/or reduced absorption) with increasing doses of BIC above 100 mg, mean exposure of BIC increases nearly proportionally between the 50 mg and 100 mg doses (when BIC is administered alone). Hence, the differences in the effect of food when BIC 100 mg is given alone and when BIC 50 mg is given as part of BIC/F/TAF cannot be explained based on lower solubility and/or reduced absorption of BIC with increasing doses. Another plausible hypothesis can be that co-formulating BIC as BIC/F/TAF improves solubility and/or absorption of BIC relative to administration of BIC alone. This hypothesis is supported by the fact that in trial GS-US-141-1233, under fasting conditions, the mean C_{max} and AUC of BIC after administration of BIC/F/TAF 75/200/25 mg were 31% and 27% higher, respectively, relative to administration of BIC 75 mg alone.
- After multiple dose administration of BIC 100 mg and F/TAF 200/25 mg, the mean C_{max} and AUC_{last} of TAF increased by 37% and 30%. Considering BIC is not expected to inhibit P-gp, BCRP and OATP transporters (TAF is a substrate of the aforementioned transporters), the mechanistic basis for increase in TAF exposures is not characterized. Nevertheless, since BIC/F/TAF has been administered as a FDC in Phase 3 trials where extensive safety data have been collected, the increase in TAF exposures (assuming a similar increase in TAF exposures is observed when BIC/F/TAF 50/200/25 mg is given) is not anticipated to be clinically relevant.
- Dose dependent changes in serum creatinine were observed in the trial, presumably *via* the inhibition of OCT2 and or MATE, transporters in the kidney known to mediate the uptake and efflux of creatinine, respectively.

Proposed Labeling Recommendation:

The applicant has not proposed any specific recommendations based on the results from the trial.

Considering that some of the assessments (for example assessment of the effect of food on the exposures of the individual components of BIC/F/TAF FDC; inhibitory effect of BIC on renal transporters etc) conducted as part of trial were also conducted in other trials using the clinically relevant dose and/or formulations, the conclusions from other trials will be incorporated in the labeling.

Relevant Links and information on clinical and bioanalytical sites:

Trial Report:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-141-1218\report-body.pdf

Clinical Site: SeaView Research, 3898 NW 7th Street, Miami, FL.

Bioanalytical Reports:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-141-1218\basar(b) (4)60-1430a.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-141-1218\basar(b) (4)60-1430b.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-141-1218\basar(b) (4)60-1430c.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-141-1218\basar-(b) (4)-60-1430d.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\gs-us-141-1218\basar-(b) (4)60-1430e.pdf

Bioanalytical Site: (b) (4)

Study #	GS-US-141-1487	**Study Period:** July 24, 2015 – September 9, 2015
Title	A Randomized, Blinded, Placebo Controlled Phase 1 Study Evaluating the Effect of BIC on Renal Function as Assessed by Markers of Glomerular Filtration Rate (GFR)	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: Assess renal function before, during, and after administration of BIC versus placebo via determination of actual GFR (aGFR) as assessed by iohexol clearance.

Secondary:

1) Assess renal function before, during, and after administration of BIC versus placebo *via* determination of estimated creatinine clearance ($eGFR_{CG}$), and measured 24-hour urinary creatinine excretion (mGFR).
2) Assess the pharmacokinetics of BIC after 14 days of multiple dosing
3) Assess the safety and tolerability of BIC after multiple dosing

Of note, the applicant mentions that "renal function was based on estimated glomerular filtration rate calculated using Cockcroft-Gault equation ($eGFR_{CG}$)", however, estimated CrCL [denoted as $eCrCL_{CG}$] (instead of $eGFR_{CG}$) is an accurate descriptor because the applicant used C-G equation which would provide an estimate of the creatinine clearance and not of GFR.

Rationale:

The applicant observed small, transient increases in serum creatinine in both healthy volunteers (in trial GS-US-141-1218) and HIV-1 infected subjects (GS-US-141-1219). Although creatinine is primarily eliminated by glomerular filtration and not reabsorbed or metabolized by the kidney, creatinine has been shown to be a substrate for active secretion *via* several transporters, including the human organic cation transporter 2 (OCT2), a transporter basolaterally expressed in renal tubules and Human Multidrug and Toxin Extrusion 1(MATE1) transporter, an efflux transporter expressed on the luminal membrane of the proximal tubular cells. A number of drugs from different therapeutic classes have been observed to reduce estimated creatinine clearance without affecting the rate of glomerular filtration due to their inhibitory effect on renal transporters. The results of *in vitro* study AD-141-2285 showed that BIC is an inhibitor of OCT2 (IC_{50} = 0.42 μM) and a weak inhibitor of MATE1 (IC_{50} = 8.04 μM).

The dose-dependent changes in serum creatinine observed in Studies GS-US-141-1218 and GS-US-141-1219 were presumably *via* a blockade of creatinine secretion through OCT2 and/or MATE1. The applicant conducted this trial to further characterize the mechanism behind the increase in serum creatinine observed after administration of BIC and to determine if BIC has any effect on renal function by assessment of actual glomerular filtration rate (aGFR) as measured by iohexol clearance.

Dose Selection:

BIC (75 mg): The 75 mg dose was selected because this was the dose of BIC used in the Phase 2 efficacy and safety study of BIC co-administered with F/TAF (200/25 mg) in study GS-US-141-1475). Of note, although the applicant used BIC 75 mg in the trial, the results can be extrapolated to BIC/F/TAF (50/200/25 mg) because the mean systemic exposures of BIC after administration of BIC 75 mg under moderate fat conditions are higher

than mean systemic exposures of BIC after administration of BIC/F/TAF 50/200/25 mg under fed (high fat and moderate fat) conditions. Hence, the results from this trial are expected to provide a conservative estimate of the effect of BIC on markers of GFR.

Design and PK Assessments:

Phase 1, randomized, blinded, placebo-controlled, 2-group, multiple-dose, parallel-design study.

Table 1: Trial Design

Study Day														
−28	−2	−1	1	2	3-6	7	8-13	14	15	16	17-20	21	22	27-31
														Follow-up Visit
Screening[a]	♦	●[b]	●[c]	●[c]	●[c]	●[c+b]	●[c]	●[c+b]	Washout			●[b]	▲	In-clinic visit
		■[d,f]	■[f]	■[f]		■[d,e,f]		■[d,e,f]		■[f]		■[d,f]		

a Screening procedures occurred within 28 days prior to scheduled first dose.
b Iohexol IV administration (Note: time zero = end time of iohexol IV infusion)
c Treatment A (GS-9883 75 mg) or Treatment B (GS-9883 placebo-to-match)
d Intensive iohexol PK collection following dosing on Days −1, 7, 14, and 21 through 24 hours postdose.
e Intensive GS-9883 PK collection following dosing on Day 7 through 24 hours postdose and Day 14 through 96 hours postdose.
f PD samples (blood sampling and 24-hour urine collection on Days −1, 1, 2, 7, 14, 16, and 21)
Clinic Check-in = ♦
Study Drug Dosing = ●
PK/PD/Biomarker Specimen Collection = ■
Clinic Discharge = ▲
Clinic Confinement = [redacted]

Source: Clinical Study Report, Page 24

On Days −1, 7, 14, and 21, iohexol (1500 mg as 5 mL of a 300 mg iodine/mL solution), was administered as an IV dose slowly injected over approximately 1 minute. On days when both iohexol and BIC were given, iohexol was given within 5 minutes of administration of BIC or placebo.

PK Sampling and Assessments:

Blood samples were collected for plasma PK assessments of iohexol and BIC. Pre-dose samples were collected on days -1, 7, 14, and 21. Post dose samples were collected as follows:

1) Iohexol: days -1, 7, 14, and 21: up to 24 hours post-dose.
2) BIC: day 7 (up to 24 hours post-dose) and day 14 (up to 96 hours post-dose).

The following plasma pharmacokinetic (PK) parameters of iohexol were calculated: AUC_{inf}, $CL_{iohexol}$, and % AUC_{exp}. The following plasma PK parameters of BIC were calculated: AUC_{last}, AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, CL_{ss}/F, V_z/F, and $t_{1/2}$.

PD Sampling and Assessments:

Blood samples were collected on days -1, 1, 2, 7, 14, 16, and 21 for the measurement of serum creatinine, blood urea nitrogen and electrolytes. On days -1, 7, 14, and 21 (days on which iohexol was administered), samples

were collected at 12 hours after time zero. On days 1, 2, and 16 (days on which iohexol was not administered), samples were collected at the time point consistent with 12 hours after time zero on iohexol administration days. Twenty four hour urine samples were collected on days -1, 1, 2, 7, 14, 16, and 21. On the morning of days -1, 7, 14, 16, and 21, subjects completely voided their bladders prior to start of each 24 hour collection interval and this first morning void was discarded except on the morning of days 1 and 2 where the first morning voids were included in the 24-hour specimen collection for days -1 and 1 respectively, and were not discarded.

The effect of BIC on renal function was assessed by comparing body surface area adjusted aGFR, estimated GFR (using MDRD), estimated CrCL (using Cockcroft-Gault; C-G) and measured GFR (measured 24-hour urine creatinine excretion) after administration of BIC 75 mg or placebo.

Because of some changes made to the protocol specified analyses by the applicant, no between-treatment groups or between-visit comparisons were performed for $eGFR_{MDRD}$, measured GFR was not assessed on days 1, 2, 16 and weight corrected CL_{ss}/F was not computed. Despite the aforementioned changes, the available information is sufficient to make an assessment regarding the potential mechanism for the observed increase in serum creatinine concentrations after administration of BIC.

Population: ☑ Healthy Volunteers ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations
BIC 75 mg tablets (batch # EC1504B1, Expiration date August 2016); placebo to match BIC (batch # EC1502B1, Expiration date August 2020).

RESULTS

Enrolled	40*	Completed	40	Discontinued Due to AE	0	PK Population	40	Safety Population	40

*: 20 subjects were randomized to the BIC 75 mg group and 20 subjects were randomized to the placebo group

Protocol Deviations
No protocol deviations were reported in the trial.

Demographics
The trial enrolled 25 male subjects and 15 female subjects. Median age was 40 years (range: 20 to 45 years) and median BMI was 26.6 kg/m^2 (range: 20.6-29.7 kg/m^2). Median aGFR (range) at baseline was 126 mL/min (104.4-168.9 mL/min), median $eGFR_{CG}$ (range) at baseline was 120.9 mL/min (97.6-181.1 mL/min) and median mGFR (range) at baseline was 141.9 mL/min (76.9-206.6 mL/min).

Results:

Table 2: Plasma PK parameters of BIC after 7 and 14 days of once-daily dosing of BIC 75 mg under fed conditions.

GS-9883 75 mg	Mean (%CV)	
	Day 7 N = 20	Day 14 N = 20
AUC_{tau} (h•ng/mL)	160,084.7 (23.8)	167,757.2 (24.9)
C_{max} (ng/mL)	12,079.5 (21.4)	12,356.5 (21.3)
C_{tau} (ng/mL)	4179.0 (29.9)	4373.0 (32.2)
C_{last} (ng/mL)	4179.00 (29.88)	337.84 (64.54)
T_{max} (h)[a]	2.08 (1.58, 3.08)	3.08 (2.08, 3.08)
T_{last} (h)[a]	23.93 (23.93, 23.93)	96.08 (96.08, 96.08)
$t_{1/2}$ (h)[a]	NA	19.44 (16.61, 21.22)
CL_{ss}/F (mL/h)	497.2 (26.5)	474.3 (25.1)
V_z/F (mL)	NA	12,665.8 (18.1)

NA = not applicable
a Median (Q1, Q3)
Source: final clinical study report, page 58

Pharmacokinetics of Iohexol:

Table 3: Mean (%CV) pharmacokinetic parameters of iohexol on various days after administration of BIC 75 mg or placebo

Day		BIC	Placebo
-1	AUC_{inf} (µg*hr/mL)	424.8 (11.3)	432.2 (8.6)
	CL (mL/min)	128.6 (12.1)	125.6 (8.7)
7	AUC_{inf} (µg*hr/mL)	425.6 (11.8)	409.4 (10.4)
	CL(mL/min)	128.5 (13.2)	133 (9.7)
14	AUC_{inf} (µg*hr/mL)	426.2 (10.4)	417.1 (10.4)
	CL(mL/min)	127.9 (11)	130.6 (10.6)
21	AUC_{inf} (µg*hr/mL)	431.8 (11.9)	423.4 (10.7)
	CL(mL/min)	126.6 (12.4)	128.7 (10.8)

Source: prepared by the reviewer based on information provided on page 58 of the final study report.

Table 4: BSA-Adjusted aGFR, eGFR, and mGFR and comparisons with baseline at various study days.

Treatment	Study Day			
	Day −1[a]	Day 7	Day 14	Day 21
GS-9883 75 mg (n = 20)				
Mean (95% CI) BSA-Adjusted aGFR (mL/min/1.73 m^2)	119.2 (111.1, 127.3)	119.1 (111.1, 127.0)	118.5 (111.5, 125.6)	117.3 (110.2, 124.4)
GLSM Ratio[b] (90% CI) (%)	—	99.96 (97.47, 102.52)	99.64 (97.15, 102.19)	98.57 (96.12, 101.10)
Placebo (n = 20)				
Mean (95% CI) BSA-Adjusted aGFR (mL/min/1.73 m^2)	114.5 (110.0, 119.1)	120.8 (115.5, 126.0)	118.5 (113.3, 123.6)	116.7 (111.6, 121.8)
GLSM Ratio[b] (90% CI) (%)	—	105.38 (103.06, 107.75)	103.40 (101.12, 105.72)	101.80 (99.56, 104.09)
GS-9883 75 mg (n = 20)				
Mean (95% CI) BSA-Adjusted $eGFR_{CG}$ (mL/min/1.73 m^2)	93.4 (83.6, 103.1)	81.8 (74.0, 89.6)	88.2 (80.0, 96.4)	91.3 (82.7, 99.8)
GLSM Ratio[b] (90% CI) (%)	—	87.97 (83.96, 92.17)	94.88 (90.56, 99.41)	98.20 (93.72, 102.89)
Placebo (n = 20)				
Mean (95% CI) BSA-Adjusted $eGFR_{CG}$ (mL/min/1.73 m^2)	86.4 (80.6, 92.2)	86.7 (80.9, 92.4)	91.6 (86.9, 96.3)	89.7 (84.3, 95.2)
GLSM Ratio[b] (90% CI) (%)	—	100.33 (95.82, 105.05)	106.45 (101.66, 111.46)	104.05 (99.37, 108.95)
GS-9883 75 mg (n = 20)				
Mean (95% CI) BSA-Adjusted mGFR (mL/min/1.73 m^2)	121.6 (113.5, 129.6)	119.7 (99.0, 140.4)	119.3 (111.0, 127.7)	125.8 (115.4, 136.2)
GLSM Ratio[b] (90% CI) (%)	—	93.99 (84.52, 104.53)	98.12 (88.23, 109.12)	103.07 (92.68, 114.62)
Placebo (n = 20)				
Mean (95% CI) BSA-Adjusted mGFR (mL/min/1.73 m^2)	129.4 (123.3, 135.5)	138.2 (126.6, 149.9)	138.9 (132.0, 145.8)	126.8 (118.4, 135.2)
GLSM Ratio[b] (90% CI) (%)	—	105.65 (98.54, 113.27)	107.38 (100.15, 115.13)	97.54 (90.97, 104.58)

a The Day −1 (baseline) value was the last available value prior to the start of GS-9883 or placebo dosing.
b Test / Reference. For between-visit comparisons, the Day 7, 14, or 21 value was Test and the Day −1 value was Reference.

Source: Synopsis of the final clinical study report, page 7

Table 5: Comparison of BSA-Adjusted aGFR, eGFR, and mGFR between treatment groups on days 7, 14 and 21.

Study Day	GLSM		GLSM Ratio (%) Test / Reference	90% CI (%)
	Test Treatment (GS-9883 75 mg)	Reference Treatment (Placebo)		
BSA-Adjusted aGFR Comparisons				
Day 7	116.45	121.88	95.54	91.86, 99.38
Day 14	116.08	119.58	97.07	93.82, 100.44
Day 21	114.91	117.67	97.66	93.84, 101.63
BSA-Adjusted $eGFR_{CG}$ Comparisons				
Day 7	78.99	87.34	90.44	83.85, 97.54
Day 14	85.27	92.59	92.10	86.07, 98.54
Day 21	87.74	91.04	96.38	91.20, 101.85
BSA-Adjusted mGFR Comparisons				
Day 7	112.80	136.19	82.83	70.77, 96.94
Day 14	118.97	137.01	86.83	80.61, 93.53
Day 21	124.49	124.93	99.65	90.93, 109.20

Source: Synopsis of the final clinical study report, page 8

Assessment of Serum Creatinine:

Serum creatinine was measured 12 hours after time zero at baseline (day -1) and on days 7, 14, and 21 for estimation of GFR.

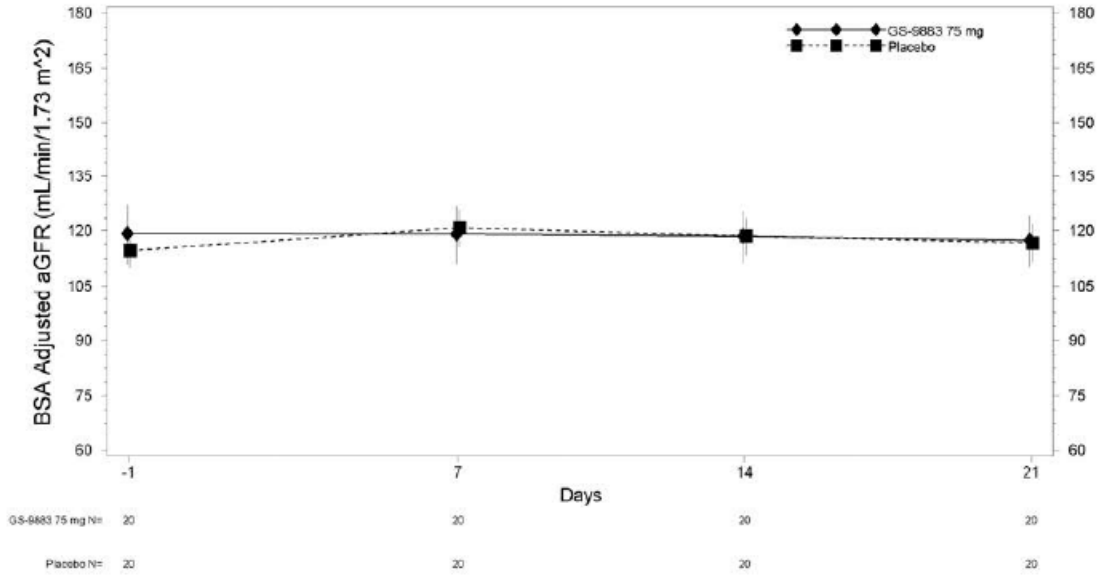
Table 6: Mean (95% CI) baseline serum creatinine and changes from baseline by study day for 14 days of once daily BIC 75 mg or placebo

Study Day	Serum Creatinine (mg/dL) Mean (95% CI)	
	GS-9883 75 mg (N = 20)	Placebo (N = 20)
Baseline (Day −1)[a]	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
Change at Day 7	0.1 (0.1, 0.2)	0.0 (−0.1, 0.1)
Change at Day 14	0.1 (0.0, 0.1)	−0.1 (−0.1, 0.0)
Change at Day 21	0.0 (0.0, 0.1)	0.0 (−0.1, 0.0)

a The Day −1 (baseline) value was the last available 12 hours after time zero value prior to the start of GS-9883 or placebo dosing.

Source: final clinical study report, page 63

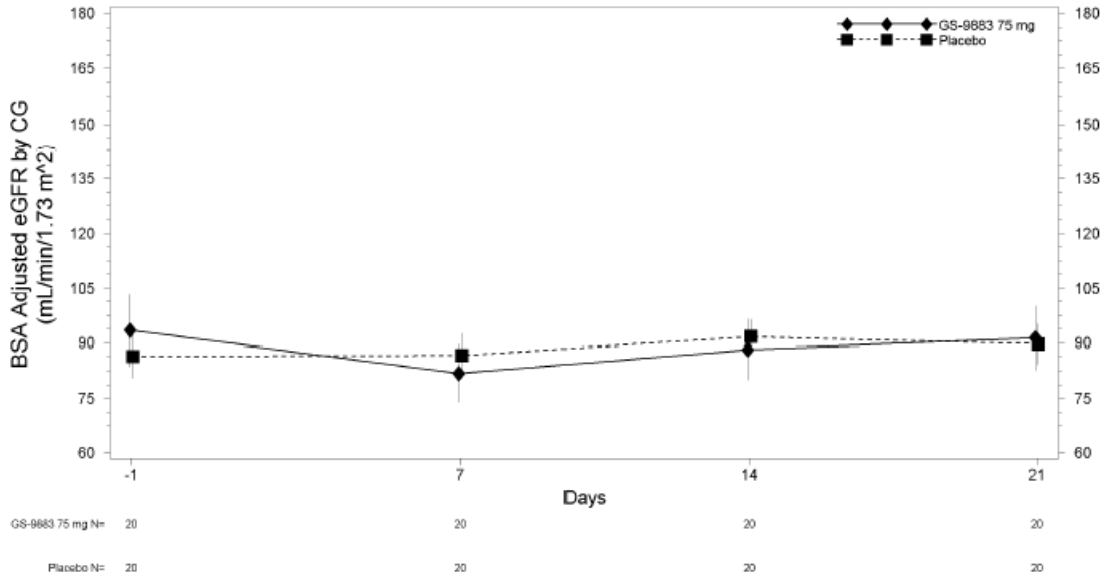
Fig 1: Mean (95% CI) BSA-Adjusted aGFR (C-G) by Study Day for 14 days of once daily BIC or placebo



The Day −1 (baseline) value was the last available value prior to the start of GS-9883 or placebo dosing.

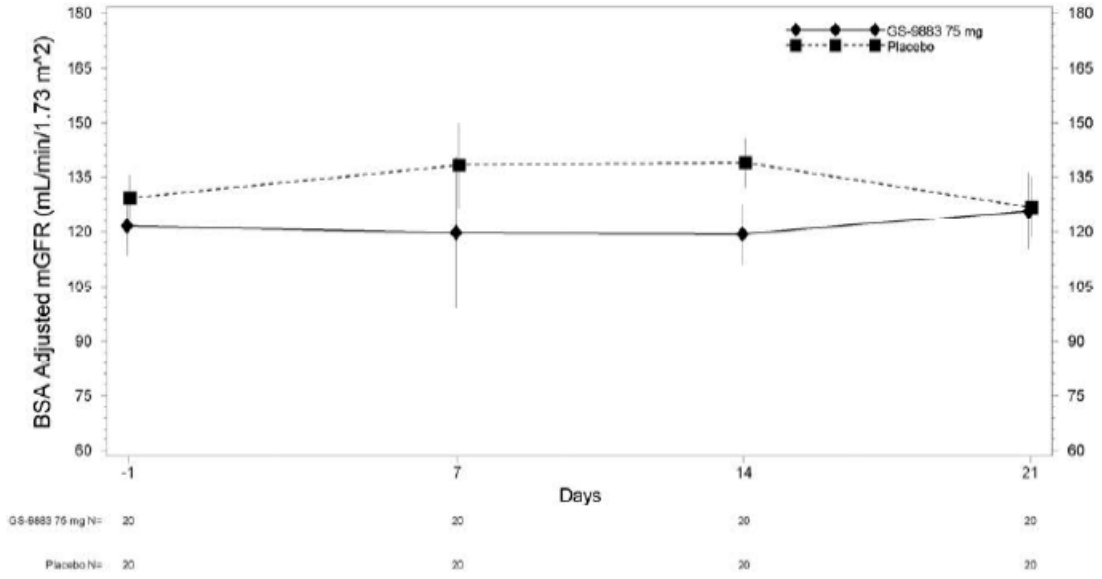
Source: Synopsis of the final clinical study report, page 59

Fig 2: Mean (95% CI) BSA-Adjusted eGFR (C-G) by Study Day for 14 days of once daily BIC or placebo



The Day −1 (baseline) value was the last available value prior to the start of GS-9883 or placebo dosing.
Source: Synopsis of the final clinical study report, page 64

Fig 3: Mean (95% CI) BSA-Adjusted mGFR by Study Day for 14 days of once daily BIC or placebo



The Day −1 (baseline) value was the last available value prior to the start of GS-9883 or placebo dosing.
Source: Synopsis of the final clinical study report, page 68

Safety:
No Grade 3 or 4 AEs, serious adverse events (SAEs), AEs leading to study discontinuation, or deaths were reported during the study.

REVIEWER ASSESSMENT	
The study design is acceptable ☑ Yes ☐ No	
Study Conduct	
▪ Bioanalytical method performance in acceptable	☑ Yes ☐ No
▪ Protocol deviations do not affect the integrity of the study	☐ Yes ☐ No ☑ N/A

Study Results

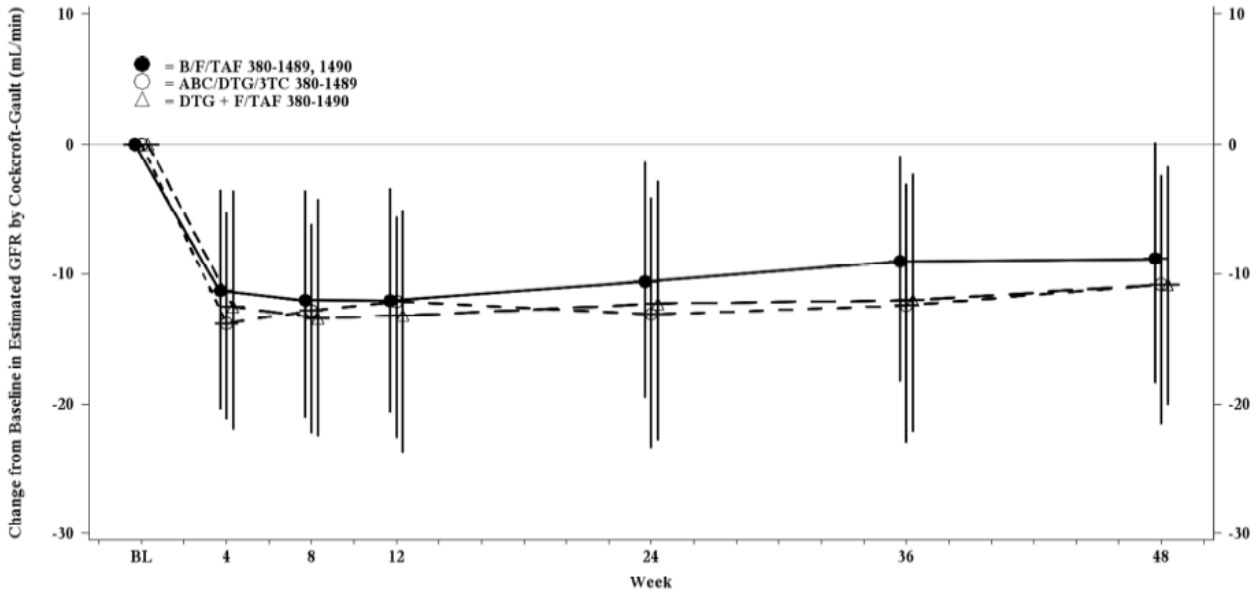
The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

The results of the trial showed that there was a decrease in the estimated creatinine clearance in the BIC group as compared with the placebo group. Considering there were no changes in the systemic clearance of iohexol (which is indicative of no changes in the actual GFR), the decrease in the estimated creatinine clearance is primarily driven by the increase in serum creatinine due to the inhibition of OCT2 and/or MATE1 by BIC. Of note, there are several articles in the literature that describe the same phenomena (no change in actual GFR but decrease in estimated CrCl due to inhibition of renal transporters) for several other drugs including another integrase inhibitor, dolutegravir (Arya V et al, *J Clin Pharmacol*, 2013, 54 (3), 279-281; Chu X et al, *Clin Pharmacol Ther*, 2016, 100 (5), 437-440; Mathialagan S et al, *J Pharm Sci*, 2017, 106 (9), 2535-2541).

Across the Phase 3 trials, changes from baseline in serum creatinine and estimated creatinine clearance were also observed which are consistent with the known inhibitory effect of BIC on OCT2 and/or MATE1.

Fig 4: Median (Q1, Q3) change from baseline in estimated creatinine clearance (ml/min) by visit in treatment naïve trials (GS-US-380-1489 and GS-US-380-1490)



BL = Baseline; Reference line represents no change from baseline (ie, y = 0).

Source: Summary of Clinical Safety, Page 62

In treatment naïve subjects, median (Q1, Q3) changes from baseline at week 48 were as follows:

- Serum creatinine: Pooled B/F/TAF 0.10 (0.03, 0.17) mg/dL; ABC/DTG/3TC 0.11 (0.03, 0.18) mg/dL; DTG+F/TAF 0.11 (0.04, 0.19) mg/dL
- eGFR$_{CG}$: Pooled B/F/TAF −8.8 (−18.4, 0.1) mL/min; ABC/DTG/3TC −10.8 (−21.6, −2.4) mL/min; DTG+F/TAF −10.8 (−20.0, −1.7) mL/min.

Of note, the magnitude of change in serum creatinine observed on day 14 (relative to baseline) in trial GS-US-141-1487 and the magnitude of change in serum creatinine observed in treatment naïve subjects at week 48 (relative to baseline) is similar (approximately 0.1 mg/dL).

Similar trends of increase in serum creatinine and decrease in estimated creatinine clearance were also observed in some other trials in the Phase 3 program.

Proposed Labeling Recommendation:
The applicant has described changes in serum creatinine in Section 6, potential for BIC to impact OCT2 and MATE 1 transporters in section 7, and the results from trial GS-US-141-1487 in section 12.2. In general, the applicant's proposal is acceptable; however, some changes to the applicant's proposed language may be made as part of labeling review.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\gs-us-141-1487\report-body.pdf

Clinical Site: SeaView Research, 3898 NW 7th Street, Miami, FL.

Bioanalytical Reports:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\gs-us-141-1487\basar (b) (4) 8328011.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\gs-us-141-1487\basar (b) (4) 60-1564.pdf

Bioanalytical Sites: (b) (4)

Study #	GS-US-380-3908	**Study Period:** May 31, 2016– July 8, 2016
Title	A Phase 1, Blinded, Placebo-Controlled, Two Period Crossover, Drug Interaction Study to Assess the Effect of Bictegravir/Emtricitabine/Tenofovir Alafenamide Fumarate (BIC/F/TAF) on Metformin Pharmacokinetics in Healthy Subjects	

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: Evaluate the effect of BIC on the PK of metformin following steady state co-administration of BIC/F/TAF FDC with metformin.

Secondary: Examine the safety and tolerability of metformin when co-administered with BIC/F/TAF FDC at steady state.

Exploratory: Evaluate the effect of BIC on the pharmacodynamics (PD) of metformin following steady state co-administration of BIC/F/TAF.

Rationale:

The results of an *in vitro* study (AD-141-2285) showed that BIC is an inhibitor of OCT2 (uptake transporter) and MATE1 (efflux transporter) in the kidney. OCT2 and MATE1 are involved in the uptake and efflux of metformin from the kidney (Liang X and Giacomini KM, *J Pharm Sci*, 2017, 106 (9), 2245-1150). The applicant conducted the trial to assess the effect of BIC/F/TAF on metformin to determine dosing recommendations upon potential co-administration of BIC/F/TAF and metformin.

Dose Selection:

BIC/F/TAF (50/200/25 mg) FDC was selected for use in the current study because it is the FDC formulation evaluated in Phase 3 trials and proposed for marketing.

Metformin: Immediate-release tablets of metformin (GLUCOPHAGE®) are available in dosage strengths of 500 mg, 850 mg, and 1000 mg. Per the prescribing information, the maximum recommended daily dose of metformin in adults is 2550 mg. Considering that BIC/F/TAF has the potential to increase metformin exposures due to inhibition of OCT2 and MATE1, the applicant used a lower dose of metformin in the trial.

Design and PK Assessments:

Blinded, multiple-dose, single center, two period, crossover study in 32 subjects randomized in a 1:1 ratio.

Treatment Sequence	Period 1 Day 1-9	Washout Day 10-12	Period 2 Day 13-21
1	Treatment A		Treatment B
2	Treatment B		Treatment A

Source: Prepared by the reviewer based on information provided in the final study report

Treatment A, Period 1:

- Placebo-to-Match (PTM) BIC/F/TAF FDC (1 tablet), administered once daily on days 1 through 9 under fasting conditions.
- Metformin 850 mg administered once daily on day 5 at 12 hours post dose of PTM.
- Metformin 500 mg administered twice daily on days 6 through 8. Morning dose of metformin was co-administered with PTM and evening dose of metformin was administered 12 hours later.
- Metformin 500 mg co-administered with PTM in the morning of day 9.

Treatment B, Period 1:

- BIC/F/TAF FDC (1 tablet), administered once daily on days 1 through 9 under fasting conditions.
- Metformin 850 mg administered once daily on day 5 at 12 hours post dose of BIC/F/TAF.
- Metformin 500 mg administered twice daily on days 6 through 8. Morning dose of metformin was co-administered with BIC/F/TAF and evening dose of metformin was administered 12 hours later.
- Metformin 500 mg co-administered with BIC/F/TAF in the morning of day 9.

Treatment A, Period 2:

- Placebo-to-Match (PTM) BIC/F/TAF FDC (1 tablet), administered once daily on days 13 through 21 under fasting conditions.
- Metformin 850 mg administered once daily on day 17 at 12 hours post dose of PTM.
- Metformin 500 mg administered twice daily on days 18 through 20. Morning dose of metformin was co-administered with PTM and evening dose of metformin was administered 12 hours later.
- Metformin 500 mg co-administered with PTM in the morning of day 21.

Treatment B, Period 2:

- BIC/F/TAF FDC (1 tablet), administered once daily on days 13 through 21.
- Metformin 850 mg administered once daily on day 17 at 12 hours post dose of BIC/F/TAF.
- Metformin 500 mg administered twice daily on days 18 through 20. Morning dose of metformin was co-administered with BIC/F/TAF and evening dose of metformin was administered 12 hours later.
- Metformin 500 mg co-administered with BIC/F/TAF in the morning of day 21.

A 3-hour oral glucose tolerance test [OGTT] (75 g glucose) was performed (on days 5 and 17 for baseline assessments and Days 9 and 21 after the last dose of metformin) at approximately 2 hours post-dose of metformin and lunch was served after completion of the OGTT. On days 1–4, 6–8, 13–16, and 18–20 (dosing days without an OGTT), a low-carbohydrate breakfast was served 30 minutes after the morning dose. On days 5, 9, 17, and 21 (dosing days with an OGTT), study treatment was administered after an overnight fast.

PK Assessments:

Plasma and Blood Sample Collection: To determine metformin concentrations in plasma and blood, blood samples were collected at pre-dose and at 0.5, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours relative to the last dose of metformin on days 9 and 21. A single blood sample for determining the trough concentration of BIC was also collected pre-dose on days 5, 9, 17, and 21. To assess serum creatinine, blood samples were collected 12 hours after the last dose of metformin of each period on days 9 and 21.

Urine Sample Collection: Urine was collected during the following intervals for urine metformin determination: 0-4, 4-8, 8-12, and 12-24 hours after the last dose of metformin in each period (on Days 9 and 21). Aliquots from the pooled 24-hour urine collections were used for 24-hour urine creatinine determination.

PD Assessments:

For OGTT analysis, blood samples were collected before ingestion of glucose and at 15, 30, 45, 60, 90, 120, 150 and 180 minutes after completion of glucose ingestion on days 5, 9, 17, and 21. Additional blood samples were collected before ingestion of glucose and at 60 minutes and 120 minutes after completion of ingestion of the glucose for lactate and active Glucagon-Like Peptide 1 (GLP-1) concentrations.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☑ Fasted ☑ Fed (depending on the

	treatment day)

Formulations
BIC/F/TAF (50/200/25 mg tablets): Batch # EN1503B2, expiration date August 2017. Placebo-to-match B/F/TAF (batch # EN1502B1; expiration date July 2020).
Metformin (Glucophage®) 850 mg (lot # 4F82276A) and 500 mg (lot # AAE8287A).

RESULTS

Enrolled	32	Completed	30*	Discontinued Due to AE	1	PK Population	30	Safety Population	30

*One subject discontinued due to AE and the second subject discontinued due to protocol violation (subject used prohibited medication resulting in a positive amphetamine urine drug screen due to unapproved use of over-the-counter nasal decongestant).

Protocol Deviations
Except the protocol deviation that led to discontinuation (described above), there were no other protocol deviations reported in the trial.

Demographics
Out of the 32 subjects enrolled in the trial, 16 subjects were male and 16 subjects were female. Median age was 33 years (range: 19 to 45), median (range) BMI was 26.2 (20.4, 29.6) kg/m^2, and $CrCL_{CG}$ (creatinine clearance estimated using Cockcroft-Gault equation) at baseline was 124.5 mL/min (range: 93.6 to 178.9).

Results:

Pharmacokinetic Evaluation:

Plasma:

Table 1: Steady State metformin plasma PK parameters following co-administration of metformin with BIC/F/TAF or placebo

	B/F/TAF with Metformin (N = 32)	Placebo with Metformin (N = 30)
AUC_{tau} (ng•h/mL)[a]	7180.3 (27.3)	5180.0 (24.8)
C_{max} (ng/mL)[a]	1353.4 (27.1)	1059.4 (25.4)
C_{tau} (ng/mL)[a]	157.9 (30.1)	122.5 (44.5)
$t_{1/2}$ (h)[b]	6.36 (5.11,7.28)	7.06 (4.73,10.02)
T_{max} (h)[b]	1.92 (1.50,2.21)	1.92 (1.50,2.50)
CL_{ss}/F (mL/h)[a]	1233.3 (25.3)	1734.9 (34.7)
V_z/F (mL)[a]	674.0 (35.9)	1056.5 (45.6)

a Mean (%CV)
b Median (Q1, Q3)
Source: Clinical Study Report, Page 54

Table 2: Steady State metformin whole blood PK parameters following co-administration of metformin with BIC/F/TAF or placebo

	B/F/TAF with Metformin (N = 32)	Placebo with Metformin (N = 30)
AUC_{tau} (ng•h/mL)[a]	7159.3 (22.5)	5289.3 (19.3)
C_{max} (ng/mL)[a]	1040.2 (22.1)	813.5 (20.7)
C_{tau} (ng/mL)[a]	326.1 (19.6)	247.9 (24.0)
$t_{1/2}$ (h)[b]	15.82 (14.64,17.68)	18.61 (16.64,20.54)
T_{max} (h)[b]	1.92 (1.92,2.50)	1.92 (1.50,1.92)
CL_{ss}/F (mL/h)[a]	1217.6 (23.1)	1644.1 (24.1)
V_z/F (mL)[a]	1711.8 (28.9)	2644.8 (26.2)

a Mean (%CV)
b Median (Q1, Q3)

Source: Clinical Study Report, Page 57

Urine:

Table 3: Steady State metformin urine PK parameters and creatinine clearance following co-administration of metformin with BIC/F/TAF or placebo

	B/F/TAF with Metformin (N = 32)	Placebo with Metformin (N = 30)
Metformin PK Parameter		
f_{e12} (%)[a]	29.7 (20.9)	32.1 (26.1)
f_{e24} (%)[a]	33.9 (19.6)	36.1 (24.6)
CL_R (mL/min)[a]	357.2 (21.5)	520.9 (20.0)
A_{e12} (mg)[a]	148.7 (20.9)	160.6 (26.1)
A_{e24} (mg)[a]	169.7 (19.6)	180.4 (24.6)
$SrCL_R$ (mL/min)[a]	232.4 (25.8)	382.4 (24.3)
Creatinine Clearance		
mGFR (mL/min)[b]	124.8 (26.60)	138.6 (23.98)

a Mean (%CV)
b Mean (SD)
$SrCL_R$, metformin clearance by tubular secretion, calculated as mGFR − CL_R. Creatinine clearance (mGFR) as measured by serum creatinine level and 24-hour urine collection of creatinine

Source: Clinical Study Report, Page 58

*Note: The equation in the footnote should be SrCLr=CLr-fu*mGFR. Where fu is the fraction of metformin not bound to plasma proteins. Per the prescribing information of metformin, there is negligible binding of metformin to plasma proteins (fu approximately 1), hence the estimate of tubular secretion computed by the applicant (without including fu) will not significantly change after including fu in the equation.*

Table 4: Statistical comparison of plasma, whole blood, and urine pharmacokinetic parameters following co-administration of metformin with BIC/F/TAF or placebo

PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	B/F/TAF with Metformin (Test) (N = 32)	Placebo with Metformin (Reference) (N = 30)	
Plasma Metformin			
AUC_{tau} (ng•h/mL)	7180.3 (27.3)	5180.0 (24.8)	139.48 (131.37, 148.09)
C_{max} (ng/mL)	1353.4 (27.1)	1059.4 (25.4)	128.10 (120.78, 135.85)
C_{tau} (ng/mL)	157.9 (30.1)	122.5 (44.5)	135.78 (120.62, 152.85)
$t_{1/2}$ (h)[a]	6.36 (5.11, 7.28)	7.06 (4.73, 10.02)	—
CL_{ss}/F (mL/min)	1233.3 (25.3)	1734.9 (34.7)	71.70 (67.53, 76.12)
V_z/F (L)	674.0 (35.9)	1056.5 (45.6)	64.92 (56.66, 74.39)
Whole Blood Metformin			
AUC_{tau} (ng•h/mL)	7159.3 (22.5)	5289.3 (19.3)	134.71 (129.54, 140.09)
C_{max} (ng/mL)	1040.2 (22.1)	813.5 (20.7)	128.18 (122.48, 134.14)
C_{tau} (ng/mL)	326.1 (19.6)	247.9 (24.0)	132.01 (125.49, 138.88)
$t_{1/2}$ (h)[a]	15.82 (14.64, 17.68)	18.61 (16.64, 20.54)	—
Urine Metformin			
f_{e12} (%)	29.7 (20.9)	32.1 (26.1)	95.47 (86.49, 105.38)
CL_R (mL/min)	357.2 (21.5)	520.9 (20.0)	68.53 (63.37, 74.11)
$SrCL_R$ (mL/min)	232.4 (25.8)	382.4 (24.3)	—

a Data are presented as median (Q1, Q3).

Source: Synopsis of Clinical Study Report, Page 7

BIC:

The applicant collected PK samples to only determine the trough concentration of BIC because the primary objective of the trial was to assess the effect of BIC/F/TAF on metformin. Mean BIC concentrations were comparable between the two treatment sequences, however the limited data did not allow for any statistical analysis.

PD Evaluation:

Table 5: Glucose PD parameters before and after metformin administration with BIC/F/TAF or placebo

	AUC_{gluc60} (min•mg/dL)	$AUC_{gluc180}$ (min•mg/dL)	G_{max} (mg/dL)	$Glucose_{60}$ (mg/dL)	G_{mean60} (mg/dL)
B/F/TAF (N = 32)					
Before Metformin Mean (SD)	8429.8 (1086.54)	21,217.8 (3868.70)	166.8 (28.91)	147.9 (40.00)	140.5 (18.11)
After Metformin Mean (SD)	7432.6 (982.37)	19,929.5 (4007.42)	143.9 (26.43)	128.2 (34.13)	123.9 (16.37)
Mean (90% CI) Difference Between Before and After Metformin	−997.2 (−1197.2, −797.2)	−1288.3 (−1967.8, −608.8)	−22.9 (−28.0, −17.8)	−19.7 (−26.5, −12.9)	−16.6 (−20.0, −13.3)
p-value[a]	< 0.001	0.003	< 0.001	< 0.001	< 0.001
Placebo (N = 31)					
Before Metformin Mean (SD)	8006.4 (1217.97)	20,766.6 (4244.17)	158.2 (30.16)	141.7 (38.95)	133.4 (20.30)
After Metformin Mean (SD)[b]	7258.1 (954.10)	19,525.7 (3352.78)	142.2 (24.65)	125.1 (33.24)	121.0 (15.90)
Mean (90% CI) Difference Between Before and After Metformin	−764.6 (−995.5, −533.8)	−1333.8 (−2014.5, −653.1)	−16.1 (−21.5, −10.8)	−17.8 (−25.6, −10.0)	−12.7 (−16.6, −8.9)
p-value[a]	< 0.001	0.004	< 0.001	< 0.001	< 0.001

a P-values were based on 2-sided Wilcoxon signed-rank test comparing parameter before and after metformin within a treatment.
b N = 30

Source: Clinical Study Report, Page 63

Table 6: Active GLP-1 levels (pmol/L) before and after metformin administration with BIC/F/TAF or placebo

	B/F/TAF (N = 32)			Placebo (N = 31)		
	Pre-Glucose	60 Minutes Post-Glucose	120 Minutes Post-Glucose	Pre-Glucose	60 Minutes Post-Glucose	120 Minutes Post-Glucose
Before Metformin Mean (SD)	0.4 (0.26)	1.8 (1.11)	1.5 (0.91)	0.4 (0.33)	2.3 (1.66)	1.3 (0.76)
After Metformin Mean (SD)	1.0 (0.64)	3.4 (1.64)	3.3 (2.10)	1.2 (0.69)[a]	4.1 (2.30)[a]	3.5 (1.89)[a]
Mean (90% CI) Difference Between Before and After Metformin	0.6 (0.4, 0.7)	1.6 (1.2, 2.0)	1.9 (1.3, 2.5)	0.8 (0.5, 1.0)	1.8 (1.1, 2.6)	2.2 (1.7, 2.6)
p-value[b]	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

a N = 30
b p-values were based on 2-sided Wilcoxon signed-rank test comparing matched timepoints before and after metformin within a treatment.

Source: Clinical Study Report, Page 69

Table 7: Lactate levels (mg/dL) before and after metformin administration with BIC/F/TAF or placebo

	B/F/TAF (N = 32)			Placebo (N = 31)		
	Pre-Glucose	60 Minutes Post-Glucose	120 Minutes Post-Glucose	Pre-Glucose	60 Minutes Post-Glucose	120 Minutes Post-Glucose
Before Metformin Mean (SD)	9.2 (4.67)	13.1 (3.14)	11.2 (2.22)	9.8 (5.82)	14.0 (3.23)	11.5 (2.90)
After Metformin Mean (SD)	9.8 (4.11)	14.7 (4.03)	13.3 (3.34)	8.9 (3.33)[a]	14.9 (3.44)[a]	13.9 (3.30)[a]
Mean (90% CI) Difference Between Before and After Metformin	0.6 (−0.6, 1.8)	1.6 (0.5, 2.6)	2.1 (1.1, 3.0)	−1.0 (−2.4, 0.4)	0.8 (−0.3, 1.9)	2.2 (1.2, 3.2)
p-value[b]	0.12	0.007	< 0.001	0.50	0.18	< 0.001

a N = 30
b p-values were based on 2-sided Wilcoxon signed-rank test comparing matched timepoints before and after metformin within a treatment.

Source: Clinical Study Report, Page 73

Table 8: Statistical analysis of glucose, active GLP-1 and lactate before and after metformin administration with BIC/F/TAF or placebo

PD Parameter	Mean (90% CI) Difference Between Before and After Metformin		Statistical Comparison of B/F/TAF vs Placebo p-value[a]
	B/F/TAF (N = 32)	Placebo (N = 30)	
Glucose			
ΔAUC_{gluc60} (mg•min/dL)	−997.2 (−1197.2, −797.2)[b]	−764.6 (−995.5, −533.8)[b]	0.261
$\Delta Glucose_{60}$ (mg/dL)	−19.7 (−26.5, −12.9)[b]	−17.8 (−25.6, −10.0)[b]	0.756
ΔG_{max} (mg/dL)	−22.9 (−28.0, −17.8)[b]	−16.1 (−21.5, −10.8)[b]	0.082
ΔG_{mean60} (mg/dL)	−16.6 (−20.0, −13.3)[b]	−12.7 (−16.6, −8.9)[b]	0.261
Active GLP-1			
Pre-Glucose (pmol/L)	0.6 (0.4, 0.7)[b]	0.8 (0.5, 1.0)[b]	0.342
60 Minutes Post-Glucose (pmol/L)	1.6 (1.2, 2.0)[b]	1.8 (1.1, 2.6)[b]	0.507
120 Minutes Post-Glucose (pmol/L)	1.9 (1.3, 2.5)[b]	2.2 (1.7, 2.6)[b]	0.546
Lactate			
60 Minutes Post-Glucose	1.6 (0.5, 2.6)	0.8 (−0.3, 1.9)	0.369
120 Minutes Post-Glucose (mg/dL)	2.1 (1.1, 3.0)[b]	2.2 (1.2, 3.2)[b]	0.729

a Statistical comparison of B/F/TAF vs placebo p-values were based on 2-sided Wilcoxon signed-rank test comparing difference before and after metformin between treatment groups.
b $p < 0.001$ for the difference between before and after metformin.

Source: Synopsis of Clinical Study Report, Page 8

Safety

No SAEs, or death were reported in the study. One subject discontinued the study due to due to an AE of grade 3 nephrolithiasis while receiving metformin with placebo.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

BIC/F/TAF increased the mean C_{max} and AUC of metformin by 28% and 40%, respectively. The fraction of metformin recovered unchanged in the urine is similar when metformin is given alone and when metformin is co-administered with BIC/F/TAF, suggesting that BIC/F/TAF did not alter the extent of absorption of metformin and the increase in the mean systemic exposure of metformin is driven primarily by reduction in renal clearance of metformin. In fact, a recent publication has shown that the increase in metformin exposures upon co-administration with other OCT2/MATE1 inhibitors such as cimetidine is due to inhibition of renal transporters and not altered absorption (Elsby et al, *Pharm Res Per*, 2017, 5(5), e00357). The renal clearance of metformin was approximately 3.75-fold higher than mGFR, thereby underscoring the importance of tubular secretion in the renal elimination of metformin. While the measured GFR (determined using 24-hour urinary output and serum creatinine concentration) was similar between the two groups, the metformin clearance by tubular secretion (SrCLr; calculated as CL_r-mGFR) was decreased by approximately 39 % when metformin was co-administered with BIC/F/TAF suggesting decrease in tubular secretion due to inhibition of renal transporters by BIC.

The approved prescribing information for metformin suggests that for drugs that reduce the clearance of metformin, consideration should be given to the benefits and risks of using metformin. One of the drugs specifically mentioned is cimetidine which increases the mean systemic exposure of metformin by 40 % (similar to the increase in metformin exposure observed with BIC/F/TAF). The results of the BIC/F/TAF-metformin trial were discussed with the clinical pharmacology review team leaders for metabolic and endocrine products. Of note, exposure-response relationship between metformin concentration and metformin-associated lactic acidosis (MALA) has not been elucidated and cases of MALA have occurred across a wide range of metformin concentrations, suggesting the need for a conservative clinical recommendation regarding concomitant use of BIC/F/TAF and metformin.

Proposed Labeling Recommendation:

Applicant's proposal (b) (4) (b) (4) **is NOT acceptable. Instead, the review team recommends the following (in consultation with clinical pharmacology team leaders of metabolic and endocrine products):**

If BIKTARVY™ is co-administered with metformin, refer to the prescribing information of metformin for assessment of the benefit and risk of concomitant use.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

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Clinical Site: SeaView Research, 3898 NW 7th Street, Miami, FL.

Bioanalytical Reports:

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Bioanalytical Sites: (b) (4)

(b) (4)

Study #	GS-US-141-1485	**Study Period**	March 3, 2015 through August 27, 2015
Title	A Phase 1 Adaptive Study to Evaluate Transporter, Cytochrome (CYP) 450-Mediated and UGT1A1 Drug-Drug Interactions between Bictegravir (BIC) and Probe Drugs		

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

The primary objectives of this study were as follows:

- To evaluate the effect of mixed UGT1A1/CYP3A4/P-gp inhibition on the PK of BIC
- To evaluate the effect of CYP3A4/P-gp/UGT1A1 induction on the PK of BIC

The secondary objectives of this study were as follows:

- To evaluate the effect of mixed UGT1A1/CYP3A4 inhibition on the PK of BIC
- To evaluate the effect of selective inhibition of CYP3A4 on the PK of BIC
- To evaluate the safety and tolerability of single BIC dose administered alone or in combination with other drugs

Rationale:

The results of *in vitro* studies show that BIC is primarily metabolized by CYP3A4 and UGT enzymes and is a substrate of P-gp transporters. Therefore, drugs that inhibit or induce UGT1A1 and CYP3A4 can affect the pharmacokinetics of BIC in humans. Similarly, drugs that affect P-gp can affect the transport of BIC. The applicant conducted this study to gain further insight into the pharmacokinetics (PK) and safety of BIC, specifically, the effects of drugs that strongly inhibit or induce the CYP3A4, UGT1A1, and P-gp, the major enzymes and transporter involved in the metabolism and transport of BIC.

Dose Selection:

BIC (75 mg): The 75mg dose was selected because this was the dose of BIC used in the Phase 2 efficacy and safety study of BIC co-administered with F/TAF (200/25 mg) in study GS-US-141-1475).

Table 1: Probe Drugs Evaluated in the Trial

Drug or Drug Combination	Enzymes and/or transporters affected	Dose(s)	Rationale for Dose Selection
Atazanavir/cobicistat (ATV/Cobi) [Cohort 1]	UGT1A1/CYP3A4/P-gp inhibitor	300 mg ATV, 150 mg Cobi	Approved once daily dose of ATV with once daily dose of COBI for treatment-naive and treatment-experienced HIV-infected adults.
Rifampin (RIF) [Cohort 2]	CYP3A4/UGT1A1/P-gp inducer	600 mg once daily	Maximum dose of RIF used for the treatment of tuberculosis and a dose commonly used for assessment of CYP/P-gp/UGT induction
Atazanavir (ATV) [Cohort 3]	UGT1A1 and CYP3A inhibitor	400 mg	Recommended dose in treatment-naive HIV-infected adults without the use of CYP3A inhibitors such as ritonavir or cobicistat

Voriconazole [Cohort 4]	CYP3A4 inhibitor	300 mg twice daily	Approved therapeutic oral dose for fungal infection and commonly used for assessment of CYP3A4 inhibition
Rifabutin [Cohort 5; adaptive cohort]	CYP3A4 and P-gp inducer	300 mg once daily	Recommended dose for treating mycobacterial infection
Darunavir/cobicistat (DRV/Cobi) [Cohort 6; adaptive cohort]	CYP3A4 inhibitor	800 mg DRV, 150 mg Cobi	Recommended doses for the treatment of HIV-1 infection in adults

Source: Summarized by the reviewer based on information provided in the study report.

Design and PK Assessments:

Phase 1, open-label, multiple-dose, multiple-cohort, adaptive design study.

Table 2: Trial Design for Cohorts 1, 3, and 4

Cohort	Day 1	Days 2-4	Days 5- 8	Day 9	Days 10-12
1	A	Washout	B	A + B	B
3	A	Washout	D	A + D	D
4	A	Washout	E	A + E	E

Treatment A = Single dose of GS-9883 75 mg administered orally in the morning under fed (Cohorts 1 and 3) or fasted (Cohort 4) conditions
Treatment B = Once daily doses of ATV 300 mg + COBI 150 mg coadministered orally in the morning under fed conditions
Treatment D = Once daily doses of ATV 400 mg administered orally in the morning under fed conditions
Treatment E = Twice daily doses of VORI 300 mg administered orally in the morning and afternoon under fasted conditions. The last dose of VORI was administered in the afternoon on Day 12.

Source: Clinical Trial Report, Page 3

Table 3: Trial Design for Cohort 2

Cohort	Day 1	Days 2-4	Days 5- 14	Day 15	Days 16-18
2	A	Washout	C	A + C	C

Treatment A = Single dose of GS-9883 75 mg administered orally in the morning under fed conditions
Treatment C = Once daily doses of RIF 600 mg administered orally in the morning under fed conditions

Source: Clinical Trial Report, Page 3

Table 4: Trial Design for Cohorts 5 and 6

Cohort	Days 1-6	Days 7-20
5	F	F + G
6	F	F + H

Treatment F = Once daily doses of GS-9883 75 mg administered orally in the morning under fasted (Cohort 5) or fed (Cohort 6) conditions
Treatment G = Once daily doses of RBT 300 mg administered orally in the morning under fasted conditions
Treatment H = Once daily doses of DRV/COBI 800/150 mg administered orally in the morning under fed conditions

Source: Clinical Trial Report, Page 3

PK Sampling:

- Cohorts 1, 3, and 4: Pre-dose and up to 96 hours post-dose on days 1 and 9. Additional pre-dose samples were collected from days 6 through 8
- Cohort 2: Pre-dose and up to 96 hours post-dose on days 1 and 15. Additional pre-dose samples were collected from days 10 through 14.
- Cohort 5 and 6: Pre-dose and up to 24 hours post-dose on days 6 and 20. Additional pre-dose samples were collected from days 3 through 5 and days 17 through 19.

The PK parameters were estimated using non-compartmental methods.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☑ Fasted ☑ Fed (depending on the cohort)

Formulations
BIC 25 mg: Lot # EC1402C1, expiration date November 2015
BIC 75 mg: Lot # EC1504B1, expiration date August 2016
Cobi: 150 mg, Lot # BB1205B1, expiration date November 2015
ATV: 200 mg, lot # 4H69459D (expiration date July 2016) and 300 mg, lot # 4J78804A (expiration date August 2016)
RIF: 300 mg, lot # ME130087, expiration date April 2016
VORI: 50 mg, lot # EX5998, expiration date August 2016 and 200 mg, lot # ET2591, expiration date June 2016
RBT: 150 mg, lot # Z657H, expiration date September 2017
DRV/COBI: 800/150 mg, lot # 15AG9145X, expiration date September 2016

RESULTS

Enrolled	90	Completed	86	Discontinued	4[1]	PK Population	55	Safety Population	56

1: Four subjects (two subjects in cohort 5 and two subjects in cohort 6) prematurely discontinued the study. One subject each in Cohort 5 and Cohort 6 discontinued due to AE, one subject in Cohort 5 withdrew consent and one subject in Cohort 6 was non-compliant with the study protocol due to positive urine drug screen.

Protocol Deviations
No protocol deviations were reported in the trial.

Demographics

Table 5: Demographic characteristics of subjects enrolled in various parts

Cohort	Median Age (in years) (min, max)	Gender (M/F)	Median BMI (in kg/m^2) (min, max)
1 (N =15)	33 (24 to 45)	9/6	25 (21.8 to 28.2)

2(N =15)	38 (24 to 45)	8/7	25.6 (21.3 to 29.6)
3(N =15)	33 (19 to 44)	11/4	26.9 (20.6 to 29.8)
4 (N =15)	33 (25 to 44)	11/4	27.4 (22.6-29.7)
5 (N =15)	37 (23 to 44)	11/4	26.6 (21.3 to 29.9)
6 (N =15)	28 (23 to 44)	11/4	26.3 (20.1 to 30)

Source: Prepared by the reviewer based on information provided in the final clinical study report.

Pharmacokinetics:

COHORT 1: Effect of UGT1A1, CYP3A4/P-gp Inhibition by ATV/Cobi on BIC

Table 6: Mean (%CV) Pharmacokinetic Parameters of BIC in the reference arm and test arm in Cohort 1

GS-9883 PK Parameter	Mean (%CV)	
	GS-9883+COBI+ATV (Test, N = 15)	GS-9883 Alone (Reference, N = 15)
AUC_{inf} (h*ng/mL)	628,290.3 (17.4)	154,433.7 (16.0)
$\%AUC_{exp}$ (%)	32.3 (12.7)	2.9 (57.3)
AUC_{last} (h*ng/mL)	422,265.1 (14.2)	149,676.5 (14.8)
C_{max} (ng/mL)	9033.3 (12.2)	6890.0 (12.3)
C_{last} (ng/mL)	2371.3 (18.5)	164.4 (53.5)
T_{max} (h)[a]	3.00 (3.00, 4.00)	3.00 (2.00, 4.00)
T_{last} (h)[a]	95.93 (95.93, 95.93)	95.93 (95.93, 95.93)
$t_{1/2}$ (h)[a]	59.99 (52.94, 63.10)	18.62 (15.87, 20.96)
V_z/F (mL)	10,395.9 (12.8)	13,141.8 (13.2)
CL/F (mL/h)	123.1 (18.9)	497.2 (15.6)

CV = coefficient of variation
a Median (Q1, Q3)

Source: final clinical study report, page 72

COHORT 2: Effect of UGT1A1, CYP3A4/P-gp Induction by RIF

Table 7: Mean (% CV) Pharmacokinetic Parameters of BIC in the reference arm and test arm in Cohort 2

GS-9883 PK Parameter	Mean (%CV)	
	GS-9883+RIF (Test, N = 15)	GS-9883 Alone (Reference, N = 15)
AUC_{inf} (h*ng/mL)	36,398.0 (21.5)	155,986.3 (41.8)
$\%AUC_{exp}$ (%)	1.1 (51.4)	3.1 (83.8)
AUC_{last} (h*ng/mL)	36,014.8 (21.8)	149,814.3 (38.5)
C_{max} (ng/mL)	5131.3 (15.7)	7118.7 (17.0)
C_{last} (ng/mL)	45.7 (41.3)	192.7 (103.2)
T_{max} (h)[a]	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)
T_{last} (h)[a]	36.00 (36.00, 36.00)	95.93 (95.93, 95.93)
$t_{1/2}$ (h)[a]	5.65 (5.30, 6.18)	18.09 (14.47, 20.75)
V_z/F (mL)	17,493.6 (18.4)	13,351.9 (18.3)
CL/F (mL/h)	2131.1 (17.0)	545.1 (32.9)

CV = coefficient of variation
a Median (Q1, Q3)

Source: final clinical study report, page 74

COHORT 3: Effect of UGT1A1 and CYP3A4 Inhibition by ATV on BIC

Table 8: Mean (%CV) Pharmacokinetic Parameters of BIC in the reference arm and test arm in Cohort 3

GS-9883 PK Parameter	Mean (%CV)	
	GS-9883+ATV (Test, N = 15)	GS-9883 Alone (Reference, N = 15)
AUC_{inf} (h*ng/mL)	638,857.0 (20.5)	154,253.8 (21.8)
$\%AUC_{exp}$ (%)	33.2 (22.3)	2.8 (70.5)
AUC_{last} (h*ng/mL)	419,141.5 (13.3)	149,558.8 (20.4)
C_{max} (ng/mL)	9110.7 (16.6)	7078.7 (13.3)
C_{last} (ng/mL)	2474.7 (26.1)	161.3 (64.7)
T_{max} (h)[a]	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)
T_{last} (h)[a]	95.93 (95.93, 95.93)	95.93 (95.93, 95.93)
$t_{1/2}$ (h)[a]	56.86 (50.70, 66.90)	17.47 (15.26, 19.81)
V_z/F (mL)	10,221.8 (12.0)	12,928.1 (13.5)
CL/F (mL/h)	122.3 (21.1)	506.6 (20.3)

CV = coefficient of variation
a Median (Q1, Q3)

Source: final clinical study report, page 76

COHORT 4: Effect of CYP3A4 Inhibition by VORI on BIC

Table 9: Mean (%CV) Pharmacokinetic Parameters of BIC in the reference arm and test arm in Cohort 4

GS-9883 PK Parameter	Mean (%CV)	
	GS-9883+VORI (Test, N = 15)	GS-9883 Alone (Reference, N = 15)
AUC_{inf} (h*ng/mL)	160,519.3 (26.9)	101,659.4 (37.2)
$\%AUC_{exp}$ (%)	7.2 (62.6)	2.2 (79.4)
AUC_{last} (h*ng/mL)	148,762.2 (27.1)	99,185.1 (36.5)
C_{max} (ng/mL)	5442.7 (33.6)	4844.0 (21.5)
C_{last} (ng/mL)	294.5 (51.1)	90.0 (75.5)
T_{max} (h)[a]	3.00 (1.50, 3.00)	2.00 (1.50, 4.00)
T_{last} (h)[a]	95.93 (95.93, 95.93)	95.93 (95.93, 95.93)
$t_{1/2}$ (h)[a]	25.45 (18.65, 28.08)	15.92 (15.12, 19.76)
V_z/F (mL)	18,212.6 (35.9)	19,684.0 (30.1)
CL/F (mL/h)	507.7 (33.4)	827.7 (34.6)

CV = coefficient of variation
a Median (Q1, Q3)

Source: final clinical study report, page 78

COHORT 5: Effect of CYP3A4/P-gp Induction by RBT on BIC

Table 10: Mean (%CV) Pharmacokinetic Parameters of BIC in the reference arm and test arm in Cohort 5

GS-9883 PK Parameter	Mean (%CV)	
	GS-9883+RBT (Test, N = 13)	GS-9883 Alone (Reference, N = 15)
AUC_{tau} (h*ng/mL)	66,164.3 (37.4)	106,486.2 (37.2)
C_{max} (ng/mL)	6140.0 (36.0)	7624.7 (35.5)
C_{tau} (ng/mL)	1212.2 (43.0)	2732.9 (40.7)
T_{max} (h)[a]	2.00 (1.50, 3.00)	1.50 (1.00, 2.00)
CL/F (mL/h)	1339.7 (52.3)	839.1 (50.3)

CV = coefficient of variation
a Median (Q1, Q3)

Source: final clinical study report, page 80

COHORT 6: Effect of CYP3A4 Inhibition by DRV/Cobi on BIC

Table 11: Mean (%CV) Pharmacokinetic Parameters of BIC in the reference arm and test arm in Cohort 6

GS-9883 PK Parameter	Mean (%CV)	
	GS-9883+DRV/COBI (Test, N = 13)	GS-9883 Alone (Reference, N = 15)
AUC_{tau} (h*ng/mL)	265,249.0 (19.3)	152,356.1 (16.2)
C_{max} (ng/mL)	17,300.0 (15.0)	11,402.0 (15.2)
C_{tau} (ng/mL)	8486.9 (24.9)	4017.3 (21.6)
T_{max} (h)[a]	3.00 (3.00, 3.00)	3.00 (3.00, 3.00)
CL/F (mL/h)	292.0 (18.1)	504.3 (15.9)

CV = coefficient of variation

Source: final clinical study report, page 82

Table 12: Statistical comparison of the pharmacokinetic parameters of BIC between test and reference treatments in various cohorts

GS-9883 PK Parameter	Test[a]	Reference[a]	%GLSM Ratio (90% CI) (Test/Reference)
Cohort 1: GS-9883 75 mg SD + ATV 300 mg QD + COBI 150 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	628,290.3 (17.4)	154,433.7 (16.0)	405.62 (376.07, 437.49)
C_{max} (ng/mL)	9033.3 (12.2)	6890.0 (12.3)	131.11 (122.71, 140.08)
$t_{1/2}$ (h)	59.99 (52.94, 63.10)	18.62 (15.87, 20.96)	
Cohort 2: GS-9883 75 mg SD + RIF 600 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	36,398.0 (21.5)	155,986.3 (41.8)	24.52 (22.00, 27.33)
C_{max} (ng/mL)	5131.3 (15.7)	7118.7 (17.0)	72.21 (67.06, 77.75)
$t_{1/2}$ (h)	5.65 (5.30, 6.18)	18.09 (14.47, 20.75)	
Cohort 3: GS-9883 75 mg SD + ATV 400 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	638,857.0 (20.5)	154,253.8 (21.8)	414.51 (381.02, 450.94)
C_{max} (ng/mL)	9110.7 (16.6)	7078.7 (13.3)	128.10 (122.95, 133.47)
$t_{1/2}$ (h)	56.86 (50.70, 66.90)	17.47 (15.26, 19.81)	
Cohort 4: GS-9883 75 mg SD + VORI 300 mg BID (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fasted			
AUC_{inf} (h*ng/mL)	160,519.3 (26.9)	101,659.4 (37.2)	161.14 (141.07, 184.06)
C_{max} (ng/mL)	5442.7 (33.6)	4844.0 (21.5)	108.94 (96.14, 123.43)
$t_{1/2}$ (h)	25.45 (18.65, 28.08)	15.92 (15.12, 19.76)	
Cohort 5: GS-9883 75 mg QD + RBT 300 mg QD (Test; N = 13) vs GS-9883 75 mg QD (Reference; N = 15); fasted			
AUC_{tau} (h*ng/mL)	66,164.3 (37.4)	106,486.2 (37.2)	62.01 (53.06, 72.47)
C_{max} (ng/mL)	6140.0 (36.0)	7624.7 (35.5)	80.37 (66.93, 96.50)
C_{tau} (ng/mL)	1212.2 (43.0)	2732.9 (40.7)	43.98 (37.14, 52.07)
Cohort 6: GS-9883 75 mg QD + DRV/COBI 800/150 mg QD (Test; N = 13) vs GS-9883 75 mg QD (Reference; N = 15); fed			
AUC_{tau} (h*ng/mL)	265,249.0 (19.3)	152,356.1 (16.2)	173.60 (161.55, 186.54)
C_{max} (ng/mL)	17,300.0 (15.0)	11,402.0 (15.2)	151.56 (140.15, 163.90)
C_{tau} (ng/mL)	8486.9 (24.9)	4017.3 (21.6)	211.43 (195.18, 229.03)

BID = twice daily; QD = once daily; SD = single dose
a Mean (%CV) for AUC_{last}, AUC_{inf}, AUC_{tau}, C_{max}, and C_{tau}; median (Q1, Q3) for $t_{1/2}$

Source: final clinical study report, page 7

Safety:

No Grade 3 or 4 AEs, serious adverse events (SAEs), or deaths were reported during the study. Two subjects had an adverse event that led to premature discontinuation of the study drug. Subject 9191-3012 in Cohort 5 prematurely discontinued study drug due to Grade 2 vomiting which has been observed previously with RBT and was considered related to study drug by the investigator. Subject 9191-3028 in Cohort 6 prematurely discontinued study drug due to a Grade 2 drug eruption (reported term: drug reaction pruritic rash), which has been observed previously with DRV/COBI and was considered related to study drug by the investigator.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Discussion:

Cohort 1: The mean C_{max} and AUC of BIC increased by 31% and 305%, respectively, when BIC was co-administered with ATV/Cobi relative to administration of BIC alone. The increase in mean C_{max} and AUC of BIC is primarily driven by inhibition of CYP3A4, UGT1A1 and P-gp transporters because BIC is a substrate of CYP3A4, UGT1A1 and P-gp.

Cohort 2: The mean C_{max} and AUC of BIC decreased by 28% and 75%, respectively, when BIC was co-administered with rifampin relative to administration of BIC alone. The decrease in mean C_{max} and AUC of BIC is primarily driven by induction of CYP3A4, UGT1A1 and P-gp transporters by rifampin because BIC is a substrate of CYP3A4, UGT1A1 and P-gp.

Cohort 3: The mean C_{max} and AUC of BIC increased by 28% and 315%, respectively, when BIC was co-administered with ATV relative to administration of BIC alone. ATV is an inhibitor of UGT1A1 and CYP3A4. In addition, ATV has been shown to be an inducer and inhibitor of P-gp transporters (based on *in vitro* data; Perloff etl, *Drug Metab Dispos*, 2005, 33(6), 764-770), hence increase in the BIC exposure is primarily driven by UGT1A1 and CYP3A inhibition and affected by a "net" (inhibition/induction) effect of ATV on P-gp.

Cohort 4: The mean C_{max} and AUC of BIC increased by 8% and 61%, respectively, when BIC was co-administered with VORI relative to administration of BIC alone. The increase in BIC exposures is most likely due to the inhibition of CYP enzymes by VORI. Of note, VORI does not affect UGT1A1 (IC_{50} > 50 µM).

Cohort 5: The mean C_{max} and AUC of BIC decreased by 20% and 38%, respectively, when BIC was co-administered with rifabutin relative to administration of BIC alone. The decrease in mean C_{max} and AUC of BIC is primarily driven by induction of CYP3A4 and P-gp by rifabutin (considering that rifabutin does not significantly alter the exposures of raltegravir, a known substrate of UGT1A1; Brainard et al, *J Clin Pharmacol*, 2011, 51(6), 943-950). The magnitude of reduction in BIC exposure due to rifabutin is less than the magnitude of reduction in BIC exposures due to rifampin because 1) rifabutin is a less potent inducer of CYP3A relative to rifampin and 2) Unlike rifampin, rifabutin does not induce UGT1A1.

Cohort 6: The mean C_{max} and AUC of BIC increased by 52% and 74%, respectively, when BIC was co-administered with DRV/Cobi relative to administration of BIC alone. The increase in mean C_{max} and AUC of BIC is primarily driven by inhibition of CYP3A4 with some involvement of P-gp inhibition by Cobi.

Applicant's Proposed Labeling Recommendations:

The applicant's proposed recommendations related to rifampin (contraindication) and rifabutin (co-administration not recommended) are acceptable based on the magnitude of changes in exposure of BIC.

Because BIC/F/TAF is a complete regimen and should not be co-administered with other antiretroviral drugs, the applicant's proposed labeling recommendations pertaining to (b) (4) will not be incorporated into the label.

Voriconazole can be administered with BIC/F/TAF without any dose adjustments.

Relevant Links and information on clinical and bioanalytical sites:

Clinical Trial Report:

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Clinical Site: Seaview Jacksonville, LLC. 7898 Baymeadows Way, Jacksonville, FL.

Bioanalytical Reports:

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Bioanalytical Site: (b) (4)

Study #	GS-US-380-3909	**Study Period**	April 4, 2016– May 20, 2016
Title	A Phase 1, Open Label, Multiple-Cohort, Multiple-Period, Fixed-Sequence, Drug Interaction Study to Evaluate the Effect of Antacid and Mineral Supplements on Bictregravir (BIC) Pharmacokinetics		

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Primary: Evaluate the effect of simultaneous administration of antacid, calcium or iron supplements with BIC/F/TAF FDC compared to administration of BIC/F/TAF alone under fasted and fed conditions on BIC PK and to evaluate the effect of staggered administration of BIC/F/TAF FDC and antacid compared to administration of BIC/F/TAF FDC alone on BIC PK.

Secondary: Evaluate the safety and tolerability of BIC/F/TAF FDC alone, and in combination with antacid, calcium, or iron supplements.

Rationale:

The applicant conducted this trial to evaluate the potential of cation-containing antacids and mineral supplements to decrease BIC exposure in healthy adult subjects and assessed two approaches for combined use if an interaction was observed: 1) Stagger administration of BIC/F/TAF and the antacid or supplement and 2) administer BIC/F/TAF with antacids or supplements following a meal as the results of trial GS-US-141-1233 indicate that relative to administration of BIC/F/TAF (50/200/25 mg) under fasting conditions, administration of BIC/F/TAF (50/200/25 mg) under moderate-fat meal and high-fat meal conditions increased the mean systemic exposure (AUC_{inf}) of BIC (by approximately 25% for both moderate-fat and high-fat conditions) and TAF (by approximately 48% under moderate fat conditions and 67% under high-fat conditions).

Dose Selection:

BIC/F/TAF (50/200/25 mg) FDC was selected because it is the FDC formulation evaluated in Phase 3 trials and proposed for marketing.

Antacid: Maximum-strength antacid was selected for use in the study because of its high divalent metal cation content. Each 5 mL of antacid oral suspension contains 400 mg of aluminum hydroxide, 400 mg of magnesium hydroxide, and 40 mg of simethicone. The highest recommended dose regimen (20 mL) was used in this study.

Calcium Carbonate: The selected dose of 1200 mg of calcium carbonate (2 × 600 mg tablets) represents a commonly used daily dose for calcium supplement. It contains about 480 mg elemental calcium and has higher elemental calcium content compared with other calcium supplements, such as calcium citrate or calcium phosphate.

Ferrous Fumarate: The selected dose of 324 mg of ferrous fumarate is a common recommend dose for iron supplement. It contains about 107 mg elemental iron and has higher elemental iron content compared with other iron supplements, such as ferrous sulfate or ferrous gluconate.

Design and PK Assessments:

The trial was designed to enroll up to 4 cohorts of 14 subjects each. Cohorts 1 through 3 were initiated in parallel and the decision to proceed to Cohort 4 was dependent upon review of preliminary PK data from Cohorts 1 and 2.

Table 1: Design of cohort 1 (all treatments were administered under fasting conditions; treatments B, C and D were administered simultaneously with treatment A)

	Cohort 1 (Fasted)							
Period	**1**		**2**		**3**		**4**	
Study Days	Day 1	Days 2-8	Day 9	Days 10-16	Day 17	Day 18-24	Day 25	Day 29
Treatment	A	Washout	B	Washout	C	Washout	D	Discharge

Treatment A: single dose of BIC/F/TAF; Treatment B: single dose of BIC/F/TAF administered simultaneously with a single dose of 20 mL maximum strength antacid oral suspension; Treatment C: single dose of BIC/F/TAF administered simultaneously with a single dose of calcium carbonate (2X600 mg tablets); Treatment D: single dose of BIC/F/TAF administered simultaneously with a single dose of ferrous fumarate (1 X 324 mg tablet)
Source: Clinical study report, page 27

Table 2: Design of cohort 2 (staggered administration by 2 hours under fasting conditions)

	Cohort 2 (Fasted)					
Period	**1**		**2**		**3**	
Study Days	Day 1	Days 2-8	Day 9	Days 10-16	Day 17	Day 21
Treatment	A	Washout	E	Washout	F	Discharge

Treatment A: single dose of BIC/F/TAF; Treatment E: single dose of BIC/F/TAF under fasting conditions administered 2 hours before single dose of 20 mL maximum strength antacid oral suspension; Treatment F: single dose of BIC/F/TAF under fasting conditions, administered 2 hours after a single dose of 20 mL maximum strength antacid oral suspension.
Source: Clinical study report, page 28

Table 3: Design of cohort 3 (simultaneous administration under fed [moderate fat breakfast; 600 calories with approximately 27% calories from fat] conditions)

	Cohort 3							
Period	**1 (Fasted)**		**2 (Fed)**		**3 (Fed)**		**4(Fed)**	
Study Days	Day 1	Days 2-8	Day 9	Days 10-16	Day 17	Day 18-24	Day 25	Day 29
Treatment	A	Washout	G	Washout	H	Washout	I	Discharge

Treatment A: single dose of BIC/F/TAF (administered under fasting conditions); Treatment G: single dose of BIC/F/TAF administered simultaneously with a single dose of 20 mL maximum strength antacid oral suspension under fed conditions; Treatment H: single dose of BIC/F/TAF administered simultaneously with a single dose of calcium carbonate (2X600 mg) under fed conditions; Treatment I: single dose of BIC/F/TAF administered simultaneously with a single dose of ferrous fumarate (1X324 mg tablet) under fed conditions
Source: Clinical study report, page 28

Table 4: Design of cohort 4 (staggered administration by 4 hours)

	Cohort 4 (Fasted, Adaptive)					
Period	**1**		**2**		**3**	
Study Days	Day 1	Days 2-8	Day 9	Days 10-16	Day 17	Day 21
Treatment	A	Washout	J	Washout	K	Discharge

Treatment A: single dose of BIC/F/TAF under fasting conditions; Treatment J: single dose of BIC/F/TAF under fasting conditions administered 4 hours before single dose of 20 mL maximum strength antacid oral suspension; Treatment K: single dose of BIC/F/TAF under fasting conditions, administered 4 hours after a single dose of 20 mL maximum strength antacid oral suspension.
Source: Clinical study report, page 28

PK Sampling and Assessments:

Serial blood samples were collected on Days 1, 9 and 17 of Cohorts 1 through 4 and Day 25 of Cohorts 1 and 3 at the following times relative to administration of BIC/F/TAF: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 hours post-dose.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☑ Fasted ☑ Fed (based on cohort)

Formulations
BIC/F/TAF (50/200/25 mg tablets; batch # EN1503B2, February 2017), maximum strength antacid (batch # SMK0763), calcium carbonate (batch # 47131), ferrous fumarate (batch # 46799)

RESULTS

Enrolled	42	Completed	41	Discontinued Due to AE	1	PK Population	41	Safety Population	41

Note: No subjects were enrolled in adaptive cohort 4. One subject in Cohort 2 discontinued due to AE.

Protocol Deviations
No protocol deviations were reported in the trial.

Demographics
Across the 3 cohorts of subjects, 29 subjects were male and 13 subjects were female. Median age was 34 years (range: 22 to 45 years) and median BMI was 26.6 kg/m^2 (range 21.6 to 29.9 kg/m^2).

Results:

Table 5: Mean pharmacokinetic PK parameters of BIC following administration of BIC/F/TAF alone or simultaneous administration of BIC/F/TAF with maximum strength antacid, calcium carbonate, or ferrous fumarate under fasting conditions (Cohort 1)

	Simultaneous Administration with B/F/TAF (Fasted)			
BIC PK Parameter	Max-Strength Antacid (N = 14)	Calcium Carbonate (N = 14)	Ferrous Fumarate (N = 14)	B/F/TAF Alone (N = 14)
AUC_{inf} (ng•h/mL)[a]	27,960.7 (52.5)	85,037.3 (43.1)	46,148.7 (32.9)	121,887.9 (24.4)
C_{max} (ng/mL)[a]	1199.8 (52.0)	3442.1 (36.9)	1667.1 (27.1)	5635.0 (18.8)
T_{max} (h)[b]	3.00 (2.00, 4.00)	1.75 (1.50, 4.00)	3.50 (3.00, 4.00)	2.00 (1.50, 3.00)
C_{24} (ng/mL)[a]	427.0 (57.4)	1222.9 (43.9)	674.8 (32.8)	1795.7 (26.3)
AUC_{last} (ng•h/mL)[a]	26,242.5 (52.8)	80,376.0 (42.5)	43,395.8 (31.4)	116,758.3 (22.8)
$\%AUC_{exp}$ (%)[a]	5.91 (62.59)	5.26 (83.94)	5.48 (70.44)	3.78 (90.15)
$t_{1/2}$ (h)[b]	20.19 (16.68, 25.16)	21.04 (17.55, 24.99)	21.88 (17.52, 25.16)	18.89 (14.56, 22.64)
CL/F (mL/h)[a]	2183.5 (45.7)	676.2 (37.9)	1187.9 (30.2)	433.2 (24.1)
V_z/F (mL)[a]	61,433.7 (27.9)	21,656.9 (48.8)	37,261.6 (27.6)	11,792.3 (18.3)

a Mean (%CV)
b Median (Q1, Q3)

Source: Clinical study report, page 54

Table 6: Mean pharmacokinetic PK parameters of BIC following administration of BIC/F/TAF alone under fasting conditions or administration of BIC/F/TAF under fasting conditions 2 hours before or after maximum strength antacid (Cohort 2)

BIC PK Parameter	Staggered Administration of B/F/TAF (Fasted)		
	2 Hours Before Max-Strength Antacid (N = 13)	2 Hours After Max-Strength Antacid (N = 13)	B/F/TAF Alone (N = 14)
AUC_{inf} (ng•h/mL)[a]	115,908.1 (30.3)	67,704.6 (47.0)	132,814.0 (27.0)
C_{max} (ng/mL)[a]	5616.2 (22.7)	2735.0 (48.3)	5920.0 (16.5)
T_{max} (h)[b]	1.50 (1.50, 2.00)	2.00 (1.50, 3.00)	3.00 (2.00, 3.00)
C_{24} (ng/mL)[a]	1699.2 (27.9)	985.6 (44.0)	2009.3 (28.3)
AUC_{last} (ng•h/mL)[a]	110,633.6 (28.8)	63,447.0 (45.8)	124,721.4 (28.0)
$\%AUC_{exp}$ (%)[a]	4.18 (49.44)	6.02 (48.72)	5.84 (148.47)
$t_{1/2}$ (h)[b]	21.75 (18.55, 24.24)	24.22 (20.13, 26.46)	20.75 (16.50, 22.82)
CL/F (mL/h)[a]	471.0 (30.8)	909.7 (47.7)	405.4 (29.9)
V_z/F (mL)[a]	14,385.7 (29.3)	31,242.2 (55.3)	11,177.2 (30.1)

a Mean (%CV)
b Median (Q1, Q3)

Source: Clinical study report, page 57

Table 7: Mean pharmacokinetic PK parameters of BIC following administration of BIC/F/TAF alone under fasting conditions or simultaneous administration of BIC/F/TAF with maximum strength antacid, calcium carbonate or ferrous fumarate under fed conditions (Cohort 3)

BIC PK Parameter	Simultaneous Administration with B/F/TAF (Fed)			B/F/TAF Alone (Fasted) (N = 14)
	Max-Strength Antacid (N = 14)	Calcium Carbonate (N = 14)	Ferrous Fumarate (N = 14)	
AUC_{inf} (ng•h/mL)[a]	50,813.5 (34.8)	94,832.8 (21.2)	77,307.8 (24.8)	93,658.3 (27.2)
C_{max} (ng/mL)[a]	2446.4 (31.4)	4105.0 (13.7)	3485.0 (23.2)	4700.7 (23.6)
T_{max} (h)[b]	3.50 (3.00, 4.00)	3.50 (2.00, 4.00)	4.00 (3.00, 4.00)	1.50 (1.50, 2.00)
C_{24} (ng/mL)[a]	803.6 (36.4)	1459.9 (22.1)	1228.7 (25.0)	1410.1 (29.7)
AUC_{last} (ng•h/mL)[a]	49,220.5 (34.8)	91,454.0 (20.1)	74,518.3 (24.0)	91,204.9 (26.5)
$\%AUC_{exp}$ (%)[a]	3.17 (31.76)	3.39 (42.46)	3.47 (39.58)	2.52 (38.86)
$t_{1/2}$ (h)[b]	17.93 (16.91, 20.18)	18.87 (18.20, 21.63)	19.34 (18.23, 22.36)	17.96 (17.48, 19.94)
CL/F (mL/h)[a]	1111.4 (37.8)	549.8 (21.7)	678.0 (20.5)	587.0 (41.1)
V_z/F (mL)[a]	29,146.3 (33.8)	15,520.6 (21.3)	19,323.7 (19.3)	15,436.2 (47.3)

a Mean (%CV)
b Median (Q1, Q3)

Source: Clinical study report, page 60

Table 8: Statistical comparison of the pharmacokinetic parameters of BIC between test and reference treatments in various cohorts

BIC PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	B/F/TAF Under Test Conditions (N = 14)	B/F/TAF Alone (Fasted) (Reference) (N = 14)	
B/F/TAF (fasted) with 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	27,960.7 (52.5)	121,887.9 (24.4)	21.23 (17.57, 25.65)
C_{24} (ng/mL)	427.0 (57.4)	1795.7 (26.3)	21.94 (17.80, 27.04)
C_{max} (ng/mL)	1199.8 (52.0)	5635.0 (18.8)	19.89 (16.46, 24.02)
B/F/TAF (fasted) with calcium carbonate (Test)			
AUC_{inf} (ng•h/mL)	85,037.3 (43.1)	121,887.9 (24.4)	66.67 (56.67, 78.42)
C_{24} (ng/mL)	1222.9 (43.9)	1795.7 (26.3)	64.89 (54.47, 77.31)
C_{max} (ng/mL)	3442.1 (36.9)	5635.0 (18.8)	58.31 (50.72, 67.04)
B/F/TAF (fasted) with ferrous fumarate (Test)			
AUC_{inf} (ng•h/mL)	46,148.7 (32.9)	121,887.9 (24.4)	37.11 (32.95, 41.80)
C_{24} (ng/mL)	674.8 (32.8)	1795.7 (26.3)	36.92 (32.59, 41.83)
C_{max} (ng/mL)	1667.1 (27.1)	5635.0 (18.8)	29.10 (25.87, 32.72)
B/F/TAF (fasted) 2 hours before 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	115,908.1 (30.3)a	132,814.0 (27.0)	86.70 (81.01, 92.78)
C_{24} (ng/mL)	1699.2 (27.9)[a]	2009.3 (28.3)	85.46 (79.92, 91.38)
C_{max} (ng/mL)	5616.2 (22.7)[a]	5920.0 (16.5)	93.40 (87.53, 99.66)
B/F/TAF (fasted) 2 hours after 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	67,704.6 (47.0)[a]	132,814.0 (27.0)	47.66 (38.26, 59.35)
AUC_{last} (ng•h/mL)	63,447.0 (45.8)[a]	124,721.4 (28.0)	47.34 (37.91, 59.12)
C_{max} (ng/mL)	2735.0 (48.3)[a]	5920.0 (16.5)	41.51 (33.25, 51.83)
B/F/TAF (fed) with 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	50,813.5 (34.8)	93,658.3 (27.2)	53.25 (44.21, 64.14)
C_{24} (ng/mL)	803.6 (36.4)	1410.1 (29.7)	56.01 (46.21, 67.88)
C_{max} (ng/mL)	2446.4 (31.4)	4700.7 (23.6)	51.46 (42.69, 62.03)
B/F/TAF (fed) with calcium carbonate (Test)			
AUC_{inf} (ng•h/mL)	94,832.8 (21.2)	93,658.3 (27.2)	103.29 (88.96, 119.93)
AUC_{last} (ng•h/mL)	91,454.0 (20.1)	91,204.9 (26.5)	102.36 (88.07, 118.98)
C_{max} (ng/mL)	4105.0 (13.7)	4700.7 (23.6)	89.58 (77.83, 103.10)
B/F/TAF (fed) with ferrous fumarate (Test)			
AUC_{inf} (ng•h/mL)	77,307.8 (24.8)	93,658.3 (27.2)	83.84 (74.07, 94.89)
C_{24} (ng/mL)	1228.7 (25.0)	1410.1 (29.7)	88.93 (78.12, 101.24)
C_{max} (ng/mL)	3485.0 (23.2)	4700.7 (23.6)	75.12 (64.82, 87.05)

a N = 13 for Test treatment

Source: Clinical study report, page 7

Safety:

No Grade 3 or 4 AEs, serious adverse events (SAEs), or deaths were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:
Integrase strand-transfer inhibitors (INSTIs) such as BIC bind to magnesium in the active site of the integrase enzyme, preventing insertion of HIV viral DNA into the host cell DNA. Drugs in the INSTI class (such as raltegravir, elvitegravir and dolutegravir) are susceptible to chelation-type drug interactions within the gut with divalent and trivalent metal cations such as magnesium, aluminum, calcium and iron.

Simultaneous administration of BIC/F/TAF (administered under **fasting** conditions) with antacids, calcium supplement, and iron supplement:

The decrease in mean systemic exposure of BIC after simultaneous administration of BIC/F/TAF (administered under fasting conditions) with antacids, calcium supplement, and iron supplement was 79%, 33%, and 63%, respectively. The decrease in BIC exposure observed in the trial can potentially compromise the efficacy of BIC/F/TAF, hence simultaneous administration of BIC/F/TAF (administered under fasting conditions) with antacids, calcium supplement, and iron supplement is not recommended. Of note, the mean decrease in BIC exposures observed with calcium supplement (33%) in this trial is similar to the mean decrease in BIC exposure (38%) observed when BIC was administered with rifabutin in trial GS-US-141-1485. The applicant's proposed recommendation ["co-administration of BIC/F/TAF and rifabutin is not recommended] was accepted by the review team.

Simultaneous administration of BIC/F/TAF (administered under **fed** conditions) with antacids, calcium supplement, and iron supplement:

The decrease in mean systemic exposure of BIC after simultaneous administration of BIC/F/TAF (administered under fed conditions) with antacids was 47%. The decrease in BIC exposure observed in the trial can potentially compromise the efficacy of BIC/F/TAF, hence simultaneous administration of BIC/F/TAF (administered under fed conditions) with antacids is not recommended.

The simultaneous administration of BIC/F/TAF with calcium supplement and iron supplement is acceptable considering that the mean PK parameters of BIC were not significantly impacted when BIC/F/TAF (administered under fed conditions) was simultaneously administered with calcium supplement and iron supplements.

Staggered (by 2 hours) administration of BIC/F/TAF (administered under **fasting** conditions) with antacids:

The decrease in mean systemic exposure of BIC after staggered administration of BIC/F/TAF (administered under fasting conditions two hours before antacid) was 14% and decrease in mean systemic exposure of BIC after staggered administration of BIC/F/TAF (administered under fasting conditions two hours after antacid) was 52 %. The decrease in mean systemic exposure of BIC after administration of BIC/F/TAF (administered under fasting conditions two hours before antacid) is not expected to be clinically relevant, however, the decrease in the mean systemic exposure of BIC after administration of BIC/F/TAF (administered under fasting conditions two hours after antacid) can potentially compromise the efficacy of BIC/F/TAF.

Proposed Labeling Recommendation:

Please refer to the Multi Disciplinary Review document for the final labeling recommendation.

Relevant Links and information on clinical and bioanalytical sites:

Trial Report:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-380-3909\report-body.pdf

Clinical Site: Seaview Research Inc. SeaView Research, 3898 NW 7th Street, Miami, FL.

Bioanalytical Reports:

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-380-3909\basar (b) (4) 60-1627.pdf

\\cdsesub1\evsprod\nda210251\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\gs-us-380-3909\basar (b) (4) -60n-1668.pdf

Bioanalytical Site: (b) (4)

Population PK analysis

Population PK models for BIC and TAF were developed and submitted by Applicant. TAF has been approved as a component of fixed-dose combination tablets, including DESCOVY and ODEFSEY. The same dose of TAF (25 mg) was used in DESCOVY and ODEFSEY as used in the B/F/TAF FDC tablet. There is no PK interaction between BIC and TAF. Therefore, the population PK analysis for TAF in this submission was not reviewed.

A population PK model for BIC was developed by Applicant based on pooled data from Studies 1233, 1991, 3909, 1999, 1489, 1490, 1878 and 1844 in healthy subjects and human immunodeficiency virus-1 (HIV-1) infected subjects. Only data from the dosing regimen of 50/200/25 mg for BIC/FTC/TAF were included in the population PK analysis.

Study 1233: The study was a single-dose Phase 1 study to evaluate relative bioavailability and food effect in healthy volunteers. A total of 56 subjects were enrolled in the study. Serial blood samples were collected on Days 1, 9, 17, and 25 at the following times relative to study drug administration: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 hours postdose.

Study 1991: The study was a single-dose Phase 1 study to investigate the PK of B/F/TAF in healthy Japanese and Caucasian subjects under fasted conditions. A total of 50 subjects (25 Japanese and 25 Caucasian) enrolled in this study. Serial blood samples were collected on Day 1 at times relative to study drug administration in the morning as follows: 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours postdose.

Study 3909: The study was a single-dose Phase 1 study to evaluate the effect of antacid and mineral supplements on PK of BIC in healthy subjects under fasted and fed conditions. A total of 42 subjects were enrolled in the study. Serial blood samples were collected on Days 1, 9, 17, and 25 at the following times relative to administration of B/F/TAF: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 and 96 hours postdose.

Study 1999: The study was a multiple-dose Phase 1 study to evaluate the drug-drug interaction between B/F/TAF and SOF/VEL/VOX in healthy subjects. A total of 30 subjects were enrolled. Serial blood samples were collected on Days 10, 20, and 30 at the following times relative to study drug administration: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours postdose.

Study 1489: The study was a Phase 3 study to evaluate the efficacy and safety of B/F/TAF in HIV-1 infected, antiretroviral treatment-naïve adults. A total of 631 subjects were enrolled and randomized to the following 2 treatment groups for 144 weeks:

Treatment Group 1: B/F/TAF (50/200/25 mg) FDC tablet + placebo-to-match ABC/DTG/3TC administered orally, once daily, without regard to food;

Treatment Group 2: ABC/DTG/3TC (600/50/300 mg) FDC tablet + placebo-to-match B/F/TAF administered orally, once daily, without regard to food.

For all subjects on study drugs, a single predose or postdose pharmacokinetic (PK) blood sample was collected at Weeks 8, 24, and 36. Additionally, at Weeks 4 and 12, a trough PK blood sample was obtained 20 to 28 hours following the last dose, and a postdose PK blood sample was obtained between 1 and 4 hours postdose following an observed dose at the clinic.

In a subset of subjects (target n = 30) at selected study sites, an intensive PK sub-study was performed at the Week 4 or 8 visit. A trough PK blood sample was obtained at the Week 4 or Week 8 visit 20 to 28 hours following the last dose of B/F/TAF, and postdose PK blood samples were obtained at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours postdose following an observed dose at the clinic.

For subjects who consented, additional blood and plasma samples were obtained at Day 1 and Week 36, and at Weeks 84 and 132, for an optional peripheral blood mononuclear cell (PBMC) substudy.

Study 1490: The study was a Phase 3 study to evaluate the efficacy and safety of B/F/TAF in HIV-1 infected, antiretroviral treatment-naïve adults. A total of 657 subjects were enrolled and randomized to following 2 treatment groups for 144 weeks:

Treatment Group 1: B/F/TAF 50/200/25 mg FDC + placebo-to-match DTG 50 mg and placebo-to-match F/TAF 200/25 mg FDC administered orally, once daily, without regard to food;

Treatment Group 2: DTG 50 mg + F/TAF 200/25 mg FDC+ placebo-to-match B/F/TAF 50/200/25 mg FDC administered orally, once daily, without regard to food.

A similar PK sampling scheme was used as mentioned in Study 1489.

Study 1878: The study was a Phase 3 study to evaluate the efficacy and safety of switching from regimens consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC to B/F/TAF in HIV-1 infected adult subjects who were virologically suppressed. A total of 578 subjects were enrolled and randomized to the following 2 treatment groups for 48 weeks:

Treatment Group 1 (B/F/TAF): Switched to an FDC of B/F/TAF administered orally once daily without regard to food;

Treatment Group 2 (Stay on Baseline Regimen [SBR]): Remained on current antiretroviral (ARV) regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally once daily with food.

For all subjects in the B/F/TAF treatment group who were on study drug, a single predose or postdose pharmacokinetic (PK) blood sample was collected at Weeks 8, 24, and 36. Additionally, at Weeks 4 and 12, a trough PK blood sample was obtained 20 to 28 hours following the last dose and a postdose PK blood sample was obtained between 1 and 4 hours postdose following an observed dose at the clinic.

In a subset of subjects in the B/F/TAF treatment group (target n = 24) at selected study sites, an intensive PK substudy was performed at the Week 4 or 8 visit. A trough PK blood sample was obtained at the Week 4 or Week 8 visit 20 to 28 hours following the last dose of B/F/TAF, and postdose PK blood samples were obtained at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours postdose following an observed dose at the clinic.

Study 1844: The study was a Phase 3 study to evaluate the efficacy and safety of switching from a regimen of DTG and ABC/3TC or ABC/DTG/3TC to B/F/TAF in virologically suppressed HIV-1 infected subjects. A total of 567 subjects were enrolled and randomized to the following 2 treatment groups for 48 weeks:

Treatment Group 1: B/F/TAF (50/200/25 mg) FDC tablet + placebo-to-match ABC/DTG/3TC administered orally, once daily, without regard to food;

Treatment Group 2: ABC/DTG/3TC (600/50/300 mg) FDC tablet + placebo-to-match B/F/TAF administered orally, once daily, without regard to food.

A similar PK sampling scheme was used as mentioned in Study 1878.

The demographics information of 8 clinical studies is summarized in Table 1. The BIC plasma concentrations versus time profile is shown in Figure 1. The percentages of patients receiving B/F/TAF and included in the population PK analysis were 100%, 50%, 100%, 100%, 99.4%, 97.5%, 99.7%, and 99.3% for Studies 1233, 1991, 3909, 1999, 1489, 1490, 1878, and 1844, respectively.

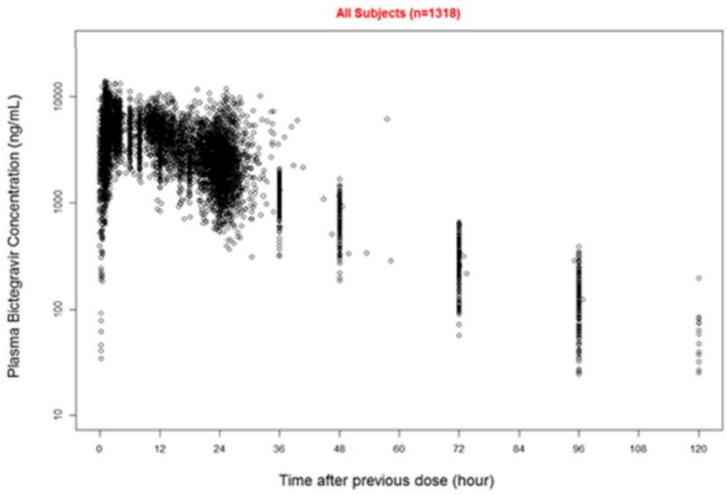
Table 1 Baseline characteristics in Phase I studies in the BIC Population PK Dataset

Characteristics	GS-US-141-1233	GS-US-380-1991	GS-US-380-3909	GS-US-380-1999
No. of subjects	28	25	42	30
No. of samples	1128	424	620	390
Continuous Covariates				
Covariates	**Median [min, max]**	**Median [min, max]**	**Median [min, max]**	**Median [min, max]**
Age (yr)	31.5 [23-45]	33 [22-52]	33.5 [22-45]	36 [21-43]
Body Weight (kg)	78.5 [51.0-97.7]	71.3 [53.6-89.8]	78.3 [62.1-95.6]	74.5 [53.0-99.0]
BMI (kg/m^2)	27.2 [20.1-29.7]	24.3 [19.5-29.6]	26.6 [21.6-29.9]	26.6 [20.3-30.0]
BSA (m^2)	1.9 [1.5-2.2]	1.8 [1.5-2.1]	1.9 [1.7-2.2]	1.9 [1.5-2.2]
Baseline CLCR (mL/min)	128.2 [95.0-173.4]	114.8 [93.9-148.3]	118.7 [91.5-167.7]	114.9 [94.8-148.2]
Categorical Covariates				
Covariates	**N**	**N**	**N**	**N**
SEXF (0/1)	17/11	13/12	29/13	19/11
RACE (1/2/3/4)	19/9/0/0	25/0/0/0	30/12/0/0	17/12/0/1
PAT (0/1)	28/0	25/0	42/0	30/0
FAST (0/1/2)	0/27/1	0/0/25	0/0/42	30/0/0
PRTEXPN (0/1/2)	28/0/0	25/0/0	42/0/0	30/0/0
BHBVCI (0/1)	28/0	25/0	42/0	30/0
BHCVCI (0/1)	28/0	25/0	42/0	30/0
CMH2RA (0/1)	28/0	25/0	42/0	30/0
CMPPI (0/1)	28/0	25/0	42/0	30/0

Characteristics	GS-US-380-1489	GS-US-380-1490	GS-US-380-1878	GS-US-380-1844
No. of subjects	312	312	289	280
No. of samples	1687	1582	1545	1376
Continuous Covariates				
Covariates	**Median [min, max]**	**Median [min, max]**	**Median [min, max]**	**Median [min, max]**
Age (yr)	31 [18-71]	33 [18-68]	48 [20-74]	47 [21-71]
Body Weight (kg)	77.2 [43.0-146.5]	76.1 [44.7-144.8]	80.0 [54.9-142.4]	80.3 [44.9-208.7]
BMI (kg/m^2)	25.1 [15.8-46.5]	25.0 [16.9-42.1]	26.2 [18.1-53.2]	26.3 [16.5-69.6]
BSA (m^2)	1.9 [1.3-2.8]	1.9 [1.4-2.8]	2.0 [1.5-2.8]	2.0 [1.4-3.2]
Baseline CLCR (mL/min)	125.9 [25-376.4]	120.6 [50-241.1]	107.1 [42.4-259.2]	100.8 [49.9-319]
Categorical Covariates				
Covariates	**N**	**N**	**N**	**N**
SEXF (0/1)	283/29	275/37	242/47	245/35
RACE (1/2/3/4)	180/112/6/14	179/93/7/33	187/79/6/17	205/58/9/8
PAT (0/1)	0/312	0/312	0/289	0/280
FAST (0/1/2)	36/177/99	30/186/96	44/172/73	30/0/0
PRTEXPN (0/1/2)	0/312/0	0/312/0	0/0/289	0/0/280
BHBVCI (0/1)	312/0	305/7	281/8	280/0
BHCVCI (0/1)	312/0	308/4	284/5	280/0
CMH2RA (0/1)	308/4	298/14	279/10	270/10
CMPPI (0/1)	297/15	282/30	260/29	245/35

Source: Applicant's population PK report for BIC, Page 26-27, Table 4-5

Figure 1 BIC concentration versus time after previous dose



Source: Applicant's population PK report for BIC, Page 28, Figure 1

A one-compartment model with first-order absorption, a lag time, and first-order elimination was developed. The effects of baseline demographic covariates (age, sex, race, body weight, BMI, and health status (healthy volunteers or HIV patients)), baseline creatinine clearance, concomitant medications, fasting status, prior treatment experience, and baseline HBV/HCV co-infection status on each of the BIC PK parameters were assessed. The final population PK model included body weight on

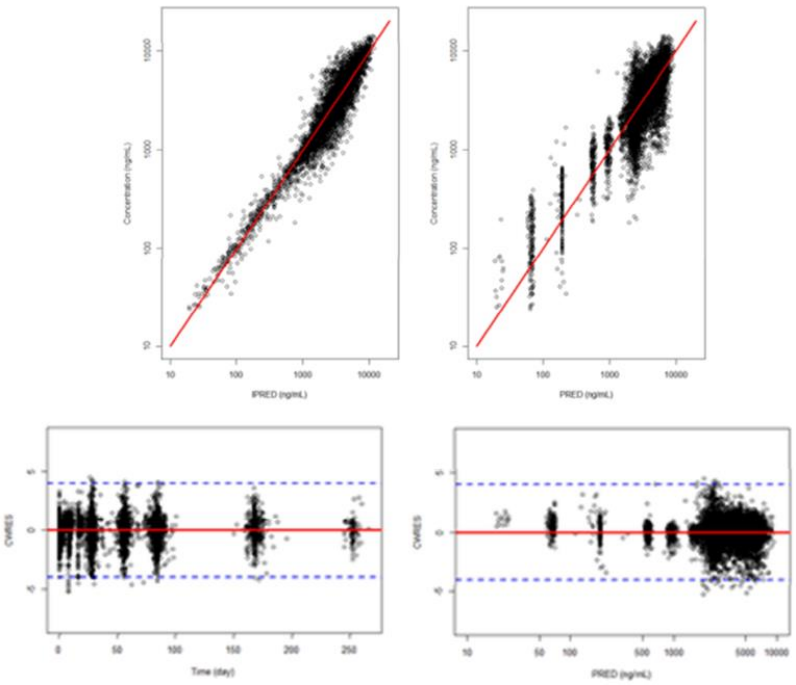
CL and Vc, health status on Vc, and proton pump inhibitors (PPI) on Ka. Final parameter estimates for BIC are listed in Table 2.

Table 2 Summary of final population PK parameters

Parameter	Parameter Description		Population Estimate (RSE%)	Percent Change from Typical	Inter-Individual Variability (RSE%)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr)	Subject with 80 kg body weight	0.504 (0.88%)	—	27.4 (5.11%)
$exp(\theta_1+\theta_5)$		Subject with 5%tile body weight	0.428	-15.1	
		Subject with 95%tile body weight	0.601	19.2	
$exp(\theta_2)$	Apparent central volume, Vc/F (L)	HIV patient with 80 kg body weight	12.5 (1.62%)	—	11.1 (26.8%)
$exp(\theta_2+\theta_6)$		HIV patient with 5%tile body weight	9.80	-21.5	
		HIV patient with 95%tile body weight	16.2	29.7	
$exp(\theta_2+\theta_7)$		HV with 80 kg body weight	11.6	-7.30	
$exp(\theta_3)$	Absorption rate constant, k_a (1/hr)	Subject without PPI usage	2.60 (7.04%)	—	124 (10.9%)
$exp(\theta_3+\theta_8)$		Subject with PPI usage	1.139	-56.2	
$exp(\theta_4)$	Lag time Tlag (hr)		0.235 (1.70%)	—	—
$\omega_{(CL,Vc)}$	Covariance between CL/F and Vc/F		0.021 (17.8%)		—
σ	Residual error		29.2 (3.53%)		—

Source: Applicant's population PK report for BIC, Page 32, Table 6

Figure 2 Goodness-of-fit plots for the final population PK model

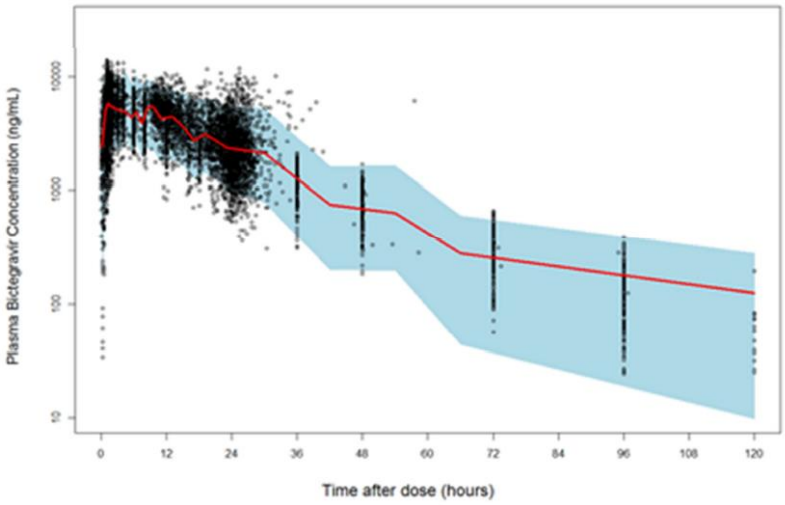


Upper left is observations vs individual predictions; upper right is observations vs population predictions; lower left is conditional weighted residuals vs time after 1st dose; lower right is conditional weighted residuals vs population predictions.

Source: Applicant's population PK report for BIC, Page 34-35, Figure 5-6

The general goodness-of-fit plot of the final Population PK model is shown in Figure 2. There was a good agreement between the predicted concentrations and the observed concentrations. No apparent bias was observed in the residuals plots over time and across predicted concentrations. The VPC plot is presented in Figure 3. The results show that the final Population PK model can adequately predict the central tendency and variability of the plasma BIC concentrations in subjects across all studies.

Figure 2 VPC of BIC plasma concentration-time profiles across all studies



Points are the observed plasma BIC concentrations. The red lines are the median of the predicted concentrations by the final PopPK model (1000 trials). The blue shaded areas are the spread (5th to 95th percentile) of the predicted concentrations.

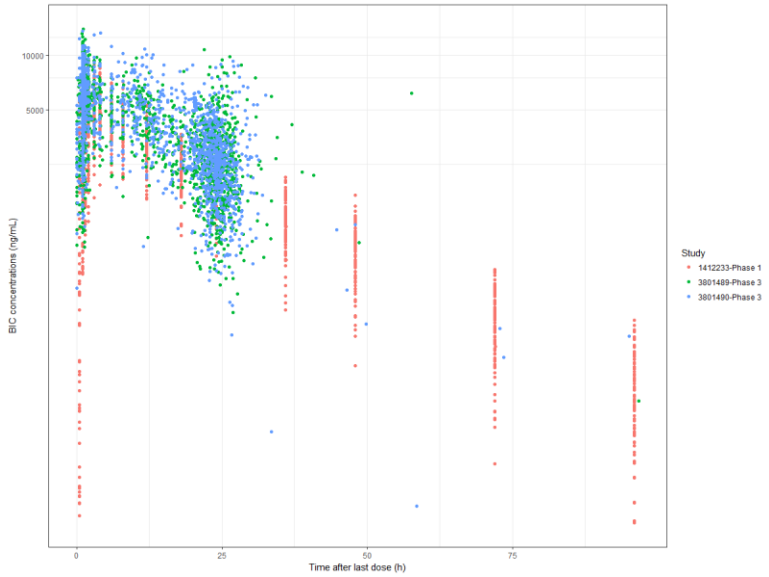
Source: Applicant's population PK report for BIC, Page 40, Figure 12

The impact of statistically significant covariates on BIC exposure was evaluated. Compared to the typical value, subjects with body weight at the 5% and 95% quantile of the population showed a -16.2% and 17.8%, -18.6% and 21.3% as well as -12.4% and 12.7% difference in AUCtau, Cmax, and Ctau, respectively. The covariate effect of baseline PPI status on BIC Ka resulted in no change in AUCtau, 4.6% lower Cmax and 2.1% higher Ctau in subjects with PPI usage compared to subjects without PPI usage. The covariate effect of health status on BIC Vc/F resulted in no change in AUCtau, 2.8% higher Cmax and 4.2% lower Ctau in healthy subjects compared to HIV-infected subjects. In summary, body weight, health status, and concomitant administration of PPIs are statistically significant covariates on the PK, but did not have a clinically significant impact on BIC exposure.

Reviewer's comments: The Reviewer verified the population PK model. The population PK model can reasonably describe the PK data pooling from 8 clinical trials in both healthy volunteers and patients. No additional covariate was identified. PPI in the population PK model was a binary covariate without further clarification such as how PPI was used, thus limited information was provided.

Two formulations of B/F/TAF FDC were used in clinical studies. The original formulation was used in Study 1233. Then the formulation was modified during Phase 3 studies (b) (4) (b) (4) *The new formulation was used in all further development, clinical and stability studies, and is identical to the designated commercial tablet formulation. The exposures of two studies were compared to see if the formulation change had a significant impact on exposure. The results showed that the exposures with two formulations overlapped and formulation did not appear to be a significant covariate on PK of BIC.*

Figure 3 Comparison of BIC PK across studies



Source: Reviewer's analysis

It is worth noting that only the dose of 50 mg for BIC was used in the population PK analysis with a narrow range of BIC concentration, which limits the range of exposure to be used in the exposure-response analysis. To conclude, the population appears to be reasonably describe the PK of BIC. The model was used to estimate PK parameters for exposure-response analysis.

Exposure-response analysis

The exposure-efficacy relationships for BIC were evaluated in ART-naive HIV-infected subjects who received B/F/TAF in Phase 3 studies (Studies 1489 and 1490) using BIC exposure estimates derived from population PK modeling without considering the contribution of TAF. A total of 584 subjects were included in the exposure-efficacy analysis accounting for 92.1% patients receiving BIC/F/TAF tablets. The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48, as determined by the US FDA-defined snapshot algorithm. Subjects with no virologic data at Week 48 were excluded from the analysis. A total of 584 HIV-infected subjects with evaluable BIC

population PK parameters (AUCtau, Cmax, and Ctau) and virologic data at Week 48 were included in the exposure-response analyses.

Table 3 presents the proportion of population quartiles of BIC exposures in HIV-infected subjects. Virologic response rates were high across all exposure ranges for BIC. The lowest exposure quartile for BIC trough concentrations (Ctau range: 757.4−1975.5 ng/mL), showed similar virologic response rates as the highest exposure quartile for BIC trough concentrations (Ctau range: 3121.0−6498.5 ng /mL). As such, no exposure-response relationship is observed following administration of B/F/TAF.

Table 3 Percentage of Subjects with HIV-1 RNA < 50 copies/mL (Snapshot Algorithm) by Population Quartiles of BIC Exposures in ART-Naive HIV-Infected Subjects based on Studies 1489 and 1490

	B/F/TAF (N = 584)
BIC AUC_{tau} Quartile Subgroups	
BIC AUC_{tau} in Quartile 1 [147, 47879.0, 72615.3, 84804.7]	146/147 (99.3%)
BIC AUC_{tau} in Quartile 2 [146, 84863.7, 92675.0, 100644.1]	144/146 (98.6%)
BIC AUC_{tau} in Quartile 3 [142, 100725.2, 108637.8, 119277.7]	139/142 (97.9%)
BIC AUC_{tau} in Quartile 4 [149, 119511.4, 132611.9, 213739.2]	146/149 (98.0%)
BIC C_{max} Quartile Subgroups	
BIC C_{max} in Quartile 1 [149, 2866.1, 4700.1, 5329.7]	149/149 (100.0%)
BIC C_{max} in Quartile 2 [143, 5333.2, 5739.0, 6136.4]	140/143 (97.9%)
BIC C_{max} in Quartile 3 [141, 6140.5, 6567.0, 7076.8]	138/141 (97.9%)
BIC C_{max} in Quartile 4 [151, 7086.6, 7779.3, 11427.4]	148/151 (98.0%)
BIC C_{tau} Quartile Subgroups	
BIC C_{tau} in Quartile 1 [149, 757.4, 1664.5, 1975.5]	148/149 (99.3%)
BIC C_{tau} in Quartile 2 [141, 1975.7, 2257.2, 2539.8]	138/141 (97.9%)
BIC C_{tau} in Quartile 3 [145, 2540.2, 2774.7, 3118.9]	143/145 (98.6%)
BIC C_{tau} in Quartile 4 [149, 3121.0, 3641.5, 6498.5]	146/149 (98.0%)

**The number in box brackets are number of subjects, minimum values, median values and maximum values, respectively.*

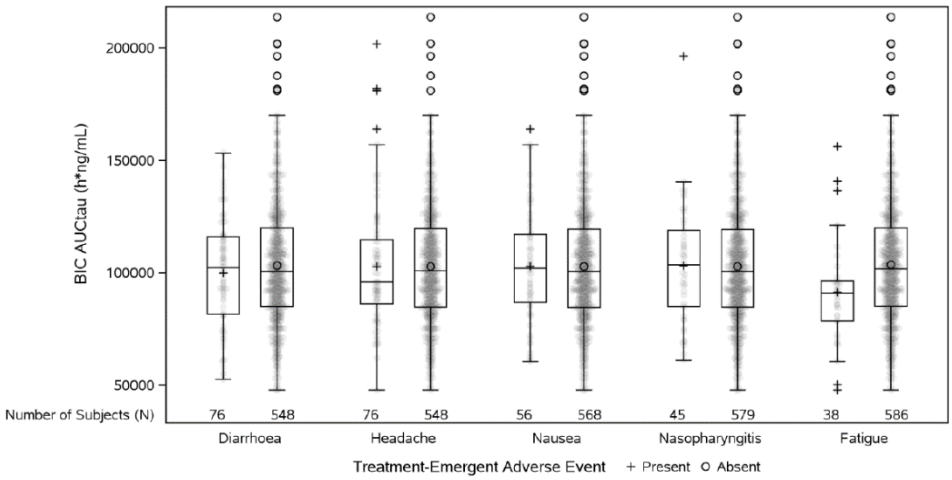
Source: Applicant's summary of clin pharm, Page 116, Table 35

The exposure-safety relationships for BIC were evaluated in ART-naive HIV-infected subjects in Phase 3 studies (Studies 1489 and 1490) who received B/F/TAF using BIC exposure estimates (AUCtau and Cmax) derived from population PK modeling. A total of 624 subjects were included in the exposure-efficacy analysis accounting for 98.4% patients receiving BIC/F/TAF tablets. The safety endpoints were incidence of the 5 most common AEs observed in subjects receiving B/F/TAF in pooled Phase 3 studies. These AEs (incidences) were diarrhea (12.1%), headache (12.0%), nausea (9.0%), nasopharyngitis (7.1%), and fatigue (6.0%). No other AEs with a > 10% incidence occurred.

Figure 4 and Figure 5 present box plots of BIC AUCtau and Cmax, respectively, by presence or absence of common AEs in subjects receiving B/F/TAF. BIC exposures (AUCtau and Cmax) were similar regardless of the presence or absence of the evaluated adverse effect, indicating a lack of

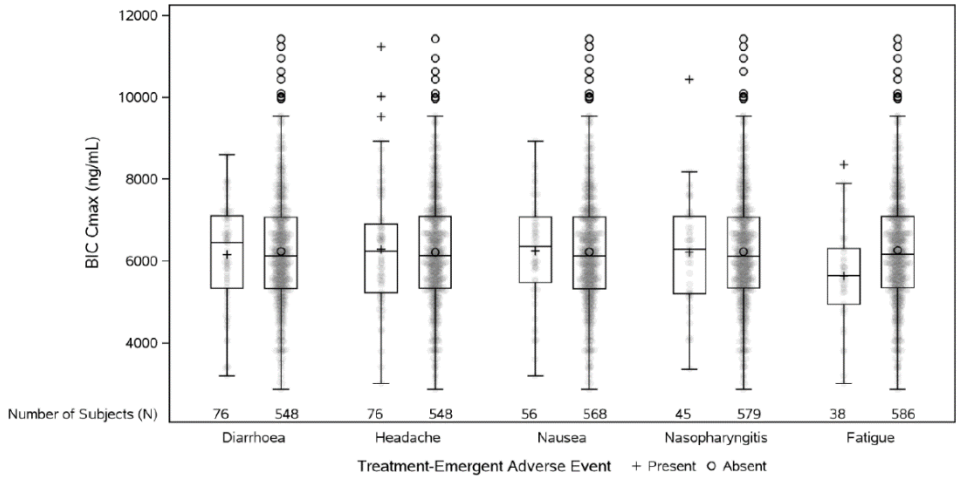
association between BIC exposure and common AEs of diarrhea, headache, nausea, nasopharyngitis, and fatigue.

Figure 4 Box Plots of BIC AUCtau by Presence or Absence of Selected Adverse Events in Phase 3 Studies



Source: Applicant's summary of clin Pharm, Page 123, Figure 11

Figure 5 Box Plots of BIC Cmax by Presence or Absence of Selected Adverse Events in Phase 3 Studies



Source: Applicant's summary of clin Pharm, Page 124, Figure 12

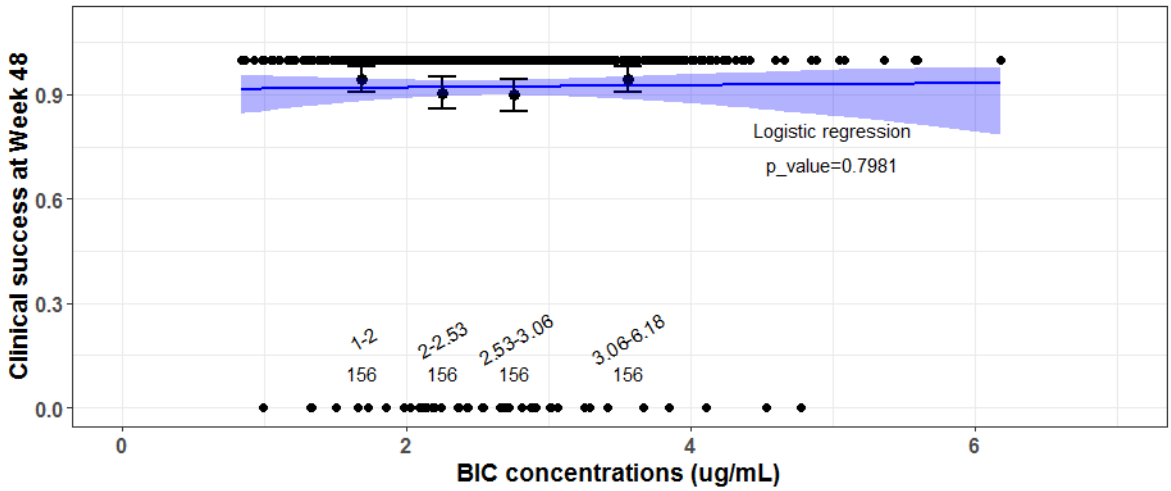
Reviewer's comments: The Reviewer repeated the exposure-efficacy analysis using estimated Ctau and AUCtau from population PK analysis based on two Phase 3 studies (Studies 1489 and 1490) (see equations below). The efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48.

$$AUCtau = \frac{DOSE}{CL}$$

$$Ctau = \frac{F \times DOSE \times Ka}{Vc \times (Ka - \frac{CL}{Vc})} \times (\frac{e^{-\frac{CL}{Vc} \times TIME}}{1 - e^{-\frac{CL}{Vc} \times TIME}} - \frac{e^{-Ka \times TIME}}{1 - e^{-Ka \times TIME}}$$

The Reviewer used the data of integrated summary of efficacy (ISE) and did not exclude the subjects with no virologic data at Week 48, which were considered as non-responder. A total of 624 subjects were included in the exposure-efficacy analysis (a total of 634 subjects were included in ISE dataset but only 624 subjects had PK information based on the population PK analysis).

Figure 6 Exposure-response analysis for efficacy for BIC



Source: Reviewer's analysis

Table 4 Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Population Predicted Quartiles of BIC Exposures in ART-Naive HIV-Infected Subjects based on Studies 1489 and 1490

Quantile of BIC trough concentrations at W 48 (ng/mL)	*No. of subject*	*%patients with HIV-1 RNA levels < 50 copies/mL at Week 48*
Q1 (≥844.2-1998.5)	*156*	*94*
Q2 (≥1998.5 -2531.6)	*156*	*90*
Q3 (≥2531.6-3068.4)	*156*	*90*
Q4 (≥3068.4-6178.2)	*156*	*94*

Source: Reviewer's analysis

A similar analysis was conducted using AUCtau as PK measurement.

Table 5 Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Population Predicted Quartiles of BIC Exposures in ART-Naive HIV-Infected Subjects based on Studies 1489 and 1490

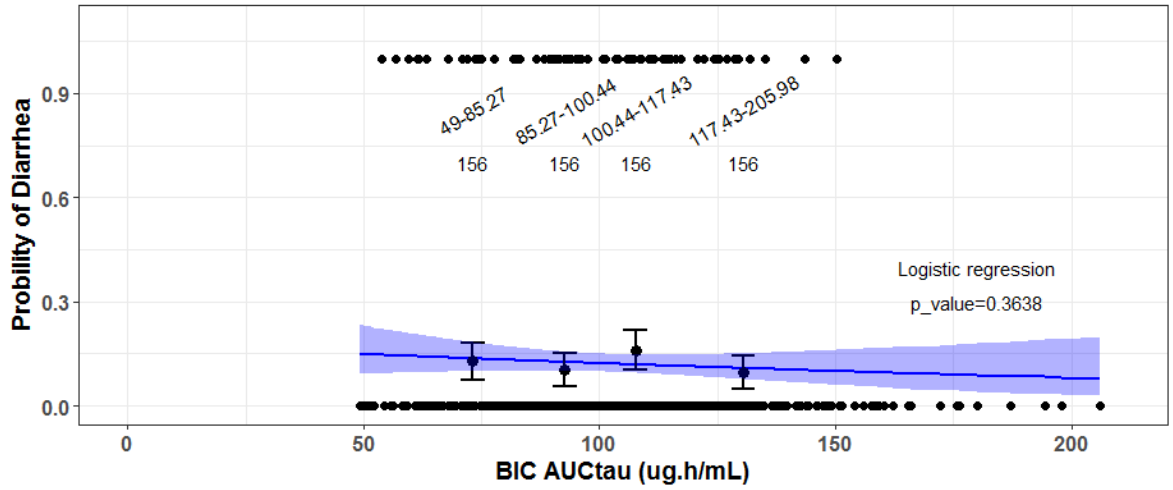
Quantile of BIC AUCtau at Week 4 (ng·h/mL)	*No. of subject*	*%patients with HIV-1 RNA levels < 50 copies/mL Week 48*
Q1 (≥49173.5-85291.0)	*156*	*93*
Q2 (≥85291.0 -100462.8)	*156*	*92*
Q3 (≥100462.8-117682.2)	*156*	*89*
Q4 (≥117682.2-205983.0)	*156*	*94*

Source: Reviewer's analysis

The results confirmed Applicant's analysis that no exposure-response relationship was identified for the primary efficacy endpoint and the response rate was consistently high at four exposure quantiles without consideration of contributions from other drugs in the regimen.

The Reviewer also repeated the exposure-safety analysis using AUCtau estimated from population PK model based on two Phase 3 studies (Studies 1489 and 1490). Two safety endpoints were analyzed including diarrhea and headache, as the event rates of both endpoints were more than 10%. A total of 624 subjects were included in exposure-safety analysis with 76 subjects (12.2%) experiencing diarrhea and 77 subjects (12.3%) experiencing headache in the treatment arm over 48 weeks.

Figure 7 Exposure-response analysis for probability of diarrhea for BIC



Source: Reviewer's analysis

The results suggest no significant exposure-response relationship was identified between AUCtau and probability of diarrhea. A similar result was obtained for probability of headache in which the logistic regression showed that the p value was 0.913.

In summary, the exposure-response relationships for efficacy and safety show the current dose (50 mg) of BIC would provide a sufficient high exposure for efficacy and a reasonable safety profile. As 50 mg

of BIC was the only dose used in the exposure-response analysis, the impact of other dose regimens cannot be evaluated.

INDIVIDUAL REVIEW OF IN VITRO STUDIES

Link to Individual Study Reviews	Title	EDR Link
AD-141-2295	Bi Directional Permeability of BIC through Caco-2 Cell Monolayers	EDR Link
AD-141-2287	In Vitro Protein Binding Determination of BIC by Equilibrium Dialysis	EDR Link
AD-141-2311	Human Hepatic Microsomal Binding of BIC	EDR Link
AD-141-2312	In Vitro Assessment of Blood Distribution of Bictegravir	EDR Link
AD-141-2289	In Vitro Metabolism of BIC in Hepatic Microsomal Fractions	EDR Link
AD-141-2290	Cytochrome P450 Metabolic Reaction Phenotyping of BIC	EDR Link
AD-141-2291	UDP-Glucuronosyl Transferase Phenotyping of BIC	EDR Link
AD-141-2273	In Vitro Inhibition Assessment of BIC with human P-gp and BCRP	EDR Link
AD-141-2274	In Vitro Assessment of BIC Inhibition of Human OATP1B1 and OATP1B3	EDR Link
AD-141-2275	In Vitro Assessment of BIC as a Substrate for Human OATP1B1 and OATP1B3	EDR Link
AD-141-2278	Bidirectional Permeability of BIC Through Monolayers of P-glycoprotein and BCRP Over-expressing Cells	EDR Link
AD-141-2285	In Vitro Assessment of BIC Inhibition of Human OCT2 and MATE1	EDR Link
AD-141-2292	Induction Potential of BIC Assessed In Vitro	EDR Link
AD-141-2293	In Vitro Assessment of Human Cytochrome P450 Inhibition Potential of BIC	EDR Link
AD-141-2294	In Vitro Assessment of Human UGT1A1 Inhibition Potential of BIC	EDR Link
AD-141-2305	Induction Potential of BIC Assessed in Human Hepatocytes	EDR Link
AD-141-2308	In Vitro Assessment of Human Hepatic Microsomal Cytochrome P450 Mechanism-Based Inhibition Potential of BIC	EDR Link
AD-141-2310	In Vitro Inhibition Study of BIC with the human OAT1, OAT3, and BSEP transporters	EDR Link
AD-141-2313	Drug-Drug Interaction Liability Assessment of BIC	EDR Link

Study # (EDR Link)	AD-141-2295 (EDR Link)
Title	Bi Directional Permeability of BIC through Caco-2 Cell Monolayers
Objectives	To assess the absorption potential of BIC by doing bi-directional permeability studies in vitro using monolayers of Caco-2 cells

Methods

Experiments are run using an HBSS donor buffer from Invitrogen containing additional 10mM HEPES, 15mM Glucose with pH adjusted to pH 6.5. The receiver well uses HBSS buffer supplemented with 1% BSA, 10mM HEPES, 15 mM Glucose and the pH adjusted to pH 7.4. After an initial equilibration with donor buffer, transepithelial electrical resistance (TEER) values are read to test membrane integrity. The experiment is started by the addition of donor buffers containing test compounds and 100 µl of solution is taken at 1 and 2 hours from the receiver compartment. Removed buffer is replaced with fresh buffer and a correction is applied to all calculations for the removed material. Each compound is tested in 2 separate replicate wells for each condition. All samples are immediately collected into 400 µl 100% acetonitrile acid to precipitate protein and stabilize test compounds. Cells are dosed on the apical or basolateral side to determine forward (A to B) and reverse (B to A) permeability. Permeability through a cell free trans-well is also determined as a measure of cellular permeability through the membrane and non-specific binding. To test for non-specific binding and compound instability, the total amount of drug is quantitated at the end of the experiment and compared to the material present in the original dosing solution as a percent recovery. Samples are analyzed by LC/MS/MS. The apparent permeability (Papp) and % recovery was calculated using the following equation:

$P_{app} = (dR/dt) X\ Vr/(A\ X\ D_0)$

$\%\ Recovery = 100\ X\ ((V_r\ X\ R_{120}) + (V_d\ X\ D_{120}))/(V_d\ X\ D_0)$

dR/dt is the slope of the cumulative concentration in the receiver compartment versus time in µM/s based on receiver concentrations measured at 60 and 120 minutes.
V_r and V_d is the volume in the receiver and donor compartment in cm^3, respectively.
A is the area of the cell monolayer (0.33 cm^2).
D_0 and D_{120} is the measured donor concentration at the beginning and end of the experiment, respectively.
R_{120} is the receiver concentration at the end of the experiment (120 minutes).

Results

Table 1: Bi Directional Permeability of BIC through Caco-2 Cell Monolayers

Target Conc. (µM)	Direction	Initial Conc. (µM)	Recovery (%)	P_{app} (10^{-6} cm/s)			Efflux Ratio
				R1	R2	Average	
10	Cell-Free	7.5	106.1	26.6	---	26.6	4.4
	Forward	7.9	100.8	7.0	5.4	6.2	
	Reverse	8.5	121.9	23.9	30.5	27.2	
88	Cell-Free	79.1	127.3	26.0	---	26.0	1.5
	Forward	88.1	108.3	11.8	17.8	14.8	
	Reverse	97.6	127.2	18.3	27.0	22.6	

Source: Study Report, Page 8
Note: "R1" and "R2" refers to 2 separate replicate wells

Conclusions

BIC showed high forward permeability through monolayers of Caco-2 cells. Decrease in efflux ratio upon increasing BIC concentration suggests saturable efflux transport.

Study # (EDR Link)	AD-141-2287 (EDR Link)
Title	In Vitro Protein Binding Determination of BIC by Equilibrium Dialysis
Objectives	Assess the extent of protein binding of BIC in plasma from Sprague-Dawley rat, beagle dog, cynomolgus monkey, rhesus monkey and human, and to measure the relative binding in human plasma and cell culture medium by direct competitive dialysis

Methods

Equilibrium dialysis assay: Pooled plasma (from at least 3 males and 3 females) was used from Sprague-Dawley rat, beagle dog, cynomolgus monkey, rhesus monkey, and human. Sodium EDTA was used as the anticoagulant. The cell culture media (CCM) had the same composition as that used for cell-based antiviral potency assays.

Plasma protein binding assay: Equilibrium dialysis was conducted at 37°C using Sprague-Dawley rat, beagle dog, cynomolgus monkey, rhesus monkey, and human plasma spiked with BIC at final concentrations of 2 μM. The dialysis was performed in triplicate for 3 hours. Prior to the study, dialysis membrane was soaked for approximately one hour in 0.133 M phosphate buffer, pH 7.4. Spiked plasma (1 mL) and compound-free phosphate buffer (1 mL) were placed into opposite sides of the assembled dialysis cells. The dialysis cells were rotated slowly in a 37°C water bath for 3 hr. For assessment of recovery, plasma samples were drained into pre-weighed polypropylene tubes containing 1 mL of buffer, and buffer samples were drained into pre-weighed tubes containing 1.0 mL of blank plasma of the matching species. Post-dialysis plasma and buffer weights were measured and recorded for calculations.

Competitive protein binding assay: Competitive equilibrium dialysis was conducted at 37°C with opposed dialysis cells containing 100% human plasma or CCM containing 10% FBS. Both matrices were spiked with BIC to the final concentrations of 2 μM. Prior to the study, dialysis membrane was soaked for approximately one hour in 0.133 M phosphate buffer, pH 7.4. Spiked plasma (1 mL) and CCM (1 mL) were placed into opposite sides of the assembled dialysis cells and dialysis was allowed to continue for 24 hours with gentle rotation. For assessment of recovery, plasma samples were drained into pre-weighed polypropylene tubes containing 1 mL of CCM (without compound) and CCM samples were drained into pre-weighed tubes containing 1 mL of related blank plasma. Post-dialysis plasma and CCM weights were measured and recorded for calculations. Samples were deproteinated by treatment with four volumes of [redacted] (b) (4) as the LC-MS internal standard. Samples were centrifuged 15,000 rpm at 4°C for 15 min and aliquots of the supernatant were subject to LC-MS/MS.

The % unbound of BIC in plasma dialyzed against phosphate buffer were calculated as follows:

% unbound= 100 X (C_f/C_t) where C_f is the post-dialysis buffer concentration and C_t is the post dialysis cell culture medium or plasma concentration, respectively. The relative binding of an analyte in plasma and CCM, determined by competitive equilibrium dialysis was calculated as C_{plasma}/C_{CCM} where C_{plasma} and C_{CCM} are the corrected post-dialysis concentrations in plasma and CCM, respectively.

Results

Table 1: Protein Binding of BIC in Plasma from Different Species

Matrix	Conc. (µM) [a]	Free Fraction (%)[b]	Study
Human Plasma	2	0.25 ± 0.01	QPS# 60D-1333
Beagle Dog Plasma	2	1.24 ± 0.06	
Sprague-Dawley Rat Plasma	2	0.01 ± 0.00	
Cynomolgus Monkey Plasma	2	0.31 ± 0.01	
Rhesus Monkey Plasma	2	0.32 ± 0.02	

a Initial concentration in protein-containing dialysis cell

b Mean ± Standard Deviation (n = 3)

Source: Study Report, Page 9

Table 2: Relative Protein Binding of BIC in CCM and Human Plasma

Matrices	Conc. (µM) [a]	Ratio[b]	Mean Ratio[c]	Study
CCM to Human Plasma shift	2	37.2	43.6 ± 7.7	Gilead# 130606-402
		41.5		Gilead# 130607-403
		52.2		Gilead# 130621-406

a Initial concentration in protein-containing dialysis cell

b Values are mean (n = 2)

c Values are the mean ± standard deviation of 3 determinations.

Source: Study Report, Page 9

Conclusions

At a concentration of 2 µM, the free fraction of BIC in human plasma is 0.25 %.

Study # (EDR Link)	AD-141-2311 (EDR Link)
Title	Human Hepatic Microsomal Binding of BIC
Objectives	Assess the free fraction of 3 µM BIC in the presence of human hepatic microsomal fraction (0.5 mg/mL)

Methods

Pooled human hepatic microsomal fraction was diluted to 0.5 mg protein/mL with 0.1 M potassium phosphate buffer, pH 7.4. BIC or quality control (amitriptyline; used as positive control because it is highly bound to microsomes) was added to a final concentration of 3 µM (final DMSO concentration 0.5% v/v). This solution was then dialyzed in duplicate against an equal volume of 0.1 M potassium phosphate buffer, pH 7.4. The apparatus was a HT Dialysis HTD 96 (Teflon 96-well micro-equilibrium device) with regenerated cellulose membrane strips pre-soaked in buffer before use. After equilibration overnight at 37°C, under an atmosphere of 5% (v/v) CO_2 at 95% humidity, the concentrations of compound in the buffer and microsomal fraction were determined by LC/MS/MS.

The proportion unbound in the microsomal fraction was determined from the ratio of the concentration of the compound in buffer to that in the microsomal fraction ($f_u = C_{buffer}/C_{microsomal\ fraction} X100$).

Results

Table 1: Fraction Unbound of BIC and Amitriptyline in Human Hepatic Microsomal Fraction

Compound	Identity	Fraction Unbound (%)			Recovery (%)
		Rep. 1	Rep. 2	Mean	
Bictegravir	Test compound	82.9	89.7	86.3	80.9
Amitriptyline	Quality control compound	24.5	25.6	25.0	71.9

Compound concentration was 3 µM and microsomal fraction concentration was 0.5 mg/mL

Source: Study Report, Page 8

Conclusions

Bictegravir exhibited low propensity to bind to human hepatic microsomal fraction (mean unbound fraction 86.3%) and therefore, not anticipated to significantly affect the prediction of intrinsic clearance of BIC.

Study # (EDR Link)	AD-141-2312 (EDR Link)
Title	In Vitro Assessment of Blood Distribution of Bictegravir
Objectives	Determine the blood/plasma concentration ratio of BIC in rat, dog, cynomolgus monkey, rhesus monkey and human

Methods

Heparinized blood samples from Sprague-Dawley rat, beagle dog, cynomolgus monkey, rhesus monkey and human ($n \geq 3$) were obtained and the hematocrit values determined. Reference plasma and reference cell fractions were then prepared by centrifugation. Bictegravir or positive controls were incubated in triplicate, at an initial concentration of 0.5 µM (except for chlorthalidone, 10 µM), with blood or reference plasma or reference cell fraction for 60 min at 37°C and then chilled on ice. Blood samples were then centrifuged at 4°C to separate the cellular and soluble fractions. Concentrations of compound in the reference plasma samples, reference cell samples, plasma fractions from blood, and cellular fractions from blood were then determined by LC-MS/MS after deproteination with ice cold methanol. Blood cell fractions were first lysed by three cycles of freeze-thaw.

Blood/Plasma concentration ratio (CPR) and whole blood/plasma concentration ratios (λ) were calculated using the following equations:

$$CPR = {}^{Cell}/_{RBC} \bullet {}^{Plasma}/_{Sol}$$

$$\lambda = CPR \bullet H + (1 - H)$$

Cell	Concentration in the cellular fraction from incubated blood
RBC	Concentration in reference cell fraction
Sol	Concentration in the soluble fraction from incubated blood
Plasma	Concentration in the reference plasma fraction
H	Hematocrit

Results

Table 1: Blood Cell/Plasma Concentration Ratios (CPR) and Whole Blood/Plasma Concentration Ratios (λ) for BIC and Controls (Mean ± SD, n = 3)

	Bictegravir		Control	
Species	**CPR**	**λ**	**Compound**	**λ**
Sprague-Dawley Rat	0.05 ± 0.02	0.58 ± 0.01	Chlorthalidone	35.0 ± 6.1
Beagle Dog	0.17 ± 0.06	0.60 ± 0.03	Chloroquine	4.3 ± 0.7
Cynomolgus Monkey	0.14 ± 0.02	0.65 ± 0.01	Methazolamide	60.7 ± 13.7
Rhesus Monkey	0.11 ± 0.05	0.62 ± 0.02	Methazolamide	107.9 ± 30.0
Human	0.19 ± 0.07	0.64 ± 0.03	Methazolamide	9.0 ± 8.0

Source: Study Report, Page 8

Conclusions

At a concentration of 0.5 µM, the whole blood/plasma ratio in human blood is 0.64.

Study # (EDR Link)	AD-141-2289 (EDR Link)
Title	In Vitro Metabolism of BIC in Hepatic Microsomal Fractions
Objectives	Predict the hepatic metabolic clearance of BIC by assessing the rate of metabolism in pooled hepatic microsomal fractions prepared from Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, rhesus monkeys and humans

Methods

Pooled hepatic microsomes were diluted in 0.1 mM potassium phosphate buffer to 1.0 mg/mL final protein concentration. Alamethicin was added to the microsomal fraction to permeabilize the membrane to allow access of the UDP-glucronic acid (UDPGA) co-substrate to the active site of the UDP glucuronosyl transferase (UGT) enzymes. The final concentration was 25 µg/mL (ratio 25 µg alamethicin/mg microsomal protein) and the microsomes were then placed on ice for 15 min prior to the start of the reaction. [^{3}H] BIC was added to a final concentration of 1 µM (final ethanol concentration 0.5% v/v). GS-9160, known to be metabolized by oxidative and UGT enzymes, was used as a positive control substrate. The metabolic reaction was warmed to 37°C and initiated by the addition of a cofactor mix that consisted of 1.55 mM NADP, 3.3 mM glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 5 mM UDP-glucuronic acid and 3.3 mM MgCl2, all dissolved in 0.1 M potassium phosphate buffer. Aliquots were removed after 2, 12, 25 45 and 65 min and quenched by the addition of 2 volumes of 0.1% (v/v) trifluoroacetic acid (TFA) in 5% water / 95% acetonitrile (v/v). The samples were mixed for 10 min and then centrifuged at 3000 □□g for 60 min. An aliquot of the supernatant was analyzed.

Metabolic stabilities in microsomal fractions were determined by measuring the rates of appearance of radiolabeled metabolites (novel radiolabeled peaks) from the tritiated BIC substrate. The area of the parent peak determined at each time point was expressed as a percentage of the total area of (metabolite peaks + parent peak) at that time point.

% of parent remaining at time t (C_t) was calculated from the following equation:

$C_t = 100\% \times A_p / (A_m + A_p)$, where

A_p parent peak area at time t

A_m total peak area of all metabolites formed at time t

Data (% of parent remaining) were plotted on a semi log scale and fitted using an exponential decline model:

$C_t = C_0 \bullet e^{-K \bullet t}$, where

C_t % of parent remaining at time = t

C_0 % of parent remaining at time = 0

t time

K First order elimination rate constant

The intrinsic hepatic clearance was calculated as follows:

$CL_{int} = {}^{K \bullet V \bullet Y}/_{P}$, where

CL_{int} Intrinsic hepatic clearance (L/hr/kg body weight)

V Incubation volume (L)

Y Microsome protein yield (mg protein/kg body weight)

P Mass of protein in the incubation (mg)

Table 1: Values Used for Calculation of the Predicted Hepatic Clearance from Microsomal Stability

Species	Hepatic Microsomes			Q_h (L/hr/kg)
	V (L)	P (mg)	Y (mg/kg)	
Sprague-Dawley Rat	0.001	1.0	1800	4.2
Beagle Dog	0.001	1.0	1440	1.8
Cynomolgus Monkey	0.001	1.0	810	1.6
Rhesus Monkey	0.001	1.0	1350	2.3
Human	0.001	1.0	1160	1.3

Source: Study Report, Page 8

The hepatic clearance was predicted using the following equation:

$$CL_h = (CL_{int} \bullet Q_h)/(CL_{int} + Q_h)$$, where

CL_h Predicted hepatic clearance (L/hr/kg body weight)

CL_{int} Intrinsic hepatic clearance (L/hr/kg body weight)

Q_h Hepatic blood flow (L/hr/kg body weight)

Results

Table 2: In Vitro Metabolism of BIC in Hepatic Microsomes

Species	$t_{½}$ (min)	Predicted Hepatic Cl (L/hr/kg)	Predicted Hepatic Extraction (%)
Sprague-Dawley Rat	49	1.21	29
Beagle Dog	108	0.29	16
Cynomolgus Monkey	63	0.43	27
Rhesus Monkey	76	0.41	18
Human	194	0.17	13

Source: Study Report, Page 9

Conclusions

Based on the predicted hepatic extraction ratio (13 %), BIC is a low extraction ratio drug, and therefore, its elimination is expected to be affected by fraction unbound and the hepatic intrinsic clearance.

Study # (EDR Link)	AD-141-2290 (EDR Link)
Title	Cytochrome P450 Metabolic Reaction Phenotyping of BIC
Objectives	Determine the potential for major human cytochrome P450 enzymes to metabolize BIC

Methods

BIC (final concentration 2 μM) or positive controls were incubated with individual CYP preparations (final CYP concentrations 100 pmol/mL) in 0.1 M phosphate buffer pH 7.4. They were pre-incubated at 37°C prior to the addition of NADPH (final concentration 1.3 mM) to initiate the reaction. Incubation of BIC was also performed using control insect cell microsomal fraction (no CYP enzymes present) to reveal any non-CYP degradation. The final incubation volume was 250 μL. Positive control substrates were incubated at the approximate K_M for their metabolism and were phenacetin (40 μM), bupropion (40 μM), paclitaxel (10 μM), diclofenac (4 μM), S mephenytoin (30 μM), dextromethorphan (5 μM) or terfenadine (2.5 μM).

For positive controls, aliquots were removed after incubation for 0, 15, 30 and 45 min at 37°C. The reactions were stopped by the addition of a mixture of (b) (4) containing the LC-MS internal standard (IS). For incubations with tritiated BIC, aliquots were removed after incubation for 0 and 45 min. The reactions were stopped by the addition of a mixture of acetonitrile, water and trifluoroacetic acid (TFA) (95: 4.9: 0.1 v/v/v). Following protein precipitation and centrifugation, the positive control sample supernatants were analyzed by specific LC-MS/MS methods, and the peak area ratio of the analyte to that of the IS was used for quantification. For tritiated BIC, supernatants were analyzed by LC-radiochromatography and the peak area of radioactivity was used for quantification.

Formation of radioactive metabolites from tritiated BIC was quantified using the following equation: % metabolite formation=100 % X (metabolite peak area at 45 min/sum of all peak areas at 45 min).

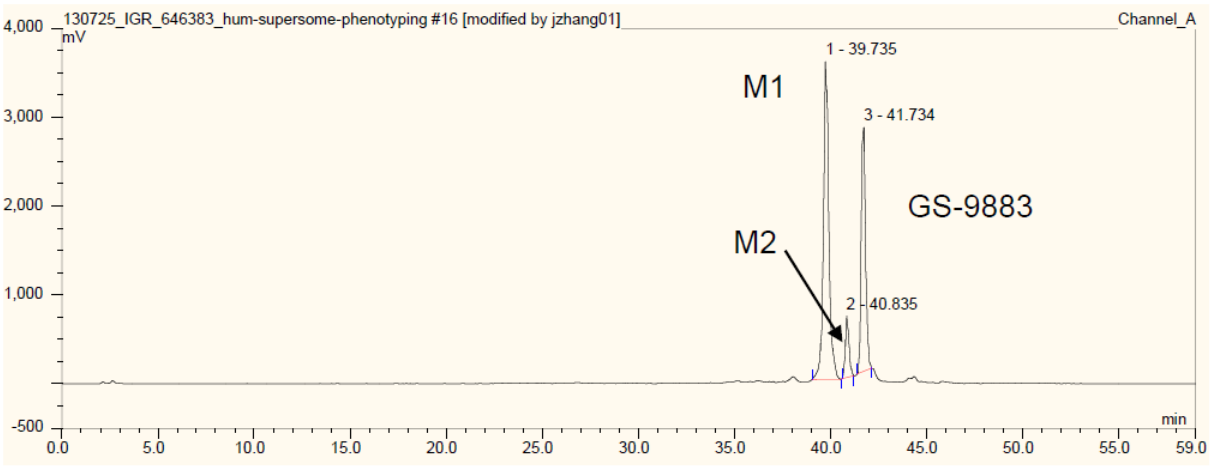
For metabolism of the positive controls, either the rate of metabolite formation or the percent remaining of the control substrate were calculated by the following equations:

Rate of metabolite formation: (Metabolite peak area ratio (PAR) at 45 minutes-metabolite PAR at 0 minutes)/45 minutes

Percent of control substrate remaining: 100 % X (substrate PAR at 45 minutes/substrate PAR at 0 minutes)

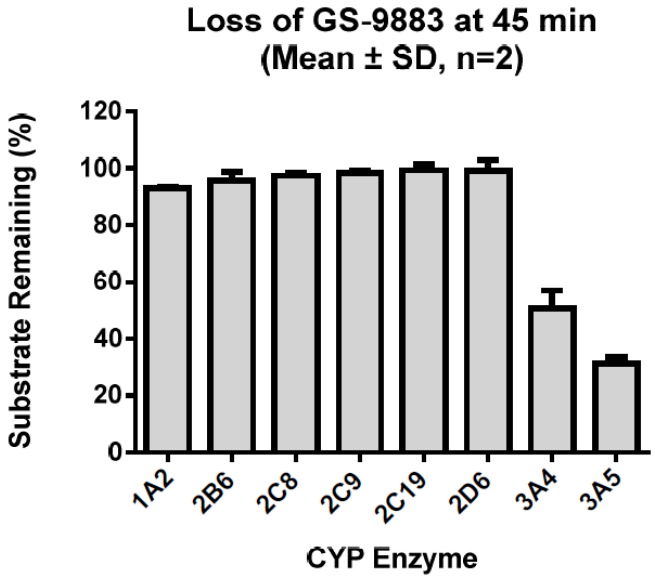
Results

Fig 1: Radiochromatogram of Metabolized[^{3}H-BIC]



Source: Study Report, Page 8

Fig 2: Comparison of Extent of Metabolism of BIC by Recombinant CYP Enzymes



Source: Study Report, Page 12

Table 1: Rates of Metabolism of Control Substrates and Generation of Metabolites from BIC by Major Human CYP enzymes

Enzyme	Positive Control Metabolism			GS-9883 Metabolism	
	Substrate	Rate of metabolite formation (min^{-1})	Loss of parent at 45 min	% M1 at 45 min	% M2 at 45 min
CYP1A1	Phenacetin	--	6.8%	ND	ND
CYP2B6	Bupropion	0.141	--	ND	ND
CYP2C8	Paclitaxel	0.008	--	ND	ND
CYP2C9	Diclofenac	0.004	--	ND	ND
CYP2C19	S Mephenytoin	0.020	--	ND	ND
CYP2D6	Dextromethorphan	0.014	--	ND	ND
CYP3A4	Terfenadine	0.032	--	39	1.9
CYP3A5	Terfenadine	0.032	--	55	7.0

ND = not detected

Source: Study Report, Page 9

Note: There appears to be an error in the listing of enzymes (first column from the left) in the table above. Instead of "CYP1A1", the table should state "CYP1A2" considering phenacetin is a substrate of CYP1A2.

Conclusions

BIC is metabolized by CYP3A4/5 and two metabolites of BIC (M1 and M2) were detected after incubation with CYP3A4 and CYP3A5. BIC is not a substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 enzymes.

Study # (EDR Link)	AD-141-2291 (EDR Link)
Title	UDP-Glucuronosyl Transferase Phenotyping of BIC
Objectives	Determine the potential for major human UDP glucuronosyl transferase enzymes to metabolize BIC

Methods

Individual Supersome preparations (final concentrations 2 mg protein/mL) were diluted in 0.1 M potassium phosphate buffer pH 7.4. BIC (final substrate concentration 5 µM) or control substrates were added and the metabolic reactions initiated by the addition of the co-substrate, UDP-glucuronic acid (final concentration 2 mM). Positive control substrates were raloxifene (3 µM), trifluoperazine (3 µM), 7-hydroxy-coumarin (10 µM), 4-hydroxyestradiol (10 µM) or scopoletin (10 µM). Aliquots were removed after 0 and 65 min at 37°C. The reactions were stopped by the addition of a mixture of (b) (4) containing internal standard. Following protein precipitation and centrifugation, the sample supernatants were analyzed by LC-MS/MS.

Analysis of BIC glucuronides was achieved by targeted scanning for an analyte with the appropriate mass and fragmentation. BIC ($C_{21}H_{18}F_3N_3O_5$) has a monoisotopic mass of 449.12 Da. A direct glucuronide of GS-9883 (parent mass + 176) would have a monoisotopic mass of 625.12 Da. The mass spectrometer was thus set to quantify $[M+H]^+$ ions of the glucuronide precursors and the corresponding product masses from loss of the glucuronide moiety. Because no BIC glucuronide standard was available, the peak area ratio was used to quantify the generation of the glucuronide of BIC, to allow comparison of the rates between the tested enzymes. For metabolism of the positive controls, the turnover is reported as the fraction of substrate remaining after 60 min incubation, compared to that at zero time.

Results

Table 1: Rates of Metabolism of Control Substrates and of Formation of BIC Glucuronide by Major Human UGT Enzymes

Enzyme	Positive Control	Positive control (% remaining at 60 min)	Glucuronide formation of GS-9883 ($PAR^1 \times 10^{-3}$ at 60 min)
UGT1A1	Raloxifene	26	12.0
UGT1A3	Raloxifene	52	1.0
UGT1A4	Trifluoperazine	69	ND
UGT1A6	7-Hydroxycoumarin	< 10	ND
UGT1A7	7-Hydroxycoumarin	33	ND
UGT1A8	7-Hydroxycoumarin	74	1.0
UGT1A9	7-Hydroxycoumarin	< 10	3.0
UGT1A10	Raloxifene	12	ND
UGT2B4	4-Hydroxyestradiol	45	ND
UGT2B7	4-Hydroxyestradiol	< 10	ND
UGT2B15	Scopoletin	< 10	ND
UGT2B17	4-Hydroxyestradiol	42	ND

ND = Not detected

1 PAR = Peak area ratio of analyte to internal statndard

Source: Study Report, Page 8

Conclusions

Of the 12 human UGT enzymes tested, UGT1A1 is the major isoform for the glucuronidation of BIC. BIC was not a substrate for recombinant human UGT 1A4, 1A6, 1A7, 1A10, 2B4, 2B7, 2B15 or 2B17. There was very slow turnover by UGT1A3, 1A8 and 1A9.

Study # (EDR Link)	AD-141-2273 (EDR Link)
Title	In Vitro Inhibition Assessment of BIC with human P-gp and BCRP
Objectives	Assess the inhibition of P-gp and BCRP by BIC in vitro using cell lines transfected with individual transporters and fluorescent model substrates

Methods

MDCKII cells were maintained in Dulbecco's Modification of Eagle's Medium (DMEM) with sodium pyruvate, Glutmax, 1% Pen/Strep, and 10% fetal bovine serum in an incubator set at 37° C, 90% humidity and 5% CO_2. MDCKII cells were seeded in 96-well black cell culture plates with clear bottoms at densities of 5 x 10^4 cells/well for Pgp and 2 x 10^4 cells/well for BCRP and grown to confluence. For the Pgp assay, test compounds were serially diluted in DMSO and then spiked into cell culture medium (without fetal bovine serum[FBS]) containing 10 µM calcein AM and incubated for 1 hour. Following the removal of media containing calcein AM and test compound, cells were washed five times with 1M PBS buffer containing magnesium and calcium. Wells were immediately analyzed for calcein fluorescence at an excitation of 494 nm and an emission of 517 nm. For the BCRP assay, test compounds were serially diluted with DMSO and then spiked in cell culture medium (without FBS) containing 1 µM pheophorbide A (PhA) and incubated for 18 hours with MDCKII-BCRP cells. Following the removal of media containing PhA and test compound, cells were then washed five times with 1M PBS buffer containing magnesium and calcium. Wells were immediately analyzed for PhA fluorescence at an excitation of 415 nm and an emission of 675 nm.

The dose-dependent inhibition of Pgp-mediated efflux of calcein-AM and BCRP-mediated efflux of PhA by BIC was tested at six concentrations ranging from 0.33 to 80 µM. The % inhibition was calculated as follows:

$$\textbf{Ratio (R)} = TF_{Pgp} / TF_{WT}$$

$$\textbf{Ratio (R)} = TF_{BCRP} / TF_{WT}$$

$$\textbf{\% Inhibition} = ((R^{I} - R^{NI}) / (1 - R^{NI})) \times 100\%$$

Where,

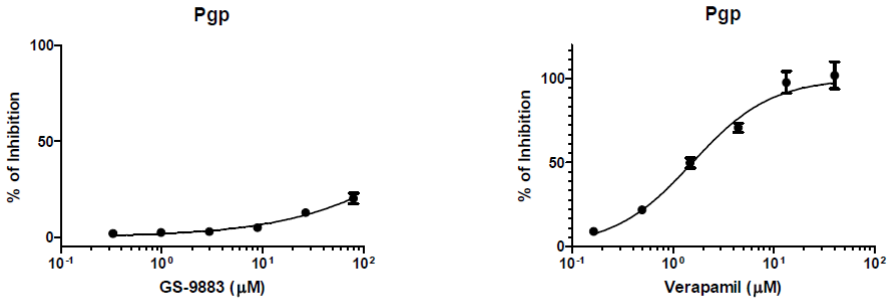
TF is total fluorescence

$\mathbf{R^{I}}$ and $\mathbf{R^{NI}}$ represent the ratio observed in the presence and absence of test compound, respectively.

IC_{50} (defined as the test article concentration needed to inhibit the maximal transporter specific transport by 50 %) values were calculated using non-linear fitting of % inhibition versus concentration to a sigmoidal curve with a variable Hill Coefficient.

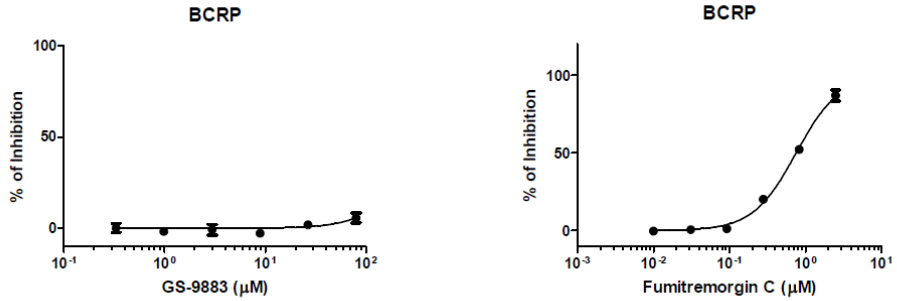
Results

Fig 1: Inhibition of P-gp Mediated Transport of 10 µM Calcein-AM by BIC and Verapamil (graph shows average of duplicate measurements from two independent assays)



Source: Study Report, Page 9

Fig 2: Inhibition of BCRP-Mediated Transport of 1 µM Pheophorbide A by BIC and Fumitremorgin C (graph shows average of duplicate measurements from two independent assays)



Source: Study Report, Page 9

Table 1: Inhibition of P-gp Mediated Transport of Calcein AM and BCRP-Mediated Transport of Pheophorbide A by BIC and Control Compounds (graph shows average of duplicate measurements from two independent assays)

	Efflux Transporters IC_{50} (µM)	
Transporters	**Pgp**	**BCRP**
GS-9883	> 80	> 80
Verapamil	1.6 ± 0.27	N/A
Fumitremorgin C (FTC)	N/A	0.76 ± 0.04

Source: Study Report, Page 8

Conclusions

BIC showed weak dose-dependent inhibition of Pgp-mediated Calcein AM transport with 20 % inhibition observed at the highest concentration tested (80 µM). BIC showed 6 % inhibition of BCRP-mediated pheophorbide A (PhA) transport at 80 µM. The applicant assessed the drug-drug interaction liability of BIC (AD-141-2313) and the results indicate at the steady state C_{max} of BIC observed after multiple dose administration of BIC/F/TAF (~14 µM), BIC is not expected to inhibit P-gp transporters.

Study # (EDR Link)	AD-141-2274 (EDR Link)
Title	In Vitro Assessment of BIC Inhibition of Human OATP1B1 and OATP1B3
Objectives	Assess the inhibition of the solute carrier (SLC) influx transporters OATP1B1 and OATP1B3 by BIC *in vitro* using cell lines transfected with the individual transporters and fluorescent model substrates.

Methods

Chinese Hamster Ovary (CHO) cells, either wild type or transfected with the genes encoding human OATP1B1 and OATP1B3, were maintained in Dulbecco's Modification of Eagle's Medium (DMEM) containing 1,000 mg / L D-glucose, L-glutamine, 25 mM HEPES buffer, and 110 mg/L sodium pyruvate, 1% Pen/Strep, 10% fetal bovine serum, 0.05 mg / mL L-proline and 0.5 mg / mL of geneticin G-418. Cells were maintained in incubators set at 37ºC, 90 % humidity and 5 % CO_2. OATP1B1 and OATP1B3 overexpressing cells were seeded in BioCoat Poly-D-Lysine coated 96 well black cell culture plates with clear bottoms at a density of 1 x 10^5 cells/well. Sodium butyrate (10 mM) was added to the OATP1B1 and OATP1B3 cells to increase the protein expression level, and the cells were grown to confluence overnight. The assay buffer contained 142 mM NaCl, 5 mM KCl, 1 mM KH_2PO_4, 1.2 mM $MgSO_4$, 1.5 mM $CaCl_2$, 5 mM Glucose and 12.5 mM HEPES (pH 7.4). After removal of the media and before adding test compounds, the cells were washed twice with 37ºC assay buffer followed by a 0.5 h pre-incubation with assay buffer. Test compounds were serially diluted in DMSO at 250 fold of final test concentrations to create the compound spiking solutions. Compounds were then spiked into assay buffer containing 2 µM Fluo 3 and incubated with cells for 1 h. Following removal of assay buffer containing Fluo 3 and test compound, cells were washed 3 times with 200 µl of ice cold assay buffer and then lysed at room temperature for 15 minutes in a lysis buffer containing 0.05 % SDS in a 1 mM $CaCl_2$ solution. Wells were analyzed for Fluo 3 fluorescence at an excitation of 485 nm and emission of 530 nm.

Cell viability was monitored, and calculated as % fluorescence in WT cells as follows:

$$\% \text{ viability} = [(TF\ WT_I) / (TF\ WT_{NI})] \times 100\ \%$$

Where,

WT_I represents the fluorescence in the presence of test article for wild type cells

WT_{NI} represents the fluorescence in the absence of test article for wild type cells.

The % transport inhibition by test article was calculated as follows:

$$\% \text{ inhibition} = (1 - ((OATP_I - WT_{NI}) / (OATP_{NI} - WT_{NI})) * 100$$

Where,

$OATP_I$ represents the fluorescence in the presence of test article for either OATP1B1 or OATP1B3 overexpressing cells.

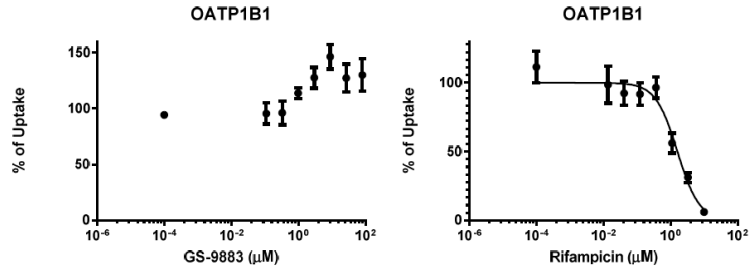
$OATP_{NI}$ represents the fluorescence in the absence of test article for either OATP1B1 or OATP1B3 overexpressing cells.

WT_{NI} represents the fluorescence in the absence of test article for wild type cells.

IC_{50} (defined as the test article concentration needed to inhibit the maximal transporter specific transport by 50 %) values were calculated using non-linear fitting of % inhibition versus concentration to a sigmoidal curve with a variable Hill Coefficient.

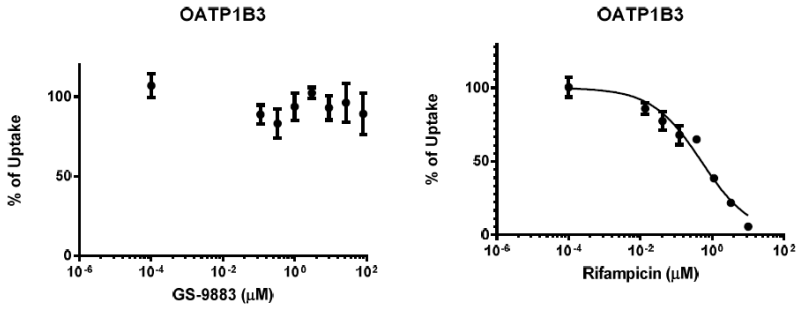
Results

Fig 1: Inhibition of OATP1B1 Mediated Transport of 2 µM Fluo 3 in CHO Cells by BIC and Positive Control Rifampin (graph shows average of duplicate measurements from two independent assays)



Source: Study Report, Page 9

Fig 2: Inhibition of OATP1B3 Mediated Transport of 2 µM Fluo 3 in CHO Cells by BIC and Positive Control Rifampin (graph shows average of duplicate measurements from two independent assays)



Source: Study Report, Page 9

Table 1: Inhibition of OATP1B1/1B3 Mediated Transport of Fluo 3 by BIC and Rifampin (Control Compound)

Compounds	Uptake Transporters IC_{50} (µM)	
	OATP1B1	OATP1B3
GS-9883	> 80	> 80
Rifampicin	1.6 ± 0.6	0.49 ± 0.19

Source: Study Report, Page 8

Conclusions

BIC did not show dose dependent inhibition of OATP1B1 and OATP1B3 when tested up to 80 µM.

Study # (EDR Link)	AD-141-2275 (EDR Link)
Title	In Vitro Assessment of BIC as a Substrate for Human OATP1B1 and OATP1B3
Objectives	Assess whether BIC is a substrate for the uptake transporters OATP1B1 and OATP1B3 using nontransfected and transfected Chinese Hamster Ovary (CHO) cells

Methods

CHO cells, either wild type or transfected with the genes encoding human OATP1B1 and OATP1B3, were maintained in Dulbecco's Modification of Eagle's Medium (DMEM) containing 1,000 mg/L D-glucose, L-glutamine, 25 mM HEPES buffer, and 110 mg/L sodium pyruvate, 1% Pen/Strep, 10% fetal bovine serum, 0.05 mg / mL L-proline and 0.5 mg/mL of geneticin G-418. Cells were maintained in incubators set at 37ºC, 90% humidity and 5% CO_2.

On the day before the assay, 10 mM sodium butyrate was added to the OATP1B1 and OATP1B3 cells to increase the protein expression level and cells were grown to confluence overnight. The assay buffer contained 142 mM NaCl, 5 mM KCl, 1 mM KH_2PO_4, 1.2 mM $MgSO_4$, 1.5 mM $CaCl_2$, 5 mM Glucose and 12.5 mM HEPES (pH7.4). After removal of the media, cells were washed with 1x PBS and treated with 5 mL of 0.05% trypsin. The cells were then resuspended with 37 C assay buffer at 3 x 10^6 cells/mL and 100 µL of the cell suspension was aliquotted to each well on a 48 well plate for a 30 min pre-incubation at 37 C. All test compounds were diluted to 3 fold of final target concentration in assay buffer and equilibrated at 37 C for 30 min. The assay was started by adding 50 µL of test compound solution to the 48-well plate containing cell suspension, mixed and incubated at 37ºC for 1 min. The respective dilution factors take the cell density to 2 x 10^6 cells/mL and the compound test concentration to the targeted level. The entire reaction mixture was overlaid onto pre-prepared microcentrifuge tubes containing 100 µL of aqeuous solution (bottom layer) and100 µL of filtration oil (middle layer; 74.5:25.5 silicon oil:mineral oil mix) and then centrifuged immediately at 13,000g for 30 sec. The samples were frozen overnight in -80ºC freezer. Using a tubing cutter, the microcentrifuge tubes were cut in the middle and the bottom layer is collected in an eppendorf tube. Samples were extracted with organic solvents for analysis by LC/MS/MS.

The rate of uptake into cells was determined by the following formula:

Rate of uptake = [(concentration of compound in cell lysate) * volume of sample] /

[Incubation time (minute) * millions of cells in sample]

All compounds were evaluated in the presence and absence of 40 µM rifampicin, a known OATP inhibitor. BIC was assessed at 1 µM, a value >10-fold lower than the previously determined IC_{50} (> 80 µM; results from study AD-141-2274).

Results

Table 1: Uptake Rates and Ratios for BIC and Control Compounds in Non-Transfected and transfected CHO Cells

Uptake Rate (pmole/minute/1.0x10^6 cells)	GS-9883 1.0 µM	Atorvastatin 0.1 µM	Antipyrine 10µM
CHO-WT	48	1.2	31
CHO-OATP1B1	43	5.1	32
CHO-OATP1B3	41	5.3	32
OATP1B1 / WT Ratio	0.9	4.4	1.0
OATP1B3 / WT Ratio	0.9	4.5	1.0

Source: Study Report, Page 9

Table 2: Uptake Rates for BIC and Control Compounds in Non-Transfected and transfected CHO Cells in the presence of 40 µM Rifampicin

Uptake Rate (pmole/minute/1.0x10^6 cells)	GS-9883 1.0 µM	Atorvastatin 0.1 µM	Antipyrine 10µM
CHO-WT	33	0.9	29
CHO-OATP1B1	39	1.1	38
CHO-OATP1B3	36	1.2	35

Source: Study Report, Page 9

Table 3: Uptake Ratios for BIC and Control Compounds in Non-Transfected and transfected CHO Cells in the presence of 40 µM Rifampicin

Uptake Ratio Cpd alone / cpd+rifampicin	GS-9883 1.0 µM	Atorvastatin 0.1 µM	Antipyrine 10µM
CHO-WT	1.4	1.3	1.1
CHO-OATP1B1	1.1	4.5	0.8
CHO-OATP1B3	1.1	4.6	0.9

Source: Study Report, Page 9

Conclusions

BIC did not appear to be a substrate of OATP1B1 and OATP1B3. The rate of uptake of BIC in CHO-OATP1B1 and CHO-OATP1B3 cells was comparable to the rate of uptake in non-transfected cells. Further, the rate of uptake was not significantly affected in any cell lines with addition of rifampicin, a known inhibitor of OATP1B1.

Study # (EDR Link)	AD-141-2278 (EDR Link)
Title	Bidirectional Permeability of BIC Through Monolayers of P-glycoprotein and BCRP Over-expressing Cells
Objectives	To determine if BIC is a substrate for P-gp and/or BCRP

Methods

MDCKII cells were maintained in Dulbecco's Modification of Eagle's Medium (DMEM) with sodium pyruvate and glutagro, supplemented with 1% Pen/Strep and 10% fetal bovine serum in an incubator set at 37ºC, 90% humidity and 5% CO_2. MDCKII cells were grown to confluence over 5 days on 24 well PET (polyethylene-terephthalate) plates (BD Biosciences). Experiments were run using HBSS donor buffer from Invitrogen containing additional 10mM HEPES, 15mM Glucose adjusted to pH 6.5. The receiver well had HBSS buffer supplemented with 1% BSA and the pH was adjusted to 7.4. After an initial equilibration with transport buffer, transepithelial electrical resistance (TEER) values were read to test membrane integrity. The experiment was started by the addition of dosing solutions containing test compounds. At 1 and 2 hr time points, 100 µl samples were taken from the receiver compartment. Removed buffer was replaced with fresh buffer and a correction was applied to all calculations for the removed material. Each compound was tested in 2 separate replicate wells for each condition. All samples were immediately collected and 400 µl 100% acetonitrile with 0.4% formic acid was added to precipitate protein and stabilize the test compounds. Cells were dosed on the apical or basolateral side to determine forward (A to B) and reverse (B to A) permeability. Permeability through a cell free transwell was also determined as a measure of membrane passive permeability and non-specific binding. To test for non-specific binding and compound instability, the total amount of drug was quantified at the end of the experiment and compared to the material present in the original dosing solution as a percentage of recovery. Samples were analyzed by LC/MS/MS.

The apparent permeability, P_{app}, and % recovery were calculated as follows:

$$\mathbf{P_{app} = (d_R / d_t) \times V_r / (A \times D_0)}$$

$$\mathbf{\% \ Recovery = 100 \times ((V_r \times R_{120}) + (V_d \times D_{120})) / (V_d \times D_0)}$$

Where,

$\mathbf{d_R / d_t}$ is the slope of the cumulative concentration in the receiver compartment versus time in µM/s based on receiver concentrations measured at 60 and 120 minutes.

$\mathbf{V_r}$ and $\mathbf{V_d}$ is the volume in the receiver and donor compartment in cm3, respectively.

A is the area of the cell monolayer (0.33 cm2).

$\mathbf{D_0}$ and $\mathbf{D_{120}}$ is the measured donor concentration at the beginning and end of the experiment, respectively.

$\mathbf{R_{120}}$ is the receiver concentration at the end of the experiment (120 minutes).

Results

Table 1: Bidirectional Permeability of BIC in Wild Type and MDR1 Transfected MDCKII Cells

Cell Type	Direction	Initial Conc. (µM)	Recovery (%)	P_{app} (10-6 cm/s)			Efflux Ratio
				R1	R2	Avg.	
MDCKII-WT	Cell-Free	5.7	118	31.9		31.9	
	Forward	5.8	105	15.8	21.3	18.6	1.3
	Reverse	6.1	95	20.9	25.7	23.3	
MDCKII-MDR1	Forward	6.2	100	7.8	4.8	6.3	7.5
	Reverse	4.9	133	43.0	52.2	47.6	
MDCKII-MDR1 (10 µM CsA)	Forward	8.5	85	15.3	9.7	12.5	2.4
	Reverse	7.4	120	29.2	31.4	30.3	

Source: Study Report, Page 7

The bidirectional permeability of probe P-gp substrate vinblastine was tested on the same assay plates and showed a 4.2-fold increase in efflux ratios in MDCKII-MDR1 cells relative to the results in the MDCKII-WT cells.

Table 2: Bidirectional Permeability of BIC in Wild Type and BCRP Transfected MDCKII Cells

Cell Type	Direction	Initial Conc. (µM)	Recovery (%)	P_{app} (10-6 cm/s)			Efflux Ratio
				R1	R2	Avg.	
MDCKII-WT	Cell-Free	5.7	117.9	31.9		31.9	
	Forward	5.8	105.1	15.8	21.3	18.6	1.3
	Reverse	6.1	94.9	20.9	25.7	23.3	
MDCKII-BCRP	Forward	6.3	101.2	9.0	7.1	8.1	6.5
	Reverse	4.9	135.6	48.5	56.1	52.3	
MDCKII-BCRP (10 µM Ko134)	Forward	7.9	91.3	19.5	18.4	19.0	2.0
	Reverse	6.8	130.4	37.6	39.8	**38.7**	

Source: Study Report, Page 8

The bi-directional permeability of the BCRP substrate prazosin was tested on the same assay plates and showed a ~7-fold increase in efflux ratio in MDCKII-BCRP cells relative to results in MDCKII-WT cells.

Conclusions

BIC is a substrate for P-gp and BCRP transporters based on the increases in efflux ratios in P-gp and BCRP over-expressing cells compared to non-transfected cell and decrease in the efflux ratios in the presence of Pgp and BCRP inhibitors.

Study # (EDR Link)	AD-141-2285 (EDR Link)
Title	In Vitro Assessment of BIC Inhibition of Human OCT2 and MATE1
Objectives	Assess the potential of BIC to inhibit human renal transporters OCT2 and MATE1

Methods

MDCKII cells were maintained in minimal essential medium (MEM) with 1% Pen/Strep, 10% fetal bovine serum, and 0.25mg/mL hygromycin B in an incubator set at 37ºC, 90% humidity and 5% CO_2. 24 hours prior to assay, media containing 5mM sodium butyrate were added to MDCKII cells in flask and cells were grown to 80-90% confluence. On assay day, cells were trypsinized and re-suspended in Krebs-Henseleit Buffer (KHB), pH 7.4.at 5 x 10^6 million cells/mL. Cells were pre-incubated for 15 minutes in assay plate before addition of inhibitor or substrate.

For OCT2 inhibition assay, test compounds were serially diluted in DMSO and then spiked (2 µL) into in 0.4 mL KHB buffer containing non-transfected or OCT2-transfected cells and incubated for 10 minutes. Assay was initiated with the addition of 0.1 mL of 100 µM ^{14}C-TEA in KHB buffer (20 µM final concentration after mixing). The concentration of TEA is based on the K_m. After 10 minutes of incubation, the assay mixture was quenched with addition of 0.5mL of ice-cold 1X PBS buffer. Samples were then centrifuged at 1000 rpm for 5 min and supernatants were removed. Wash steps were repeated four times with ice-cold PBS. Finally, the cell pellets were lysed with 0.2N NaOH and let sit at room temperature for at least 30 min to ensure complete lysis. Samples were then analyzed on liquid scintillation counter.

Studies were performed using MATE1 over-expressed CHO-cells and non-transfected CHO cells. Before experiments, the medium was removed and cells rinsed with Krebs-Henseleit buffer pH 7.3. Uptake experiments were carried out at 37°C in Krebs-Henseleit buffer pH 7.3 containing the TEA and BIC or the solvent. Organic solvent concentration was equal in each well and did not exceed 1% V/V. After the experiment, cells were rinsed with Krebs-Henseleit buffer and lysed with 0.1 M NaOH. The amount of TEA inside the cells was determined by liquid scintillation.

Fractional transport activities were calculated from the equation:

$Activity\ \% = (A-B)/(C-D) \times 100$

Legend:

A: translocated amount of substrate in the presence of TA on transfected cells

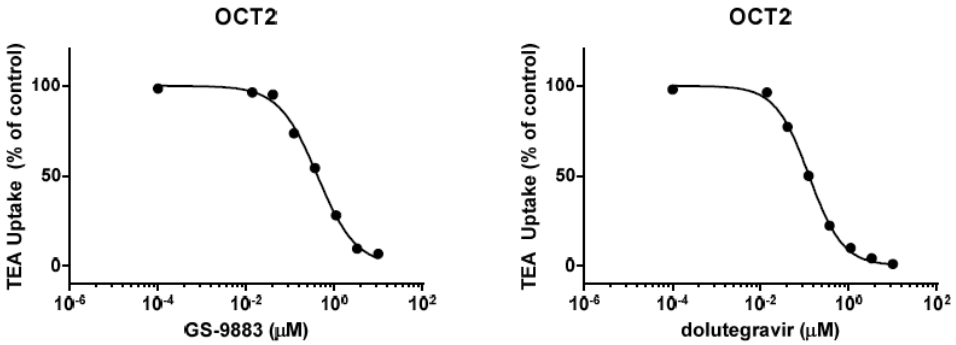
B: translocated amount of substrate in the presence of TA on parental cells

C: translocated amount of substrate in the presence of solvent on transfected cells

D: translocated amount of substrate in the presence of solvent on parental cells

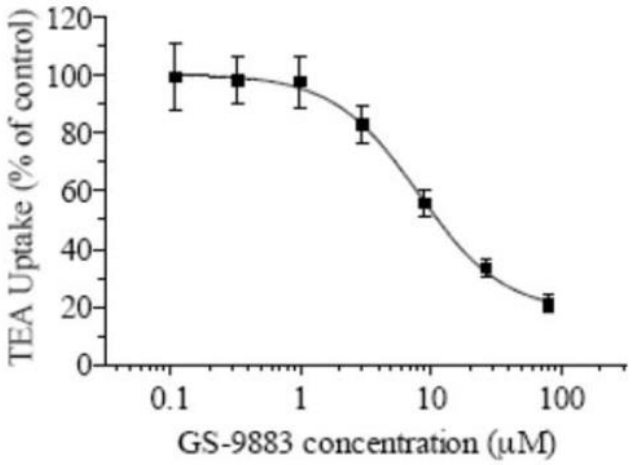
Results

Fig 1: BIC and Dolutegravir (positive control) Inhibition of OCT2 Mediated Transport of TEA



Source: Study Report, Page 8

Fig 2: BIC Inhibition of MATE1 Mediated Transport of TEA



Source: Study Report, Page 9

Table 1: BIC Inhibition of OCT2 and MATE1 Mediated Transport of TEA

	IC_{50} (μM)		% Inhibition at highest tested concentration	
Transporters	**OCT2**	**MATE1**	**OCT2**	**MATE1**
GS-9883	0.42	8.0	94% at10 μM	79% at 80 μM
dolutegravir	0.13	N/A	98% at 10 μM	N/A
quinidine	N/A	N/A	N/A	100% at 100 μM

Source: Study Report, Page 9

Conclusions

BIC was shown to be an inhibitor of OCT2 and MATE in vitro. Comparison of IC_{50} values suggests that BIC is a more potent inhibitor of OCT2 transporters as compared with MATE transporters. Further, dolutegravir appears to be a more potent inhibitor of OCT2 as compared with BIC.

Study # (EDR Link)	AD-141-2292 (EDR Link)
Title	Induction Potential of BIC Assessed In Vitro
Objectives	Assess the potential for AhR- and PXR mediated induction of metabolizing enzymes and transporters by BIC

Methods

A stock solution of BIC in dimethyl sulfoxide (DMSO) with a final concentration of 10 mM was prepared and used in all experiments.

Table 1: Various Drugs and Concentrations Investigated in the AhR and PXR Assessment

Inducing Agent	Concentrations Investigated (µM)	
	AhR Assessment	PXR Assessment
	CYP1A2-DRE Cells	DPX2 Cells
Rifampicin	—	0.1, 0.5, 1, 5, 10, 20
β-Naphthoflavone	0.1, 0.5, 1, 5, 10, 20	—
GS-9883	0.15, 0.5, 1.5, 5, 15, 50	0.15, 0.5, 1.5, 5, 15, 50

Source: Study Report, Page 6

Assessments of induction were done using Puracyp's hepatoma-derived cell lines, CYP1A2-DRE and DPX2. DPX2 cells are stably transformed with an expression vector for human PXR and a reporter gene vector containing the enhancer regions of CYP3A4 linked to luciferase. CYP1A2-DRE cells are transformed with an expression vector for human AhR and the rug/Dioxin Response Element (DRE) of the human CYP1A2 gene linked to a luciferase reporter.

P100 dishes containing DPX2 or CYP1A2-DRE cells were trypsinized and counted. The DPX2 and 1A2DRE cells were plated in a 96-well plate at a density of 20,000 cells/well. Plates were maintained at 37°C, in an atmosphere of 5% CO_2/95% air (v/v) and 95% relative humidity for 24 hours to allow cell recovery. Dosing solutions of the test articles were prepared such that the final concentration of DMSO in the incubations was 0.1% (v/v). For AhR and PXR activation in hepatoma cells, positive controls and the DMSO negative control were also included on each plate. The medium on the cells was replaced with medium containing the test articles listed below (150 µL final volume/well) in three wells per article (3 replicates). Plates were returned to culture conditions for 24 hours.

Following 24 hours of exposure to the test articles, medium was replaced with 25 µL of phosphate-buffered saline and 25 µL CellTiter-Fluor assay buffer. The plates were incubated for a further 1 hour and fluorescence determined in a Perkin-Elmer Victor 2 fluorometer (excitation 400 nm, emission 510 nm). Following the toxicity assessment, 50 µL of ONE-Glo™ luciferase substrate was added. The plates were incubated at room temperature for 5 minutes and then luminescence determined in a BMG luminometer. Each luminescence value was normalized to the corresponding fluorescence value obtained from the viability determination described above. Triplicate values were averaged and the fold induction determined by comparison with the appropriate DMSO vehicle control concentration.

Results

Table 1: Human PXR Activation by BIC and Positive Control

Concentration	Fold Activation Compared to 0.1% (v/v) DMSO Control	
	GS-9883	Rifampicin
0.1 µM	-	1.26
0.15 µM	0.93	-
0.5 µM	0.97	3.02
1 µM	-	4.45
1.5 µM	1.03	-
5 µM	1.48	8.74
10 µM	-	10.4
15 µM	2.75	-
20 µM	-	10.8
50 µM	4.22	-

Source: Study Report, Page 8

Table 2: Human AhR Activation by BIC and Positive Control

Concentration	Fold Activation Compared to 0.1% (v/v) DMSO Control	
	GS-9883	β-Naphthoflavone
0.1 µM	-	1.09
0.15 µM	0.72	-
0.5 µM	0.49	2.20
1 µM	-	3.22
1.5 µM	0.50	-
5 µM	0.48	13.9
10 µM	-	23.5
15 µM	0.63	-
20 µM	-	24.5
50 µM	0.90	-

Source: Study Report, Page 9

Conclusions

There is minimal potential for activation of AhR and PXR regulated genes by BIC at clinically relevant concentrations after steady state administration of BIC/F/TAF 50/200/25 mg.

Study # (EDR Link)	AD-141-2293 (EDR Link)
Title	In Vitro Assessment of Human Cytochrome P450 Inhibition Potential of BIC
Objectives	Evaluate the potential for BIC to inhibit activities seven major human drug-metabolizing cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A).

Methods

A stock solution of BIC in dimethyl sulfoxide (DMSO) with a final concentration of 10 mM was prepared and used in all experiments.

Cytochrome P450 Enzyme Inhibition Assay: Test compound (up to 100 μM) was incubated with human liver microsomes and NADPH in the presence of individual probe substrates. All assays were designed so that conditions were linear with respect to time and protein concentration. Substrates were present at concentrations equal to or lower than their respective Km values. The reactions were terminated by the addition of (b) (4) containing internal standard. The samples were then centrifuged, and the supernatants were combined, for the simultaneous analysis of acetaminophen, 4-hydroxybupropion, 6α-hydroxypaclitaxel, 4-hydroxy-tolbutamide, 4'-hydroxymephenytoin, dextrorphan, and 1'-hydroxymidazolam plus internal standard. 6β-Hydroxytestosterone with internal standard was measured separately. Formic acid (final concentration = 0.1% v/v) in deionized water was added to the final sample prior to analysis.

CYP1A2 Inhibition: The assay follows the formation of acetaminophen from phenacetin (substrate concentration 30 μM) over 5 min at 37°C. Microsomal protein, NADPH and DMSO concentrations were 0.25 mg/mL, 1.0 mM and 0.25% (v/v), respectively. α-Naphthoflavone was the positive control inhibitor and was run in parallel.

CYP2B6 Inhibition: The assay follows the formation of 4-hydroxybupropion from bupropion (substrate concentration 110 μM) over 5 min at 37°C. Microsomal protein, NADPH and DMSO concentrations were 0.1 mg/mL, 1.0 mM and 0.3% (v/v), respectively. Ticlopidine was the positive control inhibitor and was run in parallel.

CYP2C8 Inhibition: The 6α-hydroxylation of paclitaxel was determined using 0.25 mg/mL human hepatic microsomal protein and a substrate concentration of 7.5 μM. The reaction was initiated by the addition of NADPH (final concentrations 1.0 mM). Under these conditions product formation was linear to at least 30 min. Montelukast was used as an enzyme-selective positive control inhibitor.

CYP2C9 Inhibition: The formation of 4-hydroxytolbutamide from tolbutamide substrate (120 μM) was determined after 60 min incubation at 37°C. Microsomal protein, NADPH, and DMSO concentrations were 1 mg/mL, 1 mM, and 0.25% (v/v), respectively. Sulfaphenazole was the positive control inhibitor and was run in parallel.

CYP2C19 Inhibition: The formation of 4'-hydroxymephenytoin from S-mephenytoin substrate (25 μM) was determined after 60 min incubation at 37°C. Microsomal protein, NADPH, and DMSO concentrations were 0.5 mg/mL, 1 mM, and 0.25% (v/v), respectively. Tranylcypromine was the positive control inhibitor and was run in parallel.

CYP2D6 Inhibition: The formation of dextrorphan from dextromethorphan substrate (5 μM) was determined after 30 min incubation at 37°C. Microsomal protein, NADPH, and DMSO concentrations were 0.5 mg/mL, 1 mM, and 0.25% (v/v), respectively. Quinidine was the positive control inhibitor and was run in parallel.

CYP3A Inhibition: Two assays for CYP3A activity were used. The formation of 1'-hydroxymidazolam from midazolam (2.5 μM) was determined after 5 min incubation at 37°C. Microsomal protein, NADPH, and DMSO concentrations were 0.25 mg/mL, 1 mM, and 0.26% (v/v), respectively. The formation of 6β-hydroxytestosterone from testosterone (50 μM) was determined after 5 min incubation at 37°C. Microsomal protein, NADPH, and DMSO concentrations were 0.5 mg/mL, 1 mM, and 0.26% (v/v), respectively. For both assays, ketoconazole was the positive control and was run in parallel.

IC_{50} Determinations for Human CYP Enzyme Activities: Data were graphed and reaction velocities were calculated from the rates of formation of the metabolites and were compared to those seen with the vehicle control (100 % activity). IC_{50} values were calculated by log-linear interpolation of the enzyme activity vs. inhibitor concentration data.

Results

Table 1: Effect of BIC on Human Hepatic Microsomal CYP Activities

Conc. (μM)	Activity Remaining (%)							
	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A (MDZ)	CYP3A (T6β)
0.4	98.3	95.7	94.9	100.0	100.0	93.4	95.5	98.6
1.0	100.0	94.1	100.0	100.0	100.0	97.0	97.5	99.0
4.0	97.2	94.7	95.6	90.1	100.0	100.0	100.0	96.4
10.0	95.8	91.6	95.5	91.6	100.0	97.4	100.0	85.0
40	92.9	94.5	85.4	73.6	77.3	95.0	99.1	81.0
100	100.0	86.7	76.5	59.6	58.0	99.3	65.7	66.2
IC_{50} (μM)	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100

MDZ: Midazolam 1'-hydroxylase, T6β: Testosterone 6β-hydroxylase

Source: Study Report, Page 12

Table 2: Effect of Control Inhibitors on Human Hepatic Microsomal CYP Activities

Conc. (μM)	Activity Remaining (%)							
	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A (MDZ)	CYP3A (T6β)
0.012	82.1	--	99.3	--	--	79.5	81.5	98.0
0.03	66.8	--	99.9	--	--	61.1	68.7	96.5
0.04	--	--	--	96.1	--	--	--	--
0.1	--	90.6	--	85.6	--	--	--	--
0.12	32.7	--	87.5	--	--	30.1	33.2	67.7
0.2	--	--	--	--	94.7	--	--	--
0.25	--	80.1	--	--	--	--	--	--
0.3	17.6	--	88.1	--	--	17.5	17.5	32.8
0.4	--	--	--	58.0	--	--	--	--
0.5	--	--	--	--	90.8	--	--	--
1.0	--	58.6	--	37.7	--	--	--	--
1.2	9.0	--	48.5	--	--	7.0	4.6	4.8
2.0	--	--	--	--	86.5	--	--	--
2.5	--	38.4	--	---	--	--	--	--
3.0	6.8	--	19.7	--	--	4.9	2.5	2.0
4.0	--	--	--	17.8	--	---	--	--
5.0	--	--	--	--	68.6	--	--	--
10	--	19.2	--	12.6	--	--	--	--
20	--	--	--	--	31.4	--	--	--
25	--	12.3	--	--	--	--	--	--
50	--	--	--	--	14.9	--	--	--
IC_{50} (μM)	0.06	1.7	1.1	0.62	10	0.05	0.06	0.17

CYP1A2, α-napthoflavone; CYP2B6, ticlopidine; CYP2C8, montelukast; CYP2C9, sulfaphenazole; CYP2C19, tranylcypromine; CYP2D6, quinidine; CYP3A, ketoconazole

Note: Control Inhibitors: CYP1A2, α-Naphthoflavone (0–3 μM); CYP2B6 ticlopidine; CYP2C8 Montelukast (0–3 μM); CYP2C9, Sulfaphenazole (0–10 μM); CYP2C19, Tranylcypromine (0–50 μM); CYP2D6, Quinidine (0–3 μM); CYP3A, Ketoconazole (0–3 μM).
Source: Study Report, Page 13

Conclusions

At concentrations up to 100 μM, BIC showed minimal inhibitory effect on the activities of human hepatic microsomal CYP1A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A enzymes (IC_{50} > 100 μM). Considering that the mean steady state C_{max} of BIC after administration of BIC/F/TAF 50/200/25 mg is approximately 14 μM, BIC is unlikely to significantly affect the pharmacokinetics of drugs metabolized by these enzymes.

Study # (EDR Link)	AD-141-2294 (EDR Link)
Title	In Vitro Assessment of Human UGT1A1 Inhibition Potential of BIC
Objectives	Evaluate the potential for BIC to inhibit the activity of human microsomal UGT1A1

Methods

A stock solution of BIC in dimethyl sulfoxide (DMSO) with a final concentration of 30 mM was prepared and used in all experiments.

The 3-glucuronidation of β-estradiol at the phenolic hydroxyl group has been shown to be catalyzed primarily by UGT1A1 (Itaaho et al, Drug Metab Dispos, 2008; 36(11), 2307-2315). Atazanavir has been demonstrated to be a potent, selective inhibitor of this activity and is thus was used as a positive control (Zhang D et al, Drug Metab Dispos, 2005; 33(11), 1729-1739). Ritonavir, another HIV protease inhibitor, is a weaker inhibitor. The K_m for β-estradiol 3-glucuronidation by UGT1A1 has previously been determined to be 60.6 μM and the substrate concentration of 17 μM used by Fisher and co-workers, and employed in this study was below the K_m (Fisher et al, Drug Metab Dispos, 2000; 28 (5), 560-566; Itaaho et al, Drug Metab Dispos, 2008; 36(11), 2307-2315) The chromatographic method used in the study separates the UGT1A1-selective 3-glucuronide metabolite of estradiol from the other, 17 β-glucuronide metabolite.

The final reaction mixture was composed of 0.3 mg/mL hepatic microsomal protein, 50 μg alamethicin/mg microsomal protein, 5 mM UDP-glucuronic acid, 10 mM magnesium chloride, 1 mM D-saccharic acid 1,4-lactone, 17 μM β-estradiol and 0.1 M potassium phosphate buffer pH 7.4. Diluted microsomal fraction was incubated on ice for 15 minutes with alamethicin, magnesium chloride and saccharic acid lactone. Substrate and inhibitor were then added and the mixture warmed to 37°C for 5 minutes. The reaction was initiated by the addition of UDP glucuronic acid in potassium phosphate buffer. The incubation continued at 37°C with shaking for 45 minutes and aliquots were removed at intervals of 15 minutes. Reactions were terminated by addition of two volumes of [redacted] (b) (4) as the internal standard. Organic solvent was then evaporated at 30°C and the samples reconstituted by vigorous mixing in 5 mM aqueous ammonium formate containing 5% (v/v) formic acid. Product formation was linear for at least 30 minutes with the microsomal fraction used in these experiments. Concentrations of inhibitor of up to 300 μM were tested.

Data were graphed and reaction velocities were calculated from the rates of formation of the metabolites and were compared to those seen with the vehicle control (100% activity). IC_{50} values were calculated by non-linear regression and a sigmoidal three parameter inhibition model.

Results

Table 1: UGT1A1 Activity as a Fraction of Control Activity Remaining for BIC and Positive Control Inhibitors

Inhibitor Concentration (nM)	% Activity Remaining[a]		
	Atazanavir	Ritonavir	GS-9883
300000	7	7	37
100000	9	11	64
30000	11	21	94
10000	15	34	86
3000	32	51	87
1000	44	73	89
300	76	87	94
100	82	82	97
30	107	100	96
10	100	100	100

a Mean, N=2

Source: Study Report, Page 11

Table 2: Effect of BIC and Positive Control Inhibitor on the Activity of Human Hepatic Microsomal UGT1A1

Enzyme	Activity	Calculated IC_{50} (µM)		
		Atazanavir	Ritonavir	GS-9883
UGT1A1	β-Estradiol-3-glucuronidation	0.33	3.04	176

Source: Study Report, Page 8

Conclusions

BIC inhibited UGT1A1 with an IC_{50} of 176 µM. Considering that the mean steady state C_{max} of BIC after administration of BIC/F/TAF 50/200/25 mg is approximately 14 µM, BIC is unlikely to significantly affect the pharmacokinetics of drugs metabolized by UGT1A1.

Study # (EDR Link)	AD-141-2305 (EDR Link)
Title	Induction Potential of BIC Assessed in Human Hepatocytes
Objectives	Assess the potential for BIC to act as an inducer using human hepatocytes
Methods	

Table 1: Summary of Hepatocyte Donors Used in Study

Donor #	Lot #	Type	Age	Race	Sex	BMI
1	QHum15027	Fresh	43	Caucasian	Male	34
2	LHuf15908	Fresh	27	Caucasian	Female	30
3	LHuf15906	Fresh	28	Caucasian	Female	25.7

Source: Study Report, Page 6

Hepatocytes were plated and maintained in 24-well culture plates at 37°C under a humid atmosphere of 5% CO_2 / 95% air (v/v). The culture medium was serum-free William's E medium with appropriate supplements. BIC and positive and negative control compounds were dissolved in DMSO and the final concentration of DMSO in the dosing media was 0.1% (v/v). The exception was DMSO-free medium used for cells intended for eventual lysis to determine their LDH content. Dosing media were prepared by addition of solutions of the compounds, or DMSO vehicle, to hepatocyte culture medium. Cells were then treated by replacement of the medium in the wells with the fresh dosing media. Media were replaced at 24 hr intervals. BIC has been demonstrated to display high metabolic stability in human hepatocytes (AD-141-2288). Cells were harvested for mRNA analysis 48 hr after addition of the first dose and CYP activities were tested in the adherent monolayers 72 hr after addition of the first dose. For LDH leakage assessment, aliquots of medium were also collected at 24, 48 and 72 hr following the start of treatment, and cells treated with DMSO-free medium were harvested and lysed to provide the 100% leakage control.

Endpoints Assessed:

Assessments were performed in triplicate. Cell morphology was assessed, at 24 hr intervals, in the cultures treated with DMSO vehicle and with the highest concentration of BIC (60 µM). Endpoints were cell shape, cytoplasmic alterations, accumulation of vacuoles suggestive of swollen organelles and lipid droplets, or membrane blebbing. LDH activity in the medium was determined at 24 hr intervals. mRNA was extracted and quantified by qRT-PCR using GAPDH as the endogenous control. Gene specific primer/probe sets for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP3A4, UGT1A1, UGT1A3, UGT1A9, P-gp and GAPDH were used. Activity of CYP1A2, CYP2B6 and CYP3A was assessed in the hepatocyte monolayers in situ by addition of a cocktail of substrates (100 µM phenacetin, 50 µM bupropion and 10 µM midazolam) in culture medium to the cells (final concentration of DMSO 0.1% v/v) and then incubating for 30 min at 37°C. Following the incubation the medium was removed, and extracted with (b) (4) containing an internal standard cocktail consisting of (b) (4) and the concentrations of the metabolites in the medium were then quantified using specific LC-MS/MS methods. Flumazenil (25 µM) was tested in parallel as a negative control. The positive controls used for the sentinel endpoints for induction were omeprazole (50 µM) for CYP1A2, phenobarbital (1000 µM) for CYP2B6 and rifampicin (10 µM) for CYP3A.

LDH activity in the medium was normalized using the mean activity in the media of the time-matched DMSO control wells (0% leakage) and the mean activity in the lysates of time-matched cells that had been treated with DMSO-free medium (100% leakage).
Relative mRNA expression was determined from the threshold cycle (C_T) values for the test mRNA and the comparator (GAPDH). For fold change calculations data were normalized to the DMSO vehicle control (1-fold induction). For effects expressed as a percentage of E_{max} the data were normalized to the vehicle control (0%) and the strong positive control (100%). After determining the concentrations of metabolites in the media, rates of enzyme-specific metabolism were calculated using the assumed number of hepatocytes/well and the incubation
time. As for the mRNA data, fold change calculation data were normalized to the DMSO vehicle control (1-fold induction), and for effects expressed as a percentage of E_{max} the data were normalized to the vehicle control (0%) and the strong positive control (100%).

EC_{50} values (and 95% confidence intervals) were calculated using GraphPad Prism 6.07 using a sigmoid model constrained to a baseline value of 0% activation and, where necessary, to an E_{max} value of 100% (equal to the respective positive control). No preset criteria were used for goodness-of-fit (e.g. adjusted r^2 values). EC_{50} values for the three donors were combined using the geometric mean and geometric (multiplicative) standard deviation, as calculated below.

$$Geometric\ Mean\ EC_{50} = \sqrt[n]{\prod_{i=1}^{n} EC_{50,i}}$$

$$Geometric\ SD = 10^{\sqrt{\frac{\sum_{1=1}^{n}\left(\log_{10}\frac{EC_{50}}{Mean\ EC_{50}}\right)^2}{n}}}$$

Results

Table 1: LDH Leakage of Treated Hepatocytes (Mean ± SD, n =3 donors)

Treatment	Concentration (µM)	LDH Leakage (%)		
		24 hr	48 hr	72 hr
Flumazenil	25	-0.92 ± 1.71	-2.67 ± 3.23	-0.10 ± 3.33
Omeprazole	50	-2.50 ± 2.93	-6.98 ± 3.73	-1.14 ± 2.15
Phenobarbital	1000	-2.44 ± 2.57	-3.82 ± 5.63	-0.75 ± 3.11
Rifampicin	10	-2.93 ± 2.68	-1.39 ± 5.32	0.04 ± 3.13
GS-9883	1	-1.05 ± 1.87	-0.16 ± 3.17	0.80 ± 4.17
GS-9883	3	-2.25 ± 0.16	-3.34 ± 1.62	0.02 ± 5.98
GS-9883	10	-3.30 ± 1.29	-2.85 ± 4.79	0.32 ± 3.91
GS-9883	30	-1.75 ± 2.24	-2.29 ± 3.29	0.20 ± 5.22
GS-9883	60	-2.21 ± 1.77	-2.38 ± 5.01	0.39 ± 1.52

Source: Study Report, Page 9

CYP1A2:

mRNA Expression Data:

Table 2: Effect of treatments with BIC and Positive and Negative Controls on CYP1A2 mRNA expression in Human Hepatocytes

Treatment	Concentration	Response as Fraction of Positive Control (Mean ± SD, n=3)		
		Donor 1	Donor 2	Donor 3
DMSO	0.1%	0.0% ± 1.3	0.0% ± 0.9	0.0% ± 2.4
Omeprazole	50 µM	100.0% ± 6.0	100.0% ± 14.0	100.0% ± 8.0
Flumazenil	25 µM	-0.2% ± 1.2	1.9% ± 1.1	-1.6% ± 1.7
Bictegravir	1 µM	0.7% ± 0.8	0.5% ± 0.2	-0.5% ± 2.5
	3 µM	1.4% ± 1.6	0.5% ± 0.2	-0.9% ± 0.7
	10 µM	2.7% ± 0.9	0.4% ± 0.4	0.3% ± 1.8
	30 µM	1.0% ± 1.0	0.0% ± 0.7	5.6% ± 2.3
	60 µM	-0.2% ± 1.2	-2.3% ± 0.1	-5.3% ± 2.2

Source: Study Report, Page 10

Enzyme Activity Data:

Treatment with the positive control CYP1A2 inducer, omeprazole, resulted in mean increases in phenacetin O-deethylase activity of 18.7-, 21.6- and 6.6-fold in the three donors, confirming the responsiveness of the cells. Treatment with the negative control, flumazenil, resulted in ≤1.27-fold increase in activity. Treatment with bictegravir (1 – 60 µM) resulted in ≤1.22-fold increase in activity, corresponding to ≤1.24% of the response to the positive control.

CYP2B6:

mRNA Expression Data:

Table 3: Effect of treatments with BIC and Positive and Negative Controls on CYP2B6 mRNA expression in Human Hepatocytes

Treatment	Concentration	Response as Fraction of Positive Control (Mean ± SD, n=3)		
		Donor 1	Donor 2	Donor 3
DMSO	0.1%	0.0% ± 2.5	0.0% ± 1.8	0.0% ± 2.0
Phenobarbital	50 µM	100.0% ± 35.0	100.0% ± 13.0	100.0% ± 10.0
Flumazenil	25 µM	10.7% ± 1.6	8.2% ± 2.8	-2.0% ± 1.3
Bictegravir	1 µM	2.0% ± 2.3	3.1% ± 1.4	0.4% ± 2.0
	3 µM	8.0% ± 1.8	5.8% ± 3.2	3.1% ± 0.6
	10 µM	12.1% ± 5.0	12.0% ± 3.7	15.6% ± 1.1
	30 µM	26.1% ± 7.5	17.8% ± 7.0	35.9% ± 1.0
	60 µM	39.2% ± 9.7	20.3% ± 4.7	39.8% ± 8.1
EC_{50}		85.9	180.6	70.0
95 % Confidence Interval		69.1 – 106.9	130.5 – 249.9	57.8 – 84.8
Adjusted r^2		0.8508	0.4044	0.9017
Mean ± SD E_{max}		15.0 ± 4.9	7.3 ± 0.8	12.1 ± 1.1

Source: Study Report, Page 11

Enzyme Activity Data:

Treatment with the positive control CYP2B6 inducer, phenobarbital, resulted in mean increases in bupropion hydroxylase activity of 5.6-, 14.5- and 15.4-fold in the three donors, confirming the responsiveness of the cells. Treatment with the negative control, flumazenil, resulted in ≤1.45-fold increase in activity. Treatment with bictegravir (1 – 60 µM) resulted in ≤1.49-fold increase in activity, corresponding to ≤10% of the response to the positive control.

CYP3A4:

mRNA Expression Data:

Table 4: Effect of treatments with BIC and Positive and Negative Controls on CYP3A4 mRNA expression in Human Hepatocytes

Treatment	Concentration	Response as Fraction of Positive Control (Mean ± SD, n=3)		
		Donor 1	Donor 2	Donor 3
DMSO	0.1%	0.0% ± 0.6	0.0% ± 1.4	0.0% ± 0.4
Rifampicin	50 µM	100.0% ± 18.0	100.0% ± 18.0	100.0% ± 31.0
Flumazenil	25 µM	7.5% ± 1.9	4.0% ± 2.7	-1.8% ± 0.4
Bictegravir	1 µM	2.3% ± 1.4	6.6% ± 6.5	-0.3% ± 1.0
	3 µM	6.6% ± 1.1	6.2% ± 5.5	6.9% ± 0.3
	10 µM	20.2% ± 5.8	28.2% ± 11.6	36.4% ± 3.2
	30 µM	50.7% ± 12.3	91.0% ± 53.0	64.1% ± 6.5
	60 µM	80.5% ± 21.7	63.4% ± 25.9	59.8% ± 20.6
EC_{50}		26.5	13.9	18.9
95 % Confidence Interval		18.4 – 38.2	5.3 – 37.0	15.4 – 23.2
Adjusted r^2		0.8677	0.5830	0.9544
Mean ± SD E_{max}		28.1 ± 4.7	24.0 ± 4.1	19.1 ± 5.6

Source: Study Report, Page 12

Enzyme Activity Data:

Treatment with the positive control CYP3A inducer, rifampicin, resulted in mean increases in midazolam 1'-hydroxylase activity of 6.5-, 12.5- and 9.5-fold in the three donors, confirming the responsiveness of the cells. Treatment with the negative control, flumazenil, resulted in ≤1.38-fold increase in activity. Treatment with BIC at concentrations up to 3 µM resulted in <2-fold increase in activity. Higher concentrations resulted in bell-shaped concentration-response relationships with the peak effect at 30 µM (donors 1 and 2) or 10 µM (donor 3). The maximum effect was 3.02-fold, corresponding to 36.6% of the positive control.

Conclusions

At the clinically relevant concentrations of BIC expected after steady state administration of BIC/F/TAF (approximately 14 µM), BIC is not anticipated to be an inducer of CYP1A2, CYP2B6, and CYP3A4 enzymes.

Study # (EDR Link)	AD-141-2308 (EDR Link)
Title	In Vitro Assessment of Human Hepatic Microsomal Cytochrome P450 Mechanism-Based Inhibition Potential of BIC
Objectives	Evaluate the potential for BIC to be a mechanism-based inhibitor of the major human hepatic microsomal cytochrome P450 drug-metabolizing enzymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A.

Methods

To test the potential for BIC to act as a mechanism-based inhibitor of human CYP enzymes a two stage incubation protocol was used, with the first stage allowing inactivation of the enzyme in the absence of substrate, and the second stage being used to assay remaining enzyme activity. A 10-fold dilution was performed between the two stages to reduce the direct inhibitory effects of the test compounds. Assays were performed in duplicate. The first stage incubation contained pooled human hepatic microsomal fractions diluted in 50 mM potassium phosphate buffer pH 7.4. BIC was added to a final concentration of 100 µM, which is the approximate solubility limit under the conditions of the assays. The incubation was carried out at 37°C for 30 minutes in the absence or presence of 1 mM NADPH as the CYP cofactor. After this time the incubation mixture was diluted 10-fold with 50 mM potassium phosphate buffer pH 7.4, plus enzyme substrate (final concentration typically ~5x the apparent K_M) and fresh NADPH (1 mM final). The second-stage incubation was carried out at 37°C and then terminated by the addition of five volumes of methanol. The enzyme-specific metabolites were quantified by LC MS/MS, as described below, except for resorufin, which was quantified fluorometrically. Prior to LC MS/MS analysis the samples were centrifuged at 2500 × g for 30 min at 4°C and the resulting supernatants were diluted with deionized water containing 0.1% (v/v) formic acid and the MS internal standard (b) (4) Assay positive control mechanism-based inhibitors were tested in parallel at a concentration of 25 µM in the first-stage incubation.

CYP1A2 Mechanism-Based Inhibition: The human hepatic microsomal protein concentration in the first-stage incubation was 2.5 mg/mL. In the second-stage incubation the substrate, ethoxyresorufin, was added to a final concentration of 2.5 µM and the assay performed for 5 min. Termination was by addition of methanol and the formation of resorufin metabolite was by fluorescence (excitation 535 nm, emission 595 nm). Resveratrol and furafylline were the positive control inhibitors and were run in parallel.

CYP2B6 Mechanism-Based Inhibition: The human hepatic microsomal protein concentration in the first-stage incubation was 1 mg/mL. In the second-stage incubation the substrate, bupropion, was added to a final concentration of 550 µM and the assay performed for 5 min. Hydroxybupropion was quantified by LC/MS/MS. Ticlopidine was the positive control inhibitor and was run in parallel.

CYP2C8 Mechanism-Based Inhibition: The human hepatic microsomal protein concentration in the first-stage incubation was 1 mg/mL. In the second-stage incubation the substrate, paclitaxel, was added to a final concentration of 7.5 µM and the assay performed for 30 min. 6α-Hydroxypaclitaxel was quantified by LC/MS/MS. Gemfibrozil glucuronide was the positive control inhibitor and was run in parallel.

CYP2C9 Mechanism-Based Inhibition: The human hepatic microsomal protein concentration in the first-stage incubation was 5 mg/mL. In the second-stage incubation the substrate, diclofenac, was added to a final concentration of 100 µM and the assay performed for 5 min. 4-Hydroxydiclofenac was quantified by LC/MS/MS. Tienilic acid was the positive control inhibitor and was run in parallel.

CYP2C19 Mechanism-Based Inhibition: The human hepatic microsomal protein concentration in the first-stage incubation was 2 mg/mL. In the second-stage incubation the substrate, S-mephenytoin, was added to a final concentration of 250 μM and the assay performed for 30 min. 4'-Hydroxymephenytoin was quantified by LC/MS/MS. Ticlopidine was the positive control inhibitor and was run in parallel.
CYP2D6 Mechanism-Based Inhibition: The human hepatic microsomal protein concentration in the first-stage incubation was 5 mg/mL. In the second stage incubation the substrate, dextromethorphan, was added to a final concentration of 25 μM and the assay performed for 5 min. Dextrorphan was quantified by LC/MS/MS. Paroxetine was the positive control inhibitor and was run in parallel.

CYP3A Mechanism-Based Inhibition: Two assays for CYP3A activity were used. When using midazolam 1'-hydroxylase activity as the endpoint the human hepatic microsomal protein concentration in the first-stage incubation was 1 mg/mL. In the second-stage incubation the substrate, midazolam, was added to a final concentration of 12.5 μM. When using testosterone 6β-hydroxylase activity as the endpoint the human hepatic microsomal protein concentration in the first-stage incubation was 2.5 mg/mL. In the second-stage incubation the substrate, testosterone, was added to a final concentration of 100 μM. In both cases the second stage incubation was for 5 min and metabolites were quantified by LC/MS/MS. Positive control inhibitors were mibefradil and mifepristone and were run in parallel.

Data Analysis:

Mechanism-Based Inhibition Calculation: Inhibition was calculated as percent change in the ratio of the metabolite PAR values obtained after pre-incubations performed in the absence and presence of NADPH cofactor, and corrected for the change in activity when incubated with DMSO vehicle instead of GS-9883 or positive control inhibitor.

$$\%Change = \left(1 - \frac{PAR_{NADPH+}}{PAR_{NADPH-}} \bullet \frac{PAR_{DMSO,NADPH-}}{PAR_{DMSO,NADPH+}}\right) \bullet 100\%$$

The standard deviation for the %Change was calculated, using the variability between duplicates for the four values, by error propagation, assuming no covariance between the values. RMS_{CV} is the root-mean-square coefficient of variation for the four values.

$$SD = Ratio \bullet RMS_{CV} \bullet 100\%$$

<u>IC_{50} Shift Analysis:</u>

Potency of BIC as an inhibitor of human hepatic midazolam 1'-hydroxylase activity was determined with pooled microsomal fractions (final concentration 0.05 mg protein/mL) in 0.05 M potassium phosphate buffer, with an NADPH regenerating system and an incubation time of 5 min at 37°C. The midazolam substrate concentration was 3 μM, which matched the K_M for the activity determined under the experimental condition. BIC was included at concentrations ranging from 0 (vehicle control) to 200 μM. Upon termination of the metabolic reactions the 1'-hydroxymidazolam metabolite was quantified using a specific LC/MS/MS assay. Control inhibitors tested in parallel were troleandomycin (mechanism-based CYP3A inhibitor) and ketoconazole (reversible CYP3A inhibitor). Three assay formats were tested in duplicate; 1) Direct inhibitory potency, where no preincubation was performed, 2) Metabolism-dependent potency, where microsomal fraction, BIC and NADPH regenerating system were preincubated for 30 min at 37°C prior to addition of midazolam and 3) Time-dependent potency, where microsomal fraction and BIC were

preincubated for 30 min at 37°C (in the absence of NADPH regenerating system) prior to addition of midazolam and NADPH regenerating system. The proportion of enzyme activity remaining (compared to the vehicle control) was determined at each concentration of BIC. Where possible, IC_{50} values were calculated, using a sigmoidal model. A comparison of apparent direct and time-dependent IC_{50} values allows assessment of any metabolism-independent change in potency occurring during the pre-incubation period. If there is a negligible difference in those two potencies then a comparison of apparent direct and metabolism-dependent IC_{50} values allows assessment of mechanism-based inhibition potential.

Results

Table 1: % Change Values for Time and Cofactor-Dependent Inhibition of Major Human Hepatic Microsomal CYP Enzymes by BIC (mean ± SD)

CYP Enzyme	Probe Activity	Calculated %Change	
		Control Inhibitor[a]	GS-9883
CYP1A2	Ethoxyresorufin O-deethylase	71.4 ± 2.0 62.1 ± 2.6	-6.6 ± 5.4
CYP2B6	Bupropion 4-hydroxylase	82.8 ± 2.4	1.6 ± 8.7
CYP2C8	Paclitaxel 6α-hydroxylase	44.4 ± 3.8	6.7 ± 3.8
CYP2C9	Diclofenac 4'-hydroxylase	77.5 ± 5.0	0.6 ± 15.6
CYP2C19	S-Mephenytoin 4'-hydroxylase	55.6 ± 2.2	-1.3 ± 4.6
CYP2D6	Dextromethorphan O-demethylase	82.1 ± 0.8	12.1 ± 7.7
CYP3A	Midazolam 1'-hydroxylase	57.9 ± 2.6 78.5 ± 0.8	39.8 ± 3.7
	Testosterone 6β-hydroxylase	90.4 ± 1.8 66.8 ± 2.2	7.4 ± 9.9

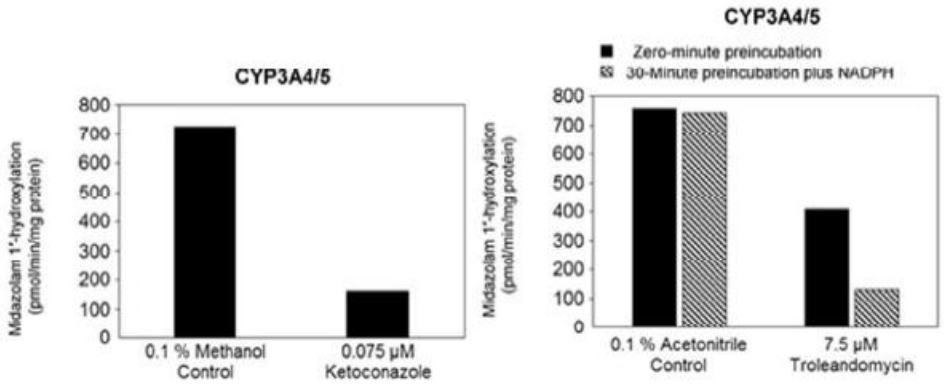
For calculation of SD, see Section 3.2.1

a. CYP1A2, furafylline and resveratrol; CYP2B6, ticlopidine; CYP2C8, gemfibrozil glucuronide; CYP2C9, tienilic acid; CYP2C19, ticlopidine; CYP2D6, paroxetine; CYP3A, mibefradil and mifepristone

Source: Study Report, Page 10

Since CYP3A activity, determined by midazolam 1'-hydroxylase, was the only enzyme activity showing potential for sensitivity to mechanism-based inhibition by BIC, this activity was evaluated further.

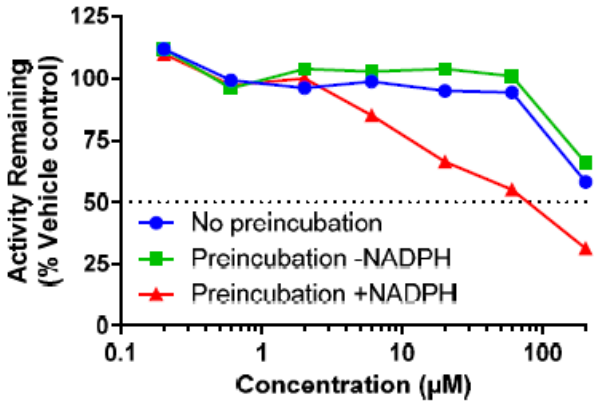
Figure 1: Responses of Positive Control Inhibitors used in the IC_{50} Shift Study



Source: Study Report, Page 11

Results from the positive controls confirmed that the assay system was capable of detecting direct and mechanism-based CYP3A inhibitors. Ketoconazole (0.075 µM) reduced activity in the direct format assay (no-preincubation) by approximately 80 %. In the metabolism-dependent format, pre-incubation with NADPH regenerating system and 7.5 µM troleandomycin decreased activity approximately 3–fold compared to pre-incubation in the absence of the NADPH regenerating system.

Figure 2: Effect of BIC on Human Hepatic Microsomal CYP3A Activity Following Preincubation in the Absence or Presence of NADPH or Without Preincubation



Source: Study Report, Page 12

The effect of BIC using the direct format (no pre-incubation) and the time-dependent format (pre-incubation without NADPH regenerating system) suggests that BIC does not act as a time dependent inhibitor of CYP3A. In both cases, an IC_{50} could not be determined as the activity remaining at the highest concentration tested (200 µM) was > 50% (58.3% for the direct format and 66.0 % for the time-dependent format, respectively). Pre-incubation with the NADPH regenerating system increased the apparent inhibitory potency of BIC, and an IC_{50} of 64.3 µM (95% confidence interval 39.7 - 104.1 µM) was obtained.

Conclusions

BIC did not show evidence for mechanism based inhibition of human hepatic microsomal enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Although BIC showed a weak potential for mechanism based inhibition of CYP3A (KI>100 µM), it is not expected to be a mechanism based inhibitor of CYP3A enzymes in vivo considering that the maximum steady state plasma concentration of BIC after administration of BIC/F/TAF 50/200/25 mg is approximately 14 µM.

Study # (EDR Link)	AD-141-2310 (EDR Link)
Title	In Vitro Inhibition Study of BIC with the human OAT1, OAT3, OCT1, and BSEP transporters
Objectives	Assess the interaction of BIC with the human transporters OAT1, OAT3, OCT1, and BSEP in vitro using cell lines or membrane vesicles transfected with the individual transporters

Methods

Table 1: Transfected Cells, Membrane Vesicles, Substrates, and Positive Control Inhibitors Used in the Transporter Inhibition Assays

Transporter	Transfected Cells	Model Substrate	Positive Control
OAT1	CHO	PAH	Benzbromarone
OAT3	Flp-In 293	Estrone 3-Sulfate	Probenecid
OCT1	CHO	TEA	Verapamil
BSEP	Sf9 cell membrane vesicles	Taurocholate	Cyclosporine A

(CHO) Chinese Hamster Ovary
(Sf9) Spodoptera frugiperda ovarian cells
(TEA) Tetraethylammonium
(PAH) Para-aminohippurate
(Flp-In 293) Parental Cells transfected with pFRT/lacZeo and selected for stable Zeocin™- resistant clones

Source: Study Report, Page 6

Uptake Assays:

The uptake transporter inhibition assays were conducted with BIC (test article; TA; concentration range used was from 0.1-100 µM) and a labelled probe substrate. Transporter specific accumulation of the probe substrate in the cells was measured as follows:

- Transporter expressing and parental cells were cultured and before experiments the medium was removed and cells rinsed with Krebs-Henseleit buffer pH 7.3.
- Inhibition experiments were carried out at 37°C in Krebs-Henseleit buffer pH 7 containing the probe substrate and TA or the solvent. Organic solvent concentration was equal in each well and did not exceed 1 V/V %.
- After the experiment cells were rinsed with Krebs-Henseleit buffer and lysed with 0.1 M NaOH.
- The amount of substrate inside the cells was determined by liquid scintillation/fluorescence reader.

The fractional transport activities were calculated from the equation:

Activity % = (A-B/C-D) X 100

where A: translocated amount of substrate in the presence of TA on transfected cells
B: translocated amount of substrate in the presence of TA on parental cells
C: translocated amount of substrate in the presence of solvent on transfected cells
D: translocated amount of substrate in the presence of solvent on parental cells

BSEP Vesicular Transport Inhibition Assay:

BIC was incubated with membrane vesicle preparations (total protein: 50 µg/well) and probe substrate, taurocholate (2 µM) in the absence or presence of ATP. Reaction mixtures were pre-incubated for 15 minutes at 37°C. Reactions were started by the addition of 25 µL of 12 mM MgATP or assay buffer (for background controls), pre-incubated separately. Reactions were stopped after 5 min by the addition of 200 µL of ice-cold washing buffer and immediate filtration via glass fiber filters mounted to a 96-well plate (filter plate). The filters were washed, dried and the amount of substrate inside the filtered vesicles determined by liquid scintillation. Cyclosporine A (20 µM) was used as the positive control inhibitor and tested in parallel. Control membranes lacking transporter expression were used as negative control. All assays were performed in duplicate.

The fractional transport activities were calculated from the equation:

Activity % = (A-B/C-D) X 100

where A: translocated amount of substrate in the presence of TA and ATP
B: translocated amount of substrate in the presence of TA
C: translocated amount of substrate in the presence of solvent and ATP
D: translocated amount of substrate in the presence of solvent

IC_{50} is defined as the test article concentration needed to inhibit the maximal transporter specific transport by 50 %. IC_{50} values were calculated using non-linear fitting of % inhibition versus concentration to a sigmoidal curve with a variable Hill Coefficient.

Results

Table 2: Inhibition of Human OAT1, OAT3, OCT1, and BSEP Transporters by BIC

Uptake Transporter Inhibition		
Transporter	**Maximum inhibition at 100 µM (% of control)**	**IC_{50} (µM)**
OAT1	NA	>100
OAT3	64	55
OCT1	13	>100
Vesicular Transport Inhibition		
Transporter	**Maximum inhibition at 100 µM (% of control)**	**IC50 (µM)**
BSEP	46	>100

Source: Study Report, Page 9

Conclusions

BIC is not anticipated to inhibit OAT1, OAT3, BSEP, and OCT1 at clinically relevant concentrations expected after steady state dosing of BIC/F/TAF.

AD-141-2313 (EDR Link):

Title: Drug-Drug Interaction Liability Assessment of BIC

Objectives: To assess the liability of BIC to cause clinical drug interactions.

Methods:

The applicant used the following values of the various parameters to calculate the BIC concentrations used for predicting the potential for drug-drug interactions.

Table 1: Values of various parameters of BIC

Parameter	Identity	Value	Source
MW	Molecular weight	449.4 g/mol	-
Dose	Maximum dose strength	50 mg (111.26 µmol)	GS-US-380-1489/1490
ka	Absorption rate constant	2.54 hr^{-1}	Bictegravir population PK report
F_a	Fraction of dose absorbed	1.0	Guidance default
F_g	Fraction of absorbed dose reaching portal vein	1.0	Guidance default
C_{max}	Steady state maximum plasma concentration	6.15 µg/mL (13.7 µM)	Bictegravir population PK report
f_u	Unbound fraction in human plasma	0.25%	AD-141-2287
BPR	Whole blood to plasma concentration ratio	0.64	AD-141-2312

Source: Clinical Study Report, Page 7

Table 2: Calculated BIC Concentrations Used in Drug Interactions

Concentration	Value
C_{max} or $[I]_1$ or $[I_1]$	13.7 µM
$C_{max,u}$	0.034 µM / 0.137 µM[a]
$[I]_{gut}$ or $[I]_g$ or $[I]_2$ or $[I_2]$	445.0 µM
$[I]_g$	15.7 µM
$[I]_h$ or $[I]_{u,inlet,max}$	0.046 µM / 0.117 µM[a]
$f_u \times [I]_{in,max}$	FDA: 0.042 µM / 0.168 µM[a]
$f_u \times [I]_{inlet,max}$	PMDA: 0.042 µM / 0.166 µM[a]

a Value calculated using f_u = 0.25% / value calculated using f_u or $f_{u,b}$ of 1.0%

Source: Clinical Study Report, Page 8

Table 3: Concentrations Relevant for Drug Interaction Assessments

Name	Identity	Calculation	Uses
C_{max} or $[I]_1$ or $[I_1]$	Steady-state peak plasma concentration	(Measured)	FDA CYP R_1, R_2, R_3, hepatic P-gp and BCRP $[I]_1$, initial test for OATPs. PMDA CYP R (inhibition and induction), hepatic P-gp and BCRP $[I_1]$.
$C_{max,u}$	Unbound C_{max}	$f_u \times C_{max}$	FDA OATs and OCTs. EMA CYP Basic Model and hepatic efflux and renal transporters. PMDA renal OATs, OCTs and MATEs.
$[I]_{gut}$ or $[I]_g$ or $[I]_2$ or $[I_2]$	Theoretical maximal intestinal lumen concentration	$Molar\ Dose / 250\,mL$	FDA CYP R_1, R_2, ($[I]_{gut}$) and P-gp, BCRP ($[I]_2$). EMA CYP3A Basic Model and intestinal efflux transporters. PMDA CYP3A R and intestinal transporter $[I]_g$ or $[I_2]$.
$[I]_g$	Modeled intestinal concentration	$F_a \times ka \times Molar\ Dose / Q_{en}$	FDA, EMA and PMDA CYP Mechanistic models Q_{en} = 18 L/hr/70 kg.
$[I]_h$ or $[I]_{u,inlet,max}$	Unbound hepatic inlet concentration	$f_{u,b}\left(C_{max,b} + F_a \times F_g \times ka \times Molar\ Dose / Q_h\right)$	FDA, EMA and PMDA CYP Mechanistic models (F_g not used explicitly in FDA calculations). EMA hepatic uptake transporters Q_h = 97 L/hr/70 kg.
$f_u \times [I]_{in,max}$ or $f_u \times [I]_{inlet,max}$	Unbound hepatic inlet concentration (hybrid plasma and blood)	$f_u\left(C_{max} + F_a \times F_g \times ka \times Molar\ Dose / Q_h\right)$	FDA hepatic uptake transporters Q_h = 1500 mL/min (90 L/hr). PMDA hepatic uptake transporters Q_h = 97 L/hr.

Source: Clinical Study Report, Page 9

Conversion to Unbound Concentrations:

The cell-based assays (the induction liability test in human hepatocytes and the tests for interactions with transporters) were performed in serum-free media so no correction of concentrations or potency values for binding is required. Binding of bictegravir to human hepatic microsomal fraction is low ($f_{u,m}$ = 0.863 at a microsomal protein concentration of 0.5 mg/mL; AD-141-2311). Nevertheless, all concentration values in microsomal assays were corrected for binding. The following relationship was used to calculate the free fraction in microsomal fractions in assays at protein concentrations other than 0.5 mg/mL.

$$f_{u,m2} = \frac{1}{1 + {C_2}/{C_1} \times {1 - f_{u,m1}}/{f_{u,m1}}}$$

C_1 is the concentration of microsomal fraction used in the free fraction determination (0.5 mg/mL) and C_2 is the microsomal protein concentration used in the assay. $f_{u,m1}$ is the measured free fraction (0.863) and $f_{u,m2}$ is the free fraction calculated under the conditions of the assay.

Conversion to K_{iu} from IC_{50}:

If the test compound acts as a competitive inhibitor of the enzyme or transporter, the equivalent K_i can be estimated from the measured IC_{50} if the ratio of the substrate concentration [S] to the affinity constant for the enzyme or transport reaction (K_M) is known. For microsomal incubations, the unbound K_i ($K_{i,u}$) is then calculated using the free fraction under the conditions of the assay ($f_{u,m}$).

$$K_i = \frac{IC_{50}}{1+[S]/K_M} \quad K_{i,u} = K_i \times f_{u,m}$$

Reversible CYP Inhibition (assessed in study AD-141-2293):

All assays yielded extents of inhibition of < 50% at the maximum concentration tested (100 μM). The slight difference in calculated $K_{i,u}$ for CYP3A using the two enzyme activities may be due to difference in microsomal protein concentrations rather than a true substrate-dependence in inhibitor sensitivity.

Table 4: Calculated K_{iu} Values for Reversible In Vitro Inhibition of CYP Enzymes by BIC

Enzyme	[HLM] (mg/mL)[a]	$f_{u,m}$[b]	IC_{50} (μM)[a]	$[S]/K_M$[a]	K_i (μM)[b]	$K_{i,u}$ (μM)[b]
CYP1A2	0.25	0.926	> 100	1.0	> 50	> 46.3
CYP2B6	0.1	0.969	> 100	1.0	> 50	> 48.5
CYP2C8	0.25	0.926	> 100	1.0	> 50	> 46.3
CYP2C9	1.0	0.759	> 100	1.0	> 50	> 38.0
CYP2C19	0.5	0.863	> 100	1.0	> 50	> 43.2
CYP2D6	0.5	0.863	> 100	1.0	> 50	> 43.2
CYP3A M	0.25	0.926	> 100	1.0	> 50	> 46.3
CYP3A T	0.5	0.863	> 100	1.0	> 50	> 43.2

a Data from AD-141-2293
b Calculated as described in this report

Source: Clinical Study Report, Page 11

CYP Induction Liability (assessed in study AD-141-2305)

These studies were performed in sandwich cultures of human hepatocytes (n = 3 donors) and assessments were made in serum-free medium so the free fraction in the assay ($f_{u,assay}$) is 1.0 and thus the free EC_{50} values ($EC_{50,u} = EC_{50} \times f_{u,assay}$) are the same as the measured EC_{50} values. E_{max} values for bictegravir itself could not be determined and are thus assumed to match those of the positive controls.

Table 5: Hepatocyte Induction Data for BIC

Endpoint	EC_{50} (μM) [SD][a]	$f_{u,assay}$	$EC_{50,u}$ (μM)	E_{max} (fold)[b]	d[c]
CYP1A2	Not an inducer	1.0	Not an inducer	17.3 ± 9.3	0.90
CYP2B6	102.8 [1.5]	1.0	102.8	11.5 ± 3.9	1.04
CYP3A4	19.1 [1.3]	1.0	19.1	23.7 ± 4.5	0.40

a Geometric mean EC_{50} (n = 3 donors) and geometric (multiplicative) SD for change in mRNA
b Fold change in mRNA elicited by the positive control (mean ± SD fold, n = 3 donors)
c Suggested scaling factor (mean ratio of E_{max} values for activity and mRNA for the positive control)

Source: Clinical Study Report, Page 12

Interaction with Transporters (assessed in study AD-141-2305)

Assessments were performed in serum-free media so the free fractions in the assay ($f_{u,assay}$) are 1.0 and thus the free IC_{50} values ($IC_{50,u} = IC_{50} \times f_{u,assay}$) are the same as the measured IC_{50} values. Assays were also performed with [S] = K_M so $K_i = IC_{50}/2$

Table 6: Interactions of BIC with transporters In Vitro

Transporter	IC_{50}	$f_{u,assay}$	$[S]/K_M$	$K_{i,u}$ (µM)	Report
P-gp	> 80	1.0	1.0	> 40	AD-141-2273
BCRP	> 80	1.0	1.0	> 40	
BSEP	> 100	1.0	1.0	> 50	AD-141-2310
OATP1B1	No inhibition	1.0	1.0	No inhibition	AD-141-274
OATP1B3	> 80	1.0	1.0	> 40	
OAT1	No inhibition	1.0	1.0	No inhibition	AD-141-2310
OAT3	55	1.0	1.0	27.5	
OCT1	> 100	1.0	1.0	> 50	
OCT2	0.42	1.0	1.0	0.21	AD-141-2285
MATE1	8.0	1.0	1.0	4.0	

Source: Clinical Study Report, Page 13

Metabolic Properties of Victim Drugs

Table 7: Metabolic Properties of Victim Drugs

Enzyme	Substrate	F_g	f_m	
CYP1A2	Theophylline	1	0.80	
CYP2B6	Efavirenz	1	0.64	
CYP2C8	Rosiglitazone	1	0.84	
CYP2C9	Warfarin	1	0.91	
CYP2C19	Omeprazole	1	0.87	
CYP2D6	Dextromethorphan	0.8	0.98	
CYP3A	Midazolam	0.57	0.89	

Source: Clinical Study Report, Page 14

Estimation of Interaction Potential:

The mechanistic net effect model (known in the PMDA Guidance document as the mechanism-based static pharmacokinetic [MSPK] model) allows combination of the effects of the drug on intestinal and liver CYP enzymes, with considerations of reversible inhibition, time dependent inhibition and induction. The full calculation is intended to predict the ratio of the area under the plasma concentration-time curve (AUC) of a victim drug in the presence of an interacting agent to the reference condition in the absence of that agent. That ratio, the AUCR, is calculated as:

$$AUCR = \frac{1}{A_g \times B_g \times C_g \times (1 - F_g) + F_g} \times \frac{1}{A_h \times B_h \times C_h \times f_m + (1 - f_m)}$$

The influences of individual components can be studied by setting all other values to 1. For example, for the FDA Guidance, where A_g and A_h refer to reversible inhibition of CYP enzymes in the intestine and liver, respectively, setting B_g, C_g, B_h and C_h to 1 allows calculation of the AUCR related solely to reversible CYP inhibition.

RESULTS:

Reversible CYP Inhibition (basic model):

In the FDA and PMDA guidance, the metric is calculated as:

$$metric = 1 + {}^{[I]}/_{K_{i,u}}$$

Where for systemic plasma levels, $[I]=C_{max}$ and is positive if metric is > 1.1. For intestinal levels, $[I]=[I_{gut}]$ and is positive if metric > 11.

In the EMA guidance, the metric is calculated as:

$$EMA\ metric = {}^{[I]}/_{K_{i,u}}$$

Where for systemic plasma levels, $[I]=C_{max,u}$ and is positive if metric is > 0.02. For intestinal levels, $[I]=[I_{gut}]$ and is positive if metric ≥10.

Table 8: Calculation Results for Basic Reversible In Vitro Inhibition of CYP enzymes by BIC

Enzyme	$K_{i,u}$ (µM)	FDA R_1	EMA Metric[a]	PMDA R
CYP1A2	> 46.3	**< 1.30**	< 0.001 / < 0.003	**< 1.30**
CYP2B6	> 48.5	**< 1.28**	< 0.001 / < 0.003	**< 1.28**
CYP2C8	> 46.3	**< 1.30**	< 0.001 / < 0.003	**< 1.30**
CYP2C9	> 38.0	**< 1.36**	< 0.001 / < 0.004	**< 1.36**
CYP2C19	> 43.2	**< 1.32**	< 0.001 / < 0.003	**< 1.32**
CYP2D6	> 43.2	**< 1.32**	< 0.001 / < 0.003	**< 1.32**
CYP3A M	> 46.3	**< 1.30**	< 0.001 / < 0.003	**< 1.30**
CYP3A T	> 43.2	**< 1.32**	< 0.001 / < 0.003	**< 1.32**
CYP3A M gut	> 46.3	< 10.6	< 9.6	< 10.6
CYP3A T gut	> 43.2	**< 11.3**	**< 10.3**	**< 11.3**

Values potentially exceeding the respective threshold are in **bold**
a Value calculated using f_u of 0.25% / value calculated using f_u of 1%

Source: Clinical Study Report, Page 15

Using the most conservative assumption of setting the IC_{50} values to the highest concentration in each assay (100 µM), the threshold outlined in the three guidances will be crossed for at least one enzyme (primarily CYP3A in the intestine), thus indicating that the Net Effect (MSPK) model should be employed.

Reversible CYP Inhibition (net effect model):

The following equations were used to calculate the intestinal and hepatic reversible inhibition components (FDA guidance refers to these components as A_g and A_h, respectively).

$$Intestinal = \frac{1}{1+{[I]_g}/{K_{i,u}}} \qquad Hepatic = \frac{1}{1+{[I]_h}/{K_{i,u}}}$$

Table 9: Calculation Results for Net Effect Reversible CYP Inhibition by BIC

Enzyme	Intestinal	Hepatic	AUCR
CYP1A2	1.0 ≥ Value > 0.75	1.00	1.00
CYP2B6	1.0 ≥ Value > 0.76	1.00	1.00
CYP2C8	1.0 ≥ Value > 0.75	1.00	1.00
CYP2C9	1.0 ≥ Value > 0.71	1.00	1.00
CYP2C19	1.0 ≥ Value > 0.73	1.00	1.00
CYP2D6	1.0 ≥ Value > 0.73	1.00	1.0 ≤ Value < 1.06
CYP3A M	1.0 ≥ Value > 0.75	1.00	1.0 ≤ Value < 1.12
CYP3A T	1.0 ≥ Value > 0.73	1.00	1.0 ≤ Value < 1.13

Source: Clinical Study Report, Page 16

The calculated AUR values are less than 1.25, thereby suggesting that BIC is not expected to be an inhibitor of the CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A.

Time Dependent Inhibition by BIC:

The results of study AD-141-2308 showed that BIC is not a time dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. There was an indication of time dependent inhibition of CYP3A, however, the potency was too weak to allow calculation of enzyme inactivation parameters (K_{iu}> 98.4 µM).

Induction:

Per the FDA and PMDA guidance, the metric is calculated as follows:

$$metric = \frac{1}{1+\frac{d \times C_{max} \times E_{max}}{C_{max}+EC_{50}}}$$

Where a value of < 0.9 is considered positive in both guidance documents. Further, if the E_{max} value is determined in hepatocyte studies (fold increase in mRNA above the vehicle control), then it must be corrected for "1-fold" induction to yield E_{max} increase ($E_{max}=E_{maxhepatocytes}-1$).

The intestinal and hepatic components of the net effect model are calculated in the same manner in all Guidance documents. For the FDA Guidance they are termed C_g and C_h, respectively, while for the EMA and PMDA Guidance documents they are termed B_g and B_h, respectively.

$$Intestinal = 1 + \frac{d \times [I]_g \times E_{max}}{[I]_g + EC_{50}} \quad Hepatic = 1 + \frac{d \times [I]_h \times E_{max}}{[I]_h + EC_{50}}$$

Table 10: Calculation Results for Induction Liability of BIC

	Hepatocyte Data			Basic	Net Effect		
Target	$EC_{50,u}$ (µM)	E_{max}[a]	d	R_3 or R	Intestinal	Hepatic	AUCR
CYP1A2	No induction	16.3	0.90	≥ 0.9	1.0	1.0	1.0
CYP2B6	102.8	10.5	1.04	**0.45**	2.39	1.00	1.0
CYP3A4	19.1	22.7	0.40	**0.21 / 0.10**[b]	5.1 / 11.2[b]	1.02 / 1.05[b]	**0.36 / 0.16**[b]

Values exceeding the respective threshold are in **bold**
a Corrected for baseline (1-fold) increase in mRNA
b Value calculated using d = 0.40 / value calculated using d = 1.0

Source: Clinical Study Report, Page 18

For CYP2B6, the calculated AUCR is 1.0 (no difference when using plasma f_u of 0.25% or plasma f_u of 1.0%) so bictegravir will not cause clinically relevant drug interactions through induction of CYP2B6. For CYP3A the calculated AUCR is 0.36 using experimentally determined values (d = 0.40 and plasma f_u 0.25%) and drops to 0.18 using Guidance defaults of d = 1.0 and plasma f_u = 1.0 %. Both values cross the threshold of AUCR < 0.8 so BIC may induce CYP3A enzymes *in vivo*, however, the results of the *in vivo* trial conducted with midazolam (GS-US-380-4270) did not suggest the potential for BIC to induce CYP enzymes *in vivo*.

Inhibition of Intestinal Efflux Transporters:

The three guidances use a similar metric for determining significance. The FDA and PMDA Guidance documents represents this as $[I]/IC_{50}$ (or K_i) ≥ 10, where [I] is variously denoted by $[I]_2$, $[I]_g$ or $[I_2]$, while the EMA Guidance represents this as $K_i \leq 0.1 \times [I]_{gut}$.

Table 11: Calculation Results for Intestinal Efflux Transporter Interactions for BIC

Transporter	$IC_{50,u}$ (µM)	$K_{i,u}$ (µM)	FDA $[I]_2/K_{i,u}$	EMA 0.1 × $[I]_{gut}$ (µM)	PMDA $[I_2]/K_{i,u}$
P-gp	> 80	> 40	**11.1**	**44.5**	**11.1**
BCRP	> 80	> 40	**11.1**	**44.5**	**11.1**

Values potentially exceeding the respective threshold are in **bold**

Source: Clinical Study Report, Page 18

Under the assumption that the $IC_{50,u}$ is equal to the maximum concentration tested (80 µM), BIC would slightly exceed the thresholds for both transporters. However, it should be noted that inhibition observed at the highest bictegravir concentration tested (80 µM) was only 20% for P-gp and 6% for BCRP (AD-141-2273) so the $K_{i,u}$ values for both transporters are likely to be much greater than 40 µM. Overall, the potential for BIC to inhibit P-gp and BCRP is very low.

Inhibition of Hepatic Uptake Transporters by BIC:

There was no detectable inhibition of OATP1B1 *in vitro* so BIC is not considered to be an inhibitor of this transporter. The FDA Guidance suggests an initial computation of C_{max}/IC_{50}, with ratios ≥ 0.1 subject to calculation of R values as follows:

$$FDA\ metric: R = 1 + {}^{[I]_{in,max,u}}\!/_{K_{i,u}} \geq 1.25$$

$$EMA\ metric: K_{i,u} \leq 25 \times [I]_h$$

$$PMDA\ metric = {}^{[I]_{inlet,max,u}}\!/_{K_{i,u}} \geq 0.25\ or\ R = 1 + {}^{[I]_{inlet,max,u}}\!/_{K_{i,u}} \geq 1.25$$

Table 12: Calculation Results for Hepatic Uptake Transporter Interactions of BIC

Transporter	$IC_{50,u}$ (µM)	$K_{i,u}$ (µM)	FDA $[I]_1/K_{i,u}$	FDA R	EMA 25 × $[I]_h$ (µM)	PMDA R
OATP1B1	Not an inhibitor		< 0.1	< 1.25	2.9	< 1.25
OATP1B3	> 80	> 40	< **0.34**	1.0	2.9	1.0
OCT1	> 100	> 50	< **0.27**	1.0	2.9	1.0

Values potentially exceeding the respective threshold are in **bold**

Source: Clinical Study Report, Page 19

For OATP1B3 and OCT1, the R values (calculated as described in the FDA and PMDA guidance) are < 1.01, and $K_{i,u}$ values are ≥ 13.8-fold higher than the EMA 25 × $[I]_h$ test (all calculated using the most conservative values of $[I]_{in,max,u}$ and $[I]_h$ with plasma f_u or blood $f_{u,b}$ = 1.0%). Thus, BIC would not be expected to inhibit any of the hepatic uptake transporters.

Inhibition of Hepatic Efflux and Renal Transporters by BIC:

The metrics, as described in the three guidance documents, were calculated:

$$FDA\ metric\ renal: {}^{C_{max,u}}/_{K_{i,u}} \geq 0.1$$

$$PMDA\ metric\ renal: K_{i,u} \leq 4 \times C_{max,u}\ or\ 1 + {}^{C_{max,u}}/_{K_{i,u}} \geq 1.25$$

$$EMA\ metric: K_{i,u} \leq 50 \times C_{max,u}$$

$$FDA\ and\ PMDA\ metric\ hepatic: {}^{C_{max}}/_{K_{i,u}} \geq 0.1$$

Table 13: Calculation Results from Hepatic Efflux Transporter and Renal Transporter Interactions for BIC

Transporter	$K_{i,u}$ (µM)	FDA $[I]_1/K_{i,u}$	FDA $C_{max,u}/K_{i,u}$[a]	EMA 50 × $C_{max,u}$ (µM)[a]	PMDA $[I_1]/K_{i,u}$	PMDA 1 + $C_{max,u}/K_{i,u}$[a]
OAT1	Not an inhibitor	NA	< 0.1	1.7 / 6.9	NA	< 1.25
OAT3	27.5	NA	0.001 / 0.005	1.7 / 6.9	NA	1.001 / 1.005
OCT1	> 50	NA	< 0.001 / < 0.003	1.7 / 6.9	NA	< 1.001 / < 1.003
OCT2	0.21	NA	**0.16 / 0.65**	**1.7 / 6.9**	NA	1.16 / **1.65**
MATE1	4.0	NA	0.01 / 0.03	1.7 / **6.9**	NA	1.01 / 1.03
Pgp	> 80	< **0.34**	NA	1.7 / 6.9	< **0.34**	NA
BCRP	> 80	< **0.34**	NA	1.7 / 6.9	< **0.34**	NA
BSEP	> 100	< **0.27**	NA	1.7 / 6.9	< **0.27**	NA

NA: Not Applicable (transporter does not fall within that classification)
Values potentially exceeding the respective threshold are in **bold**
a Value calculated using plasma f_u = 0.25% / value calculated using plasma f_u = 1.0%

Source: Clinical Study Report, Page 20

Based on the calculations shown in the table above, BIC is not expected to be an inhibitor of OAT1, OAT3 and OCT1, but expected to inhibit OCT2. If it is assumed that $IC_{50,u}$ is equal to the maximum concentration tested (80 µM) BIC would exceed the FDA and PMDA thresholds for P-gp and BCRP inhibition. However, it should be noted that inhibition observed at the highest bictegravir concentration tested (80 µM) was only 20% for P-gp and 6% for BCRP (AD-141-2273) so the $K_{i,u}$ values for both transporters are likely to be much greater than 40 µM.

Conclusions:

1) At clinically relevant concentrations, BIC would not be expected to cause drug-drug interactions with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, OAT1, OAT3, OCT1, OATP1B1 or OATP1B3.
2) Although the predictions suggest the potential for BIC to induce CYP3A and possibly be a time dependent inhibitor of CYP3A4 (albeit the potency was too weak to allow calculation of enzyme inactivation parameters [K_{iu}> 98.4 µM]), the results of the *in vivo* trial conducted with midazolam (GS-US-380-4270) did not suggest the potential for BIC to induce CYP enzymes *in vivo*.
3) BIC is expected to inhibit OCT2 transporters *in vivo* which was confirmed by the results of the drug-drug interaction trial with metformin, a substrate of OCT2 and MATE transporters (GS-US-380-3908).

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/s/

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Application Type	NDA
Application Number(s)	210251
Priority or Standard	Priority
Submit Date(s)	June 10, 2017
Received Date(s)	June 12, 2017
PDUFA Goal Date	February 12, 2018
Division/Office	DAVP/OAP
Review Completion Date	11/9/17
Established Name	Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) Fixed-Dose Combination
(Proposed) Trade Name	BIKTARVY™
Pharmacologic Class	Bictegravir is an integrase strand-transfer inhibitor (INSTI), emtricitabine and tenofovir alafenamide are nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)
Applicant	Gilead Sciences
Formulation(s)	FDC Tablet
Dosing Regimen	bictegravir 50 mg/emtricitabine 200 mg/TAF 25 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of HIV-1 infection in adults who are HIV-1 treatment-(b) (4) associated with resistance to the individual components of BIKTARVY
Recommendation on Regulatory Action	Approval

The Primary Clinical Review for NDA 210251 is complete, and has been added to the NDA/BLA Multi-disciplinary Review and Evaluation. My recommendation for this application is Approval.

Tanvir Bell, MD
Medical Officer

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/s/

TANVIR K BELL
11/09/2017

WENDY W CARTER
11/09/2017

Pharmacology/Toxicology Review

Goal Date: November 12, 2017
Completion Date: October 30, 2017
NDA #: 210251
Supporting document#: None
CDER stamp date(s): June 12, 2017
Product name: **BIKTARVY**
Indication: Treatment of HIV-1 infection in adults who are HIV-1 treatment-(b) (4) associated with resistance to the individual components of BIKTARVY
Applicant: Gilead Sciences
Reviewer: John Dubinion, Ph.D.

Recommendation: It is recommended that **BIKTARVY** be approved.

Summary: Biktarvy™, a once daily fixed-dose combination (FDC) tablet containing bictegravir (BIC; B), emtricitabine (FTC; F), and tenofovir alafenamide (TAF), is intended for the treatment of HIV-1 infection in adults. Bictegravir (previously referred to as GS-9883) is a potent integrase strand-transfer inhibitor (INSTI) that blocks HIV-1 replication, and is the only component of the FDC which has not been previously approved for use by the FDA. FTC and TAF have been approved for marketing in the U.S. as standalone agents (Emtriva® and Vemlidy®, respectively) or in multiple FDC products (Genvoya®, Descovy®, and Odefsey®).

The nonclinical safety profile of BIC was evaluated in: safety pharmacology studies in rats and monkeys; repeat-dose toxicology studies in mice, rats and monkeys for up to 4, 26, and 39 weeks, respectively; at least 2-week toxicology studies in rats to qualify impurities; phototoxicity studies in mouse fibroblasts and pigmented rats; fertility and pre- and post-natal developmental studies in rats; embryo-fetal developmental studies in rats and rabbits; genetic toxicology studies (Ames, *in vitro* chromosomal aberration and *in vivo* rat micronucleus assays); and a carcinogenicity study in transgenic mice. In addition, numerous *in vitro* and *in vivo* nonclinical pharmacokinetic studies evaluating the absorption, distribution, metabolism and excretion of BIC have been conducted in mice, rats, dogs, and monkeys, and a rat carcinogenicity study with BIC is currently in progress. Nonclinical safety studies for F/TAF to support the FDC were reviewed previously. Refer to the Pharmacology/Toxicology reviews for NDA-021500, NDA-208464, and NDA-208215 for a detailed summary of FTC, TAF, and F/TAF nonclinical data, respectively. Pharmacology/Toxicology Review is complete, and has been added to the NDA Multidisciplinary Review and Evaluation. Pharm/Tox recommendation for this application is approval.

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/s/

JOHN H DUBINION
10/30/2017

HANAN N GHANTOUS
10/30/2017

Pharmacology/Toxicology Review by Dr. John Dubinion is complete, and has been added to the NDA Multidisciplinary Review and Evaluation. Pharm/Tox recommendation for this application is approval.