Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	212950
Priority or standard	Priority
Submit date(s)	12/4/2019
Received date(s)	12/4/2019
PDUFA goal date	8/4/2020
Division/office	Division of Antivirals (DAV)
Review completion date	6/30/2020
Established name	Fostemsavir
(Proposed) trade name	RUKOBIA
Pharmacologic class	HIV-1 attachment inhibitor
Code name	FTR; GSK3684934; BMS-663068
Applicant	ViiV Healthcare
Dose form/formulation(s)	Extended-release tablet
Dosing regimen	600 mg orally twice daily
Applicant proposed indication(s)/population(s)	RUKOBIA is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Proposed SNOMED indication	89293008 Human immunodeficiency virus type I (organism)
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	RUKOBIA, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Approved SNOMED indication	40780007: Human immunodeficiency virus I infection (disorder)

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Glossary

ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reactions
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	ritonavir-boosted atazanavir
AUC	area under the curve
BAT	Basophil Activation Test
BCRP	breast cancer resistance protein
BID	twice daily
BLA	biologic license application
BMS	Bristol-Myers Squibb
CI	confidence interval
CK	creatine kinase
CNS	central nervous system
COBI	cobicistat
DDI	drug-drug interaction
DILI	drug-induced liver injury
DRV	darunavir
DRV/r	ritonavir-boosted darunavir
DRV/c	cobicistat-boosted darunavir
DTG	dolutegravir
EE	ethinyl estradiol
ECG	electrocardiogram
EN	envelope
ENF	enfuvirtide
ER	extended-release
ESRD	end-stage renal disease
ETR	etravirine
FAHI	Functional Assessment of HIV Infection
FC	fold change
FDA	Food and Drug Administration
FTR	fostemsavir
GI	gastrointestinal
GLP	good laboratory practice
GZR	grazoprevir
HBV	hepatitis B virus
HCV	hepatitis C virus

HD	high dose
HLGT	high level group term
HSR	hypersensitivity reaction
HTE	heavily treatment-experienced
IBA	ibalizumab
ICH	International Conference on Harmonisation
IND	investigational new drug
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRIS	immune reconstitution inflammatory syndrome
LANL	Los Alamos National Laboratory
LD	low dose
LOCF	Last Observation Carried Forward
M-MASRI	Modified Medication Adherence Self-Report Inventory
MDR	multidrug resistant
MPI	maximum percent inhibition
MVC	maraviroc
NDA	new drug application
NE	norethindrone
NEA	norethindrone acetate
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OBT	optimized background therapy
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PK	pharmacokinetic
PNGS	potential N-linked glycosylation sites
PPK	population pharmacokinetics
PT	preferred term
QD	once a day
RAL	raltegravir
RAP	resistance-associated polymorphism
RAS	resistance-associated substitution
RAST	radioallergosorbent test
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SF	safety factor
SMQ	Standardized Medical Query
SOC	System Organ Class
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TMR	temsavir
ULN	upper limit of normal
VOX	voxilaprevir

1. Summary of Regulatory Action

The new drug application (NDA) 212950 for fostemsavir (FTR) was submitted by ViiV Healthcare. FTR is a first-in-class human immunodeficiency virus type 1 (HIV-1) gp120-directed attachment inhibitor. The NDA was reviewed by the multidisciplinary review team. Each discipline recommended approval, and I, the signatory authority for this application, concur with those recommendations. FTR will be approved in combination with other antiretrovirals (ARVs) for the treatment of HIV-1 infection in heavily treatment-experienced (HTE) adults with multidrug-resistant (MDR) HIV-1 infection failing their current ARV regimen due to resistance, intolerance, or safety considerations.

The Applicant submitted one adequately designed Phase 3 trial that provides substantial evidence of efficacy for the approved indication. The available safety data show FTR is safe for its intended use. I concur that identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance. The overall benefit-risk is favorable as described in the Benefit-Risk Framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Integrated Assessment document and the Product Quality Review.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Human immunodeficiency virus type 1 (HIV-1) is a transmissible virus that attacks and weakens the immune system. Without effective antiretroviral therapy (ART), HIV-1 infection leads to progressive destruction of the immune system, acquired immunodeficiency syndrome (AIDS)-defining illnesses, and premature death in almost all cases. • The U.S. Centers for Disease Control and Prevention (CDC) estimates that over 1.1 million people in the U.S. are living with HIV. • Maximal and durable suppression of HIV-1 RNA restores and/or preserves the immune system and reduces HIV-associated morbidity and mortality. Most treatment-adherent patients with limited previous HIV treatment experience can maximally and durably suppress HIV-1 RNA using a combination of two or more commercially available drugs from different drug classes. • Treatment failure occurs as a result of drug resistance, drug intolerance, and suboptimal adherence. Resistance-associated substitution(s) selected by one drug often confer(s) resistance to other drugs within that drug class, which further limits treatment options. • Heavily treatment-experienced (HTE) patients have limited remaining options (1-2 available drug classes) for constructing a fully suppressive antiretroviral (ARV) regimen due to multidrug resistance, intolerance, or safety considerations.	HTE patients with limited treatment options and evidence of ongoing HIV replication despite ART are at high risk of AIDS-related morbidity and mortality.
Current Treatment Options	• For patients with multidrug resistant (MDR) HIV-1 infection, providers must individually tailor combination treatment regimens based on previous ARV exposure, cumulative viral resistance testing, drug safety and tolerability, and comorbid conditions. • The resulting ARV regimens are often burdensome, less well tolerated, and associated with inadequate HIV-1 RNA suppression.	HTE patients with limited treatment options need new and effective therapies that lack cross-resistance with commercially available products, have a favorable tolerability profile, and allow for convenient dosing.

Benefit	• Efficacy of fostemsavir (FTR) in HTE patients with limited treatment options due to multidrug resistance, intolerance, or safety considerations was established in the BRIGHTE (AI438047/205888) trial, a Phase 3 trial conducted in two parts. • For the first 8 days of the trial, subjects were randomized to FTR 600 mg twice daily (BID) or placebo in combination with their failing antiretroviral (ARV) regimen (blinded period). • After Day 8, all subjects received FTR 600 mg BID in combination with optimized background therapy (OBT) for at least 96 weeks (open-label period). • The trial enrolled 272 subjects in this cohort (Randomized Cohort). The BRIGHTE trial design was consistent with FDA's guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015). • Primary efficacy endpoint: The adjusted mean difference for change in HIV-1 RNA $\log_{10}$ copies/mL from Day 1 to Day 8 (FTR minus placebo) was -0.63 (95% CI, -0.81, -0.44), demonstrating superiority of FTR compared to placebo. • Key secondary efficacy endpoints: The proportion of subjects with decline in HIV-1 RNA >0.5 $\log_{10}$ and >1.0 $\log_{10}$ copies/mL from Day 1 to Day 8 for FTR/placebo were 66%/19% and 46%/10%, respectively. The differences between treatment groups were statistically significant. Early HIV-1 RNA decreases of >0.5 $\log_{10}$ copies/mL in prior trials have been associated with reduction in clinical disease progression according to the FDA's guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015). • Key secondary assessment: During the open-label extension phase, HIV-1 RNA <50 copies/mL was achieved in 53% and 60% of subjects at Week 24 and Week 96, respectively, supporting durability of efficacy of FTR plus OBT. Lack of a control group for assessment of durability of virologic response is a limitation. However, continuation of subjects on double-blind therapy with a failing background regimen for more than 1 to 2 weeks is not considered ethical or feasible because of the risk of developing resistance to the new agent without adequate background therapy. • Key subgroup finding: HIV-1 RNA <50 copies/mL was achieved at Week 24 in 56% of subjects who had dolutegravir (DTG) in their OBT	FTR has clearly demonstrated virologic activity in HTE patients with MDR HIV-1 infection who have limited treatment options. The clinical trial design and endpoints were appropriate for the HTE population with limited treatment options. Reductions in HIV-1 RNA levels are highly predictive of meaningful clinical benefit, and FTR functional monotherapy was superior to placebo for reducing HIV-1 RNA over 8 days. Virologic suppression was achieved and maintained with FTR plus OBT through Week 96 in a majority of subjects previously unable to achieve virologic suppression. Because the BRIGHTE trial was uncontrolled after Day 8, there is some uncertainty surrounding the contribution of FTR to the durability of virologic response. Inclusion of at least one highly potent ARV in the OBT, such as DTG if appropriate and available, increases the likelihood of a durable virologic response. Availability of FTR will provide a new and effective first-in-class treatment option for HTE patients with MDR HIV-1 infection. Patients who achieve virologic suppression with FTR plus OBT will have a reduced risk of HIV/AIDS-related morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with or without boosted darunavir (DRV/r or DRV/c) compared to 35% without DTG. • FTR antiviral activity was reduced against some CXCR4-tropic viral isolates, possibly because of overlap between tropism and FTR susceptibility determinants in gp120. • FTR antiviral activity was highly variable with a wide range in EC_{50} values across and within all HIV-1 subtypes but did not show antiviral activity in cell culture or clinically against subtype AE isolates (also known as subtype E). • Key EN RAPs S375M, M426L, M434I or M475V and Screening phenotypic fold-change in FTR susceptibility of >200 are associated with decreased Day 8 response to FTR.	The antiviral activity of FTR against HIV-1 subtypes was highly variable. The reduced FTR activity against subtype AE (E) viruses are reported in the label to allow providers to make the most informed decision about treating the appropriate patients. Given the low prevalence of key EN RAPs in the population and lack of readily available assays to assess presence of EN RAPs and FTR phenotype, the indication will not be restricted based on presence of EN RAPs or Screening FTR phenotype. FTR may be an important agent in constructing an effective ARV regimen for patients with few therapeutic options, and information is provided in the label to inform providers which patients may benefit most using FTR as a component of an ARV regimen.
Risk and Risk Management	• In addition to the Randomized Cohort of the BRIGHTE trial, a Non-randomized Cohort was enrolled and consisted of HTE subjects with no available ARV options; the Non-randomized Cohort initiated open-label FTR plus OBT on Day 1 and continued through Week 96. Safety data from the BRIGHTE trial are supplemented by 96-week data from a Phase 2b trial that enrolled less heavily treatment-experienced subjects. • The safety database meets the minimum recommended sample size of 300 to 500, as outlined by FDA's guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015). • The most common adverse drug reaction during treatment with FTR was nausea. • Other common adverse drug reactions included diarrhea, headache, abdominal pain, dyspepsia, fatigue, rash, sleep disturbance, immune reconstitution inflammatory syndrome (IRIS), somnolence, and vomiting. • A review of deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs) did not reveal any	Based on the available data, fostemsavir has a favorable safety profile. The safety database was adequate for comprehensive safety assessment of FTR for the proposed indication, patient population, dosage regimen, and duration. Safety risks have not been identified that require risk management beyond standard pharmacovigilance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patterns to suggest a significant safety risk attributable to FTR treatment. The nature and frequency of these events largely reflect an HTE population with advanced HIV infection. • Overall, there was no clear pattern of FTR-related safety issues, but the causality assessment in the BRIGHTE trial is complicated by lack of a comparator group and confounding from poor health status and concomitant medications. • The virologic failure rate of FTR in combination with OBT in the Randomized Cohort of the BRIGHTE trial through Week 96 was 25%. Emergence of genotypic and phenotypic resistance to FTR and drugs in the OBT was predominant in virologic failures. • FTR resistance substitutions do not appear to confer cross-resistance to the postattachment inhibitor, ibalizumab (IBA), or the fusion inhibitor, enfuvirtide (ENF), but in some cases may confer cross-resistance to the CCR5 inhibitor, maraviroc (MVC). • While viruses resistant to enfuvirtide were not cross-resistant to FTR, some MVC-resistant viruses (in particular, CXCR4-tropic viruses) and some IBA-resistant viruses were cross-resistant with FTR.	Virologic failure occurred in the BRIGHTE trial and was associated with emergence of resistance to FTR and drugs in the OBT. Inclusion of FTR resistance and cross-resistance data in the label provides important information to optimize FTR use in combination with other ARVs.

Conclusions Regarding Benefit-Risk

HTE patients infected with MDR HIV-1 represent a rare but important subset of patients living with HIV. Patients with MDR HIV-1 who cannot achieve complete virologic suppression with antiretroviral therapy (ART) are at high risk for AIDS-related morbidity and mortality. This population needs new and effective ARV products that lack cross-resistance with commercially available products, have a favorable tolerability profile, and allow for convenient dosing. FTR, a first-in-class HIV-1 attachment inhibitor with Breakthrough Therapy Drug designation, is one such product.

Fostemsavir has clearly demonstrated short-term virologic activity in heavily treatment-experienced patients infected with MDR HIV. The pivotal trial, BRIGHTE, demonstrated superiority of FTR compared to placebo, when added to a failing regimen, for decline in HIV-1 RNA $\log_{10}$ copies/mL after 8 days of treatment. In addition, a significantly higher percentage of subjects achieved a >0.5 $\log_{10}$ decline in HIV-1 RNA at Day 8 with FTR compared to placebo. The lack of a control group after Day 8 in the BRIGHTE trial limits the ability to precisely quantify the contribution of FTR to long-term virologic suppression. However, the contribution of FTR is reflected by the relatively high rate of virologic suppression achieved with FTR plus optimized background therapy (OBT) through Week 96 in a population previously unable to achieve virologic suppression.

The safety database for FTR was adequate for the proposed dosing regimen and intended patient population. Overall, FTR has a favorable safety profile, and safety findings can be adequately addressed in labeling and by routine pharmacovigilance. The nature and frequency of significant safety events (deaths, SAEs, and discontinuations due to AEs) and the rate of virologic failure reported in the BRIGHTE trial reflect the targeted patient population: heavily treatment-experienced patients with advanced HIV/AIDS who are failing current ART and have very few remaining treatment options.

Based upon review of all available efficacy and safety data, the benefits of FTR, in combination with other ARVs, clearly outweigh the risks for treatment of HIV-1 infection in HTE adults with MDR HIV-1 infection failing their current ARV regimen due to resistance, intolerance, or safety considerations. The availability of FTR will provide a new and effective treatment option for this patient population.

II. Interdisciplinary Assessment

3. Introduction

ViiV Healthcare seeks approval of FTR for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant (MDR) HIV-1 infection failing their current ARV regimen due to resistance, intolerance, or safety considerations. FTR is a new molecular entity, first-in-class HIV-1 gp120-directed attachment inhibitor. Specifically, FTR is a prodrug without antiviral activity that is hydrolyzed to the active moiety, temsavir (TMR). TMR binds to the gp120 subunit within the HIV-1 envelope glycoprotein gp160 and selectively inhibits the interaction between the virus and host cell CD4+ T cell receptors, thereby preventing attachment and viral entry into host cells.

Bristol-Myers Squibb (BMS) submitted an investigational new drug (IND) application for FTR to FDA on November 8, 2005 for the treatment of HIV-1 infection. Recognizing the potential therapeutic benefit of FTR to treat a serious condition and fill an unmet medical need for HTE patients with limited treatment options, FDA granted Fast Track Designation on February 16, 2011 and Breakthrough Therapy Designation on June 24, 2015. IND sponsorship changed from BMS to ViiV Healthcare on September 8, 2016, and ViiV Healthcare is the Applicant for the new drug application (NDA). Please refer to Section III.12 for complete regulatory history.

The review team identified six key review issues that had a significant impact on the overall determination of approvability of FTR. Some of these issues were identified prior to submission of the NDA, whereas others emerged during the early stages of the NDA review. In depth analyses of the benefit and risk issues can be found in Section 6.4 and Section 7.7, respectively.

- Benefit Issue 1: Assessing the impact of subjects who did not meet eligibility criteria for the BRIGHTE (AI438047/205888) trial on efficacy results
- Benefit Issue 2: Identifying baseline predictors of FTR response at Day 8
- Benefit Issue 3: FTR exposure-response relationship for subjects with high baseline FTR EC50 values
- Benefit Issue 4: Evaluating efficacy at Week 24 in subjects with dolutegravir (DTG)- and/or boosted darunavir (DRV/r or DRV/c)-containing OBT
- Risk Issue 1: FTR resistance
- Risk Issue 2: Safety implications of a photodegradant product containing a beta-lactam structure (BMT-218946)

3.1. Approach to the Review

Table 3 provides an overview of the clinical trials conducted to support the benefit-risk assessment of FTR. Results through Week 96 from the Randomized Cohort of the Phase 3 BRIGHTE trial provide the primary basis of efficacy and safety of FTR for treatment of MDR HIV-1 infection in HTE patients; results from the Non-randomized Cohort provide supportive

safety and efficacy data. The safety, dose selection, and initial demonstration of antiviral activity of FTR were supported by data through Week 96 of the Phase 2b clinical trial (AI438011/205889) conducted in patients who had prior ARV treatment experience but were not considered HTE.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations for FTR

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
AI438047/205888, BRIGHTE Trial	HTE Subjects Infected with MDR HIV-1 infection	Randomized Cohort: R, PC, DB, MC Phase 3 Trial	Blinded Period (Days 1-8): Cohort A: Fostemsavir 600 mg BID + failing ARV regimen Cohort B: Placebo + failing ARV regimen Open-Label Period (starting on Day 9): Fostemsavir 600 mg BID + OBT Duration 96 Weeks	Primary: HIV-1 RNA log_{10} change from Day 1 to Day 8 Secondary: Proportion of subjects with >0.5 log_{10} reduction for HIV-1 RNA at Day 8. Durability of response, assessed as proportion of subjects with virologic suppression (HIV-1 RNA <40 copies/mL), evaluated at Weeks 24, 48, and 96	Planned: >140 Actual: 272	Centers: 108 Countries: 22
		Non-randomized Cohort: OL MC group of the Phase 3 trial	Fostemsavir 600 mg BID + OBT	No formal hypothesis testing. Durability of response, assessed as proportion of subjects with virologic suppression (HIV-1 RNA <40 copies/mL), evaluated at Weeks 24, 48, and 96	Planned: N/A Actual: 99	

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
AI438011/ 205889	ART-experienced subjects with HIV-1 infection	R, DB, MC, active-controlled dose-ranging Phase 2b Trial	Cohort 1: FTR 400 mg BID (n=50) Cohort 2: FTR 800 mg BID (n=49) Cohort 3: FTR 600 mg QD (n=51) Cohort 4: FTR 1,200 mg QD (n=50) Cohort 5: ATV/r (n=51) All groups also received RAL + TDF Duration: 96 Weeks	Primary: Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 24 Secondary: Changes from monotherapy Baseline (monotherapy Day 1) in log_{10} HIV-1 RNA by study day during monotherapy	Actual: 251	Centers: 45 Countries: 10

Source: CSR and adsl.xpt for each trial
Abbreviations: ARV, antiretroviral; BID, twice daily; DB, double-blind; FTR, fostemsavir; HTE, highly treatment-experienced; MC, multicenter; MDR, multidrug resistant; n, number of subjects; OBT, optimized background therapy; OL, open-label; PC, placebo-controlled; R, randomized; ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

4. Patient Experience Data

The Applicant submitted a patient-reported outcome assessment (Table 4). Assessing the impact of FTR + OBT on quality of life was an exploratory endpoint. Three instruments were used to measure the impact of FTR: the EQ-5D-3L, the Functional Assessment of HIV Infection (FAHI), and the Modified Medication Adherence Self-Report Inventory (M-MASRI) Questionnaire on Adherence.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	III.16.5: Health Outcomes Endpoints
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Clinical pharmacology properties of FTR were comprehensively evaluated (Table 5).

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacology activity	
Established pharmacologic class (EPC)	Fostemsavir (FTR) is a prodrug without significant biochemical or antiviral activity that is hydrolyzed to the active moiety, temsavir (TMR), which is an HIV-1 attachment inhibitor that can also inhibit postattachment steps.
Mechanism of action	TMR binds directly to the gp120 subunit within the HIV-1 envelope glycoprotein gp160 and selectively inhibits the interaction between the virus and cellular CD4 receptors, thereby preventing attachment, and preventing postattachment steps required for viral entry into host cells. TMR inhibited the binding of soluble CD4 to surface immobilized gp120 with an IC_{50} of 14nM using an enzyme-linked immunosorbent assay (ELISA).
Active moieties	FTR is a phosphate prodrug, which is hydrolyzed to TMR (active moiety) by alkaline phosphatase in the gastrointestinal lumen. FTR was not quantifiable in most clinical samples, suggesting that FTR conversion to TMR is predominantly presystemic.
QT prolongation	At therapeutic doses, FTR does not prolong the QT interval to any clinically relevant extent. At four times the recommended dose (2400 mg BID), the mean (upper 90% confidence interval) QTcF increase was 11.2 milliseconds (13.3 milliseconds). The observed increase in QTcF was TMR concentration-dependent.
General information of TMR	
Bioanalysis	Validated HPLC/MS/MS methods were used to determine the concentrations of FTR, TMR, TMR metabolites (BMS-646915 and BMS-930644) and coadministered drugs in human plasma, urine, and feces (as applicable to individual studies).
Healthy subjects vs. patients	TMR PK are similar in healthy subjects and subjects with HIV-1 infection.
Drug exposure at steady state following the therapeutic dosing regimen	**Parameter Mean (CV%)** / **TMR[a]** C_{max} (ng/mL) / 1,770 (39.9) AUC_{tau} (ng.h/mL) / 12,900 (46.4) C_{trough} or C_{12} (ng/mL) / 478 (81.5) [a] Based on population pharmacokinetic analyses in heavily treatment-experienced adult subjects with HIV-1 infection receiving FTR 600 mg twice daily with or without food in combination with other antiretroviral drugs.
Range of effective dose(s) or exposure	The relationships between TMR exposure (C_{12}) and the efficacy endpoint in the Phase 2b trial were flat over the range of exposure achieved following FTR dose range of 400 mg BID to 800 mg BID.
Maximally tolerated dose or exposure	An MTD was not determined. The highest evaluated dose in humans was 2400 mg BID (in a TQT trial).
Dose proportionality	TMR C_{max} and AUC_{inf} increased in a slightly > dose proportional manner over a dose range of 600 mg to 1,800 mg.
Accumulation ratio	1.1 to 1.7
Time to achieve steady-state	Steady-state plasma TMR concentrations are achieved by Day 2 to 3 following administration of FTR 600 mg BID.

Characteristic	Drug Information
Bridge between to-be marketed and clinical trial formulations	The to-be-marketed FTR formulation was a film-coated tablet and was used in the pivotal BRIGHTE trial.
Absorption	
Bioavailability	Absolute bioavailability is 26.9%, which was determined in an absolute bioavailability study comparing an IV micro dose of FTR 100 µg [^{13}C]-TMR and an oral dose of FTR 600 mg ER tablet.
T_{max}	2 hours
Food effect (fed/fasted) geometric least square mean and 90% CI	**Meal Type** / **AUC GMR (90% CI)** / **C_{max} GMR (90% CI)** / **T_{max}** Standard meal vs. fasted: 1.10 (0.95, 1.26) / 0.96 (0.83, 1.10) / T_{max} prolonged from 2 h (fasted) to 4 h (fed) High-fat meal vs. fasted: 1.81 (1.54, 2.12) / 0.97 (0.81, 1.17) / T_{max} prolonged from 2 h (fasted) to 6.5 h (fed) A standard meal was comprised of approximately 423 kcal, 36% fat, 47% carbohydrates, and 17% protein; a high-fat meal was comprised of approximately 985 kcal, 59.9% fat, 27.8% carbohydrates, and 12.3% protein.
Distribution	
Steady state volume of distribution	29.5 L
Plasma protein binding	88.4% The presence of 40% adult human serum resulted in 2.1- and 1.5-fold increases of temsavir EC_{50} values against HIV-1 LAI and NL4-3 in MT-2 cells, respectively. Blood:Plasma ratio of TMR ranged from 0.79 to 0.96.
Drug as substrate of transporters	Temsavir is a substrate of P-glycoprotein (P-gp) and BCRP.
Elimination	
Mass balance results	Following administration of 300 mg [^{14}C]FTR, 89% of the administered dose was recovered in the excreta; 51% of the dose was recovered in urine (1.9% as unchanged) and 33% was recovered in feces (1.1% as unchanged). The major circulating forms in plasma were metabolites of TMR; the major metabolites were BMS-646915 (a product of hydrolysis of TMR) and BMS-930644 (M28; a product of N-dealkylation of TMR).
Clearance and apparent oral clearance	17.9 L/h (CL) and 66.4 L/h (CL/F)
Half-life	11 hours
Metabolic pathway(s)	Hydrolysis by esterases (36.1% of oral dose), Oxidation by CYP3A4 (21.2% of oral dose) UGT (<1% of oral dose)
Primary excretion pathways (% dose)	51% of the dose was recovered in urine (1.9% as unchanged) and 33% was recovered in feces (1.1% as unchanged).

Characteristic	Drug Information
Intrinsic factors and specific populations	
Body weight	Population pharmacokinetic analyses indicated that the magnitude of predicted change in TMR C_{tau} (exposure) over a body weight range of 40 kg to 150 kg was not clinically relevant and does not warrant a dose adjustment.
Age	Population pharmacokinetic analyses of subjects with HIV-1 infection from studies with FTR indicated that age up to 73 years had no clinically relevant effect on the pharmacokinetics of TMR. TMR PK data in subjects ≥65 years old is limited. Dose adjustment is not needed based on age.
Renal impairment	No dosage adjustment is required for patients with any degree of renal impairment and ESRD patients on dialysis.
Hepatic impairment	No dosage adjustment is required in patients with mild to severe hepatic impairment (Child-Pugh Score A, B, or C).
Drug interaction liability (drug as perpetrator)	
Inhibition/induction of metabolism	TMR does not inhibit or induce CYP enzymes or UGT. BMS-930644, a TMR metabolite, is an inhibitor of CYP3A.
Inhibition/induction of transporter systems	TMR inhibits transporter OATP1B1/B3. TMR and its metabolites (BMS-646915 and BMS 930644) are inhibitors of breast cancer resistance protein (BCRP). TMR and its metabolites are also inhibitors of multidrug and toxin extrusion protein (MATE)2-K. At clinically relevant concentrations, significant interactions are not expected with (MATE)2-K substrates.

Source: Reviewer's table based on data from Sections 8.1, 8.2 and Section III.14
Abbreviations: AUC, area under the curve; AUC_{inf}, area under the curve to infinity; AUC_{tau}, area under the curve during a dosing interval; BCRP, breast cancer resistance protein; BID, twice daily; C_{max}, maximum plasma concentration; C_{trough}, trough concentration; CV, coefficient of variation; CYP, cytochrome P450; GMR, geometric mean ratio; HPLC, high performance liquid chromatography; MS, mass spectrometry; MTD, maximum tolerated dose; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration; TQT, thorough QT; UGT, Uridine 5'-diphospho-glucuronosyltransferase.

5.1. Nonclinical Assessment of Potential Effectiveness

Antiviral activity of TMR (the active moiety of FTR) was assessed across tropism strains and HIV-1 subtypes. In summary:

- TMR antiviral activity was reduced against some CXCR4-tropic viral isolates. There may be overlap between tropism determinants of gp120 and the antiviral activity of TMR against gp120.
- TMR antiviral activity was variable and displayed a wide range of EC_{50} values across and within all HIV-1 subtypes.
- TMR does not show activity in cell culture or clinically against subtype AE isolates (also known as subtype E).

Antiviral Activity Against CCR5- and CXCR4-Tropic Viruses

TMR demonstrated antiviral activity against three CCR5-tropic subtype B laboratory strains with EC_{50} values ranging from 0.4 to 1.7nM. TMR had reduced antiviral activity against three of five CXCR4-tropic laboratory isolates with EC_{50} values of 14.8, 16.2 and >2,000 nM. The other two CXCR4-tropic isolates had EC_{50} values of 0.7 and 2.2nM. TMR had an EC_{50} value of 57.6nM against the one dual-tropic laboratory strain. Overall, antiviral activity of TMR against HIV-1 subtype B clinical isolates varied depending on tropism with median EC_{50} values of 3.7nM,

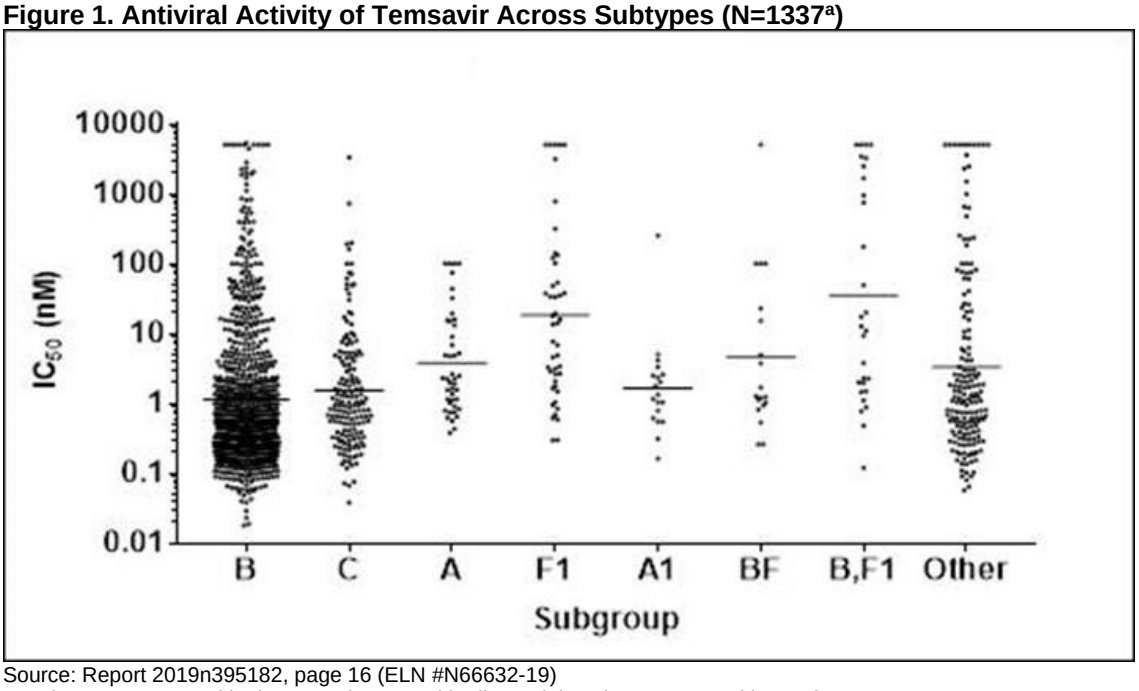
40.9nM, and 0.8nM against the CCR5-tropic viruses, CXCR4-tropic viruses, and dual/mixed viruses, respectively. Although EC_{50} values for TMR display a broad range in antiviral activity across the different tropic strains, the median EC_{50} value against CXCR4-tropic strains was higher suggesting a possible tropism effect. Tropism is determined by gp120, which is the target of TMR, so it is possible that there is overlap between tropism determinants and antiviral activity of TMR. Please refer to Section 6.4.2 for an assessment of the impact of baseline tropism on the primary efficacy endpoint in the BRIGHTE trial.

To further explore TMR susceptibility by tropism, an analysis was performed on baseline subject data from the BRIGHTE trial. Baseline phenotypic and viral tropism data was available from 361 subjects. The median TMR fold change values were similar for CXCR4-, CCR5- and dual/mixed-tropic viruses. Median fold change values for the CXCR4-, CCR5- and dual/mixed-tropic viruses were 1.1 (n=101), 1.31 (n=34) and 0.84 (n=226), respectively. The proportion of CXCR4-, CCR5- and dual/mixed tropic-viruses with TMR fold changes >100 was 15% (15/101), 18% (6/34) and 12% (26/226), respectively. Thus, these data from clinical isolates indicated there is no considerable difference in TMR phenotypic susceptibility based on viral tropism.

Antiviral Activity Against HIV-1 Subtypes

Analysis of data from 1,337 clinical samples from the FTR clinical development program shows wide variability and range in TMR antiviral activity across subtypes (Figure 1; Table 6) with EC_{50} values across subtypes ranging from 0.018nM to >5,000nM. Of all the isolates tested, 54% (719/1,337) exhibited EC_{50} values below 1nM, 80% (1,071/1,337) had EC_{50} values below 10nM and 91% (1,217/1,337) exhibited EC_{50} values below 100nM. For subtype B, in order to equal or exceed the EC_{50} values for 90% of all subtype B viruses, the Applicant calculated that a concentration of 38.34nM would be required. The majority of the subtype B isolates (84%, 740/881) had EC_{50} values below 10nM with 6% of isolates having EC_{50} values >100nM. Subtypes BF, F1 and B, F1 had higher proportions (21 to 38%) of isolates with EC_{50} values >100nM, and all five subtype AE isolates (100%) had EC_{50} values >100nM (Table 6). Additionally, from another panel of clinical isolates with non-B subtypes, TMR showed activity against three of four subtype D isolates (EC_{50} values =0.5, 1.3, 31.8, >2,000nM), but did not show activity against three subtype E (AE) isolates (EC_{50} values >1,800nM), two group O isolates (EC_{50} values >2,000nM), one HIV-2 isolate, and only moderate activity against two of three subtype G isolates (EC_{50} values 33.6, 62.4, >2,000nM).

Figure 1. Antiviral Activity of Temsavir Across Subtypes (N=1337[a])



Source: Report 2019n395182, page 16 (ELN #N66632-19)
Envelopes are grouped by known subtypes, with all remaining viruses grouped into Other.
The geometric means of each group are shown by the horizontal line.
Symbols at top of B and Other columns represent viruses without a defined IC_{50}, but rather have an IC_{50} above the highest concentration tested.
[a] 881 subtype B samples, 156 subtype C samples, 43 subtype A samples from subtype A, 17 subtype A1 samples, 48 subtype F1 samples, 29 subtype BF1 samples, 19 subtype BF samples and 5 CRF01_AE samples, 139 other.
Abbreviations: IC_{50}, half maximal inhibitory concentration.

Table 6. Range of Susceptibilities of Various Subtypes in the PhenoSense Entry

Subtype	#	EC_{50}<1nM n (%)	EC_{50}>1-<10nM n (%)	EC_{50}>10-<100nM n (%)	EC_{50}>100nM n (%)	Geometric Mean (nM)[a]
All	1337	719 (53.8)	352 (26.3)	146 (10.9)	120 (9.0)	1.73
B	881	544 (61.7)	196 (22.2)	85 (9.6)	56 (6.4)	1.15
C	156	78 (50.0)	56 (35.9)	15 (9.6)	7 (4.5)	1.53
A1	17	5 (29.4)	11 (64.7)	0 (0)	1 (5.9)	1.63
A	43	10 (23.3)	21 (48.8)	8 (18.6)	4 (9.3)	3.81
BF	19	5 (26.3)	8 (42.1)	2 (10.5)	4 (21.1)	4.55
F1	48	8 (16.7)	15 (31.3)	13 (27.1)	12 (25.0)	18.27
B, F1	29	4 (13.8)	9 (31.0)	5 (17.2)	11 (37.9)	34.91
CRF01_AE	5	0 (0)	0 (0)	0 (0)	5 (100)	-

Source: Report 2019n395182, page 17 (ELN #N66632-19)
[a] May include isolates with > MAX IC_{50} (MAX =5000nM) and >100nM IC_{50}
Abbreviations: EC_{50}, half maximal effective concentration.

In the BRIGHTE trial, subtype B was most prevalent with 84% of the subjects having subtype B HIV-1 infection (Table 7). There were similar proportions of each subtype in the randomized FTR arm as in the overall trial. Importantly, the response to FTR functional monotherapy at Day 8 in the clinical trial was assessed for each subtype by looking at the median decline in HIV-1 RNA at Day 8, the proportion of subjects with each subtype that responded at Day 8 (>0.5 log decline in HIV-1 RNA), and phenotypic FTR susceptibility (fold change [FC]) for the isolates of each subtype in the randomized FTR arm where Day 8 activity was able to be assessed. The

median decline in HIV-1 RNA at Day 8 for subjects with subtype B was 0.97 log_{10} copies/mL with 67% of subtype B subjects responding at Day 8 (Table 7). The favorable response to FTR at Day 8 by subtype B subjects is consistent with the median 1.1-FC in FTR susceptibility for isolates from subtype B subjects. In the randomized FTR arm, the two subjects infected with subtype A1 and the one subject infected with subtype AE did not respond at Day 8. The FC in susceptibility to FTR for these three isolates was 2.7, 716 and 4,747, respectively. In contrast, subjects with F1 or BF1 subtypes, which are also less susceptible to TMR in cell culture compared to subtype B, showed good virologic response at Day 8 with 64% and 70% of subjects achieving HIV-1 RNA decline >0.5 log_{10} copies/mL and a median HIV-1 RNA decline of 0.91 log_{10} and 0.88 log_{10} copies/mL, respectively (Table 7).

Table 7. Prevalence of HIV-1 Subtypes in BRIGHTE Trial and Response at Day 8 by Subtype

Subtype	Prevalence of Subtype in Trial N=371 n (%)	Randomized FTR Arm N=198 n (%)	Median Day 8 Decline in HIV-1 RNA	Number With >0.5 log_{10} Decline at Day 8	FTR FC (Median)	EC_{50} Geometric Mean (nM)[a]
A1	2 (0.5)	2 (1)	0.16	0/2	2.7, 716	1.63
AE	2 (0.5)	1 (0.5)	0	0/1	4747	>100nM
AG	1 (0.2)	-	-	-	-	-
B	312 (84)	159 (80)	0.97	107/159 (67%)	(1.1)	1.15
BF1	14 (4)	10 (5)	0.88	7/10 (70%)	(14)	34.91
C	9 (2)	5 (3)	0.84	4/5 (80%)	(3.9)	1.53
D	1 (0.2)	-	-	-	-	-
F1	22 (6)	14 (7)	0.91	9/14 (64%)	(19)	18.27
G	3 (0.8)	2 (1)	1.8	2/2	(16)	34->2,000
NA	1 (0.2)	1 (0.5)	1.1	1/1	-	-
Other	4 (1)	4 (2)	0.43	2/4	(126)	-

Source: Clinical Virology Reviewer analysis
[a] Mean for each subtype using PhenoSense Entry Assay of 1337 total isolates assayed in cell culture
Abbreviations: EC_{50}, half maximal effective concentration; FC, fold change; FTR, fostemsavir.

Reduced Antiviral Activity Against Subtype AE (E) Isolates

In total, TMR showed no antiviral activity against 14 different subtype AE isolates in peripheral blood mononuclear cell (PBMC) assays and the Phenosense Entry™ assay indicating that subtype AE (or E) viruses are inherently resistant to TMR. Genotyping of subtype AE viruses showed that there were changes at S375H and M475I, which are likely associated with TMR resistance. Subtype AE is a predominant subtype in Southeast Asia but is not found at high frequencies elsewhere throughout the world.

Only two subjects in the Randomized Cohort of the BRIGHTE trial had subtype AE virus at Screening. One subject (EC_{50} FC >4,747-fold and gp160 substitutions at S375H and M475I at baseline) did not respond to FTR at Day 8 (Table 8). The second subject (EC_{50} FC 298-fold and gp160 substitution at S375N at baseline) received placebo during functional monotherapy. Both subjects were virologically suppressed (HIV-1 RNA <50 copies/mL) at Week 96 while receiving DTG-containing OBT with FTR.

Table 8. Details of Two Subjects With Subtype AE[a]

Subject #	Arm	Screening HIV-1 RNA copies/mL	Baseline HIV-1 RNA copies/mL	Decline in HIV-1 RNA at Day 8	FTR RAPs (FC)	Failing ARV	Drugs with Resistance	OBT
112	Randomized placebo	816,148	1,102	0.47	S375N (298)	DRV/r, ABC, LAM	ABC, LPV, partial DRV	DTG, LPV/r, ABC, LAM
358	Randomized FTR	169,932	14,027	0.00	S375H M475I (4747)	DRV/r, RAL, ETR, TDF	DRV/r, RAL, ETR, partial TDF, FTC	DTG, FTC, TDF

Source: Clinical Virology Reviewer analysis
[a] Both subjects were virologically suppressed at Week 96 while receiving FTR plus OBT
Abbreviations: ABC, abacavir; AE, adverse event; ARV, antiretroviral; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; ETR, etravirine; FC, fold change; FTC, emtricitabine; FTR, fostemsavir; LAM, lamivudine; LPV, lopinavir; OBT, optimized background therapy; RAL, raltegravir; RAP, resistance-associated polymorphism; TDF, tenofovir disoproxil fumarate.

6. Evidence of Benefit (Assessment of Efficacy)

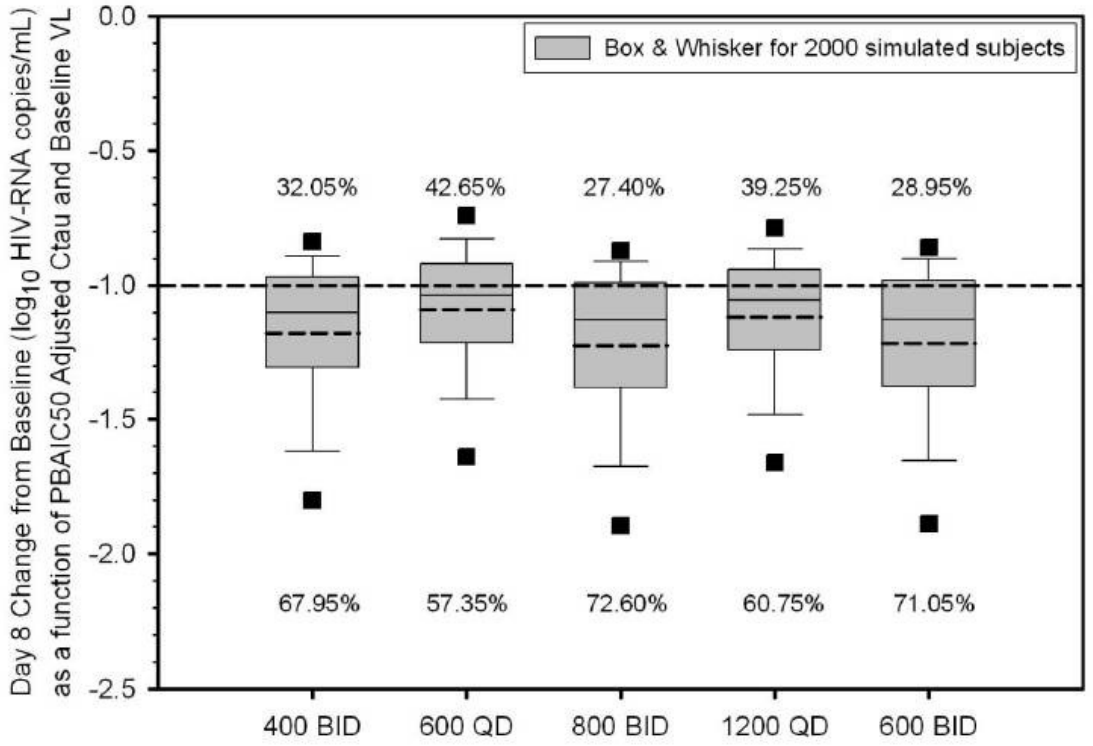
6.1. Assessment of Dose and Potential Effectiveness

The Applicant's proposed dose, 600 mg twice daily (BID), was the dose evaluated in the pivotal trial BRIGHTE and is acceptable for approval.

The dose selected for evaluation in the BRIGHTE trial was based on pharmacokinetic (PK), efficacy, and safety data from two Phase 2 trials in subjects with HIV-1 infection. AI438006/206267 was a Phase 2a trial that evaluated FTR 600 mg BID and 1,200 mg QHS in treatment-naïve subjects and FTR 1,200 mg BID in treatment-experienced (but not considered HTE) subjects. AI438011/205889 was a Phase 2b trial that evaluated FTR 400 mg BID, 600 mg BID, 800 mg BID, 600 mg once a day (QD), and 1,200 mg QD. The primary endpoint for the Phase 2a and 2b trials was a mean decline in plasma HIV-1 RNA from Day 1 to Day 8 with FTR monotherapy.

The Applicant performed an E-R analysis using the monotherapy data from the Phase 2a and 2b trials and selected 600 mg BID for the Phase 3 trial. Although 600 mg BID was not evaluated in Phase 2 trials, this dose was predicted to have a high probability of achieving an antiviral effect while minimizing the risk of QT prolongation which was observed at a 2,400 mg BID dose (see Section 5).

Figure 2. Model-Predicted Change in Plasma HIV-1 RNA From Day 1 to Day 8 and Proportions of Subjects Achieving >1 log10 copies/mL Reduction in Plasma HIV-1 RNA on Day 8 for FTR Monotherapy Regimens



Source: Summary of Clinical Pharmacology studies Page 111, Phase 2 PPK Report Figure 5.5.1-1
Abbreviations: BID, twice daily; C_{tau}, plasma concentration during a dosing interval; VL, viral load.

In the Phase 3 trial evaluating the proposed dosing regimen (600 mg BID) in HTE patients on their failing regimen, no clear E-R relationship was observed between TMR C_{tau} and changes in plasma HIV-1 RNA from Day 1 to Day 8 (during functional monotherapy) or TMR C_{tau} and efficacy endpoints at Week 24 (after subjects had been transitioned to OBT).

6.2. Design of Clinical Trials Intended To Demonstrate Benefit to Patients

6.2.1. Trial Design

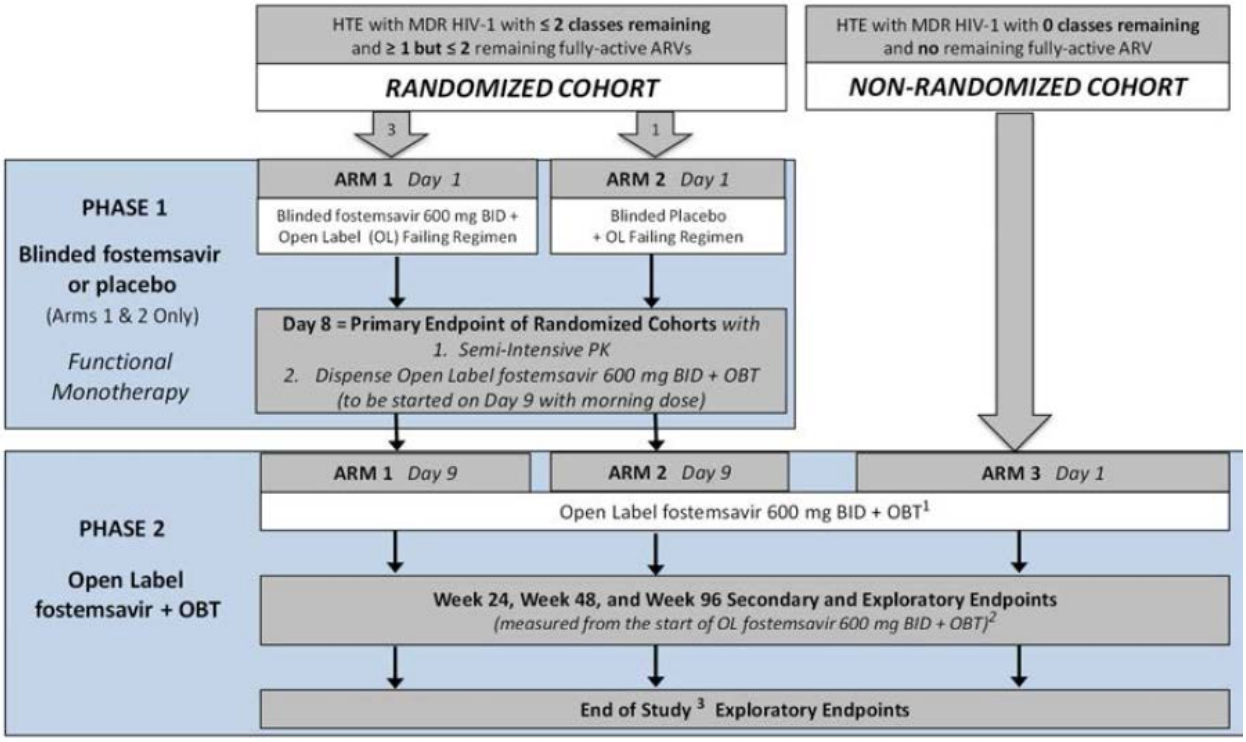
Results from the BRIGHTE trial serve as the basis of the benefit evaluation. This trial was designed in accordance with the recommendations set forth in FDA's guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015). The guidance states trials evaluating novel ARV drugs for HTE patients should be randomized, placebo-controlled, superiority trials in which subjects are randomized to receive a short duration (7 to 14 days) of the investigational drug or placebo in addition to their failing ARV regimen. The primary efficacy outcome is measured after that short duration of functional monotherapy, and then all subjects transition to open-label investigational drug plus OBT. It is not considered ethical or feasible to allow subjects to remain on double-blind therapy with a failing background regimen for more than 1 to 2 weeks because of the risk of developing resistance to the new agent without adequate background therapy.

BRIGHTE was a two-cohort Phase 3 trial conducted in HTE patients with MDR HIV-1 infection. Participation in the Randomized Cohort or Non-randomized Cohort was dictated by the number of fully active ARVs available to construct a background regimen.

- Randomized Cohort:
  - HTE subjects with MDR HIV-1 infection on a failing ARV regimen. Subjects had ≤2 ARV classes remaining with at least 1 but no more than 2 remaining fully active ARVs which could be effectively combined to form a viable new regimen, based on baseline or documented historical resistance testing and tolerability and safety concerns.
  - Subjects were randomized 3:1 to treatment with FTR 600 mg BID or placebo, respectively, in addition to their failing regimen for 8 days.
  - Randomization was stratified by baseline HIV-1 RNA (≤1,000 copies/mL or >1,000 copies/mL).
  - The primary endpoint was assessed on Day 8 after which all subjects began open-label FTR 600 mg BID in combination with OBT.
  - Virologic and immunologic responses were followed for at least 96 weeks to assess the durability of treatment with FTR.
  - Data from the Randomized Cohort provide the basis for determination of efficacy. This cohort also serves as the primary safety population.
- Non-randomized Cohort:
  - HTE subjects with MDR HIV-1 infection on a failing ARV regimen who had no remaining fully-active ARVs that could be combined in a new regimen, based on current and/or documented historical resistance testing.
  - Subjects began open-label FTR 600 mg BID + OBT starting on Day 1.
  - Virologic and immunologic responses were followed for at least 96 weeks to assess the durability of treatment with FTR.
  - The purpose of this cohort was to allow access to FTR for individuals with no remaining therapeutic options.
  - Data from the Non-randomized Cohort provide safety and supplementary efficacy information. No formal hypothesis testing was conducted.

The study schematic is summarized in Figure 3.

Figure 3. BRIGHTE Study Schema



Source: Figure 3.1-1 of the Clinical Study Protocol
[1] Subjects in the Randomized Cohort begin Open-Label Dosing on Day 9. Subjects in the Non-randomized Cohort begin Open-Label Dosing on Day 1.
[2] The start of OL fostemsavir 600 mg BID is used as the marker from which all other visits will be measured, i.e., the Week 4 visit for subjects in the Randomized Cohort will occur 4 weeks after the Day 8 visit; the Week 4 visit for subjects in the Non-randomized Cohort will occur 4 weeks after the Day 1 visit.
[3] The study is expected to be conducted until an additional option, a rollover study or marketing approval, is in place (as outlined in Section 3.2).
Abbreviations: ARV, antiretroviral; BID, twice daily; HTE, highly treatment-experienced; MDR, multidrug resistant; OBT, optimized background therapy; PK, pharmacokinetic.

6.2.2. Eligibility Criteria

Key eligibility criteria are summarized in this section and the full criteria are available in Section III.15.

Inclusion Criteria

- Men and nonpregnant women at least 18 years of age.
- Antiretroviral-experienced with documented historical or baseline resistance, intolerability, and/or contraindications to ARVs in at least three classes.
- Failing current ARV regimen with a confirmed plasma HIV-1 RNA ≥400 copies/mL (first value from Investigator within 6 months of Screening visit, with the second value obtained from screening labs). Subjects with a Screening HIV-1 RNA <400 copies/mL should be counted as screen failures; repeat testing is not permissible.
- Must have at least 1 fully active and available agent in ≤2 ARV classes, based on current and/or documented historical resistance testing, taking into account tolerability and other safety concerns. Details regarding the determination of ARV activity are provided in element 8 of the inclusion criteria (see Section III.15).

Exclusion Criteria

- Chronic untreated hepatitis B virus (HBV) (however, patients with chronic treated HBV are eligible)
- History of decompensated cirrhosis or active decompensated cirrhosis
- History of congestive heart failure or congenital prolonged QT syndrome
- Electrocardiogram abnormalities
  - QT abnormalities: Confirmed QT value >500 msec at Screening or Day 1; Confirmed QTcF value >470 msec for women and >450 msec for men at Screening or Day 1
  - Confirmed PR Interval >260 msec (severe 1st degree AV block) at Screening or Day 1
  - Confirmed second or third degree heart block at Screening or Day 1
- Laboratory evidence of hepatic impairment, significant anemia or significant thrombocytopenia (see Section III.15)

6.2.3. Statistical Analysis Plan

The Applicant and the review division agreed on the BRIGHTE statistical analysis plan prior to the trial completion.

The primary efficacy endpoint was assessed in the Randomized Cohort. The study was designed to show superior antiviral activity of FTR compared to placebo when combined with a failing regimen over a period of 8 days. At least 140 subjects were planned to be randomized 3:1 to FTR or placebo. Log_{10} HIV-1 RNA change from Day 1 to Day 8 was calculated using the HIV-1 RNA value closest to Day 8, and within an analysis visit window inclusive of Day 6 through Day 10 of blinded treatment. All tests were performed at the two-sided 0.05 alpha level. The Intent-to-Treat, Exposed population consisted of all randomized subjects who received at least one dose of study medication and was used for the primary analysis of efficacy. For the Randomized Cohort, the Intent-to-Treat, Exposed population was based on the treatment to which the subject was randomized (placebo or FTR) regardless of the treatment the subject actually received.

The primary efficacy analysis of the primary endpoint fit a one-way analysis of covariance (ANCOVA) with log_{10} HIV-1 RNA change from Day 1 at Day 8 as the dependent variable, treatment (FTR or placebo) as an independent variable, and log_{10} Day 1 HIV-1 RNA as a continuous covariate. Missing HIV-1 RNA values at Day 8 were imputed using (a) Day 1 Observation Carried Forward for subjects without a value during blinded treatment (i.e., imputing a zero change from Day 1), and (b) last observation carried forward (LOCF) for subjects with an early value during blinded treatment before the Day 8 analysis visit window.

Key secondary efficacy analyses of the randomized double-blind phase at Day 8 included a comparison of the percentage of subjects with an HIV-1 RNA decline >0.5 log_{10} and >1.0 log_{10} copies/mL from baseline in the FTR and placebo groups. Secondary assessments also included safety, durability of virologic response, immunologic response, and emergence of resistance to the investigational drug and other drugs in the regimen. These secondary assessments occurred

24, 48, and 96 weeks from the time point subjects in both groups of the Randomized Cohort received open-label FTR in combination with OBT (extension phase). The durability of virologic response (HIV-1 RNA <40, <200, and <400 copies/mL) at Week 24, 48, and 96 was assessed using the FDA Snapshot algorithm (see FDA guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015) for details) . During the course of the trial, changes in OBT were permitted. Subjects without an HIV-1 RNA value at a relevant time point due to missed visits or discontinuation or subjects who changed OBT due to lack of efficacy were counted as treatment failures. HIV-1 RNA values collected after initial OBT change due to lack of efficacy were excluded. Changes from baseline in CD4+ T cell counts and percentage of CD4+ T cells were also assessed at Weeks 24, 48, and 96.

For the open-label, single arm, Non-randomized Cohort, the durability of virologic response and immunologic response with FTR in combination with OBT was summarized at Week 24, 48, and 96.

Subgroup analyses were performed to assess the consistency of the primary efficacy analysis in the Randomized Cohort. Subgroups of interest included HIV-1 RNA categories at Day 1, CD4+ T cell categories at Day 1, HIV-1 subtype, age group, gender, geographic region, number of fully active ARVs in the initial OBT, and number of baseline polymorphisms of interest in the gp160 domain.

6.3. Results of Analyses of Clinical Trials/Studies Intended To Demonstrate Benefit to Patients

This section summarizes the subject disposition, baseline demographics and clinical characteristics, and primary and key secondary efficacy results to support the efficacy of FTR in HTE subjects with MDR HIV-1 infection. Data from the Randomized and Non-randomized Cohorts are often shown side-by-side for ease of presentation. However, the two cohorts represent discrete groups with different populations and are not intended to be compared to one another.

6.3.1. Disposition, Baseline Demographics, and Baseline Clinical Characteristics

Disposition

Subject disposition information for the BRIGHTE trial is summarized in Table 9 and Table 10. Slightly more than 50% of the patients screened for participation were enrolled in the trial. The prespecified study duration was 96 weeks. However, subjects were allowed to remain on study beyond 96 weeks in order to maintain access to FTR pending regulatory action. The majority of subjects (78%) in each randomized treatment group remained in the trial at the Week 96 data cutoff. The most frequent reasons for discontinuation in both the Randomized and Non-randomized Cohorts were lack of efficacy, nonadherence to study drug, and death.

Table 9. Subject Screening and Randomization, BRIGHTE Trial

Screening Disposition	N
Patients screened	731
Patients enrolled	383
Patients treated with FTR	371
Randomized cohort	272
FTR group	203
Placebo group	69
Non-randomized cohort	99

Source: adsl.xpt and adds.xpt; Software: Python
Abbreviation: FTR, fostemsavir.

Table 10. Subject Disposition Through Week 96, BRIGHTE Trial

Disposition Outcome	Randomized Cohort Fostemsavir N=203 n (%)	Randomized Cohort Placebo N=69 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Patients randomized				
ITT population	203	69	99	371
Per-protocol population	165	59	NA	224
Safety population	203	69	99	371
Discontinued study drug				
Lack of efficacy	9 (4.4)	3 (4.3)	6 (6.1)	18 (4.9)
Noncompliance with study drug	8 (3.9)	3 (4.3)	6 (6.1)	17 (4.6)
Death	7 (3.4)	2 (2.9)	15 (15.2)	24 (6.5)
Subject no longer meets study criteria	0 (0.0)	0 (0.0)	4 (4.0)	9 (2.4)
Withdrawal by subject	0 (0.0)	0 (0.0)	1 (1.0)	6 (1.6)
Adverse event	4 (2.0)	3 (4.3)	4 (4.0)	11 (3.0)
Lost to follow-up	4 (2.0)	4 (5.8)	1 (1.0)	9 (2.4)
Other	0 (0.0)	0 (0.0)	1 (1.0)	2 (0.5)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Source: adsl.xpt and adds.xpt; Software: Python
Abbreviations: ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group.

Baseline Demographics and Clinical Characteristics

Overall, the majority of subjects in the trial (Randomized and Non-randomized Cohorts combined) were male (78%), white (70%), and the median age was 49 years ranging from 17 to 73 years of age. Twenty-two percent (22%) of all subjects were black/African-American. Just under 30% of all subjects identified as Hispanic or Latino; data reporting was incomplete for this variable, with 33% of the randomized subjects and 18% of nonrandomized subjects reported as unknown ethnicity. The majority of randomized subjects were from North or South America (40% each), whereas the majority of nonrandomized subjects were from North America (57%).

Baseline median HIV-1 RNA was comparable across the study groups ranging from 4.3 to 4.7 $\log_{10}$ copies/mL. Median baseline CD4+ T cell count was notably lower in the Non-randomized Cohort compared to the Randomized Cohort (41 cells/mm^3 and 100 cells/mm^3, respectively) which is reflective of the differences in available ARV options between the two cohorts. Similarly, subjects in the Non-randomized Cohort had longer lifetime ART with more prior ARV regimens compared to randomized subjects.

The primary efficacy analysis compares the decline in HIV-1 RNA with FTR compared to placebo in the Randomized Cohort. Demographic factors and baseline disease characteristics were generally balanced between these two groups, as summarized in Table 11 and Table 12.

Table 11. Baseline Demographics, Safety Population, BRIGHTE Trial

	Randomized Cohort			Non-randomized Cohort
Characteristic	FTR 600 mg BID N=203	Placebo N=69	Total Randomized N=272	N=99
Sex, n (%)				
Male	143 (70)	57 (83)	200 (74)	89 (90)
Female	60 (30)	12 (17)	72 (26)	10 (10)
Age, years				
Mean (SE)	45 (1)	43 (1)	45 (1)	48 (1)
Median (min, max)	48 (18, 73)	45 (19, 66)	48 (18, 73)	50 (17, 72)
Age groups (years), n (%)				
<35	45 (22)	16 (23)	61 (22)	14 (14)
35-49	71 (35)	30 (43)	101 (37)	30 (30)
≥50	87 (43)	23 (33)	110 (40)	55 (56)
Race, n (%)				
White	137 (67)	48 (70)	185 (68)	74 (75)
Black/African American	42 (21)	18 (26)	60 (22)	23 (23)
American Indian or Alaska Native	6 (3)	1 (1)	7 (3)	1 (1)
Asian	2 (1)	0	2 (1)	0
Other	16 (8)	2 (3)	18 (7)	1 (1)
Ethnicity, n (%)				
Hispanic	61 (30)	18 (26)	79 (29)	28 (28)
Non-Hispanic	76 (37)	26 (38)	102 (38)	53 (54)
Missing	66 (33)	25 (36)	91 (33)	18 (18)
Region, n (%)				
North America	79 (39)	29 (42)	108 (40)	56 (57)
South America	80 (39)	25 (36)	105 (39)	14 (14)
Europe	38 (19)	13 (19)	51 (19)	27 (27)
Rest of world	6 (3)	2 (3)	8 (3)	2 (2)

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice daily; FTR, fostemsavir.

Table 12. Baseline Clinical Characteristics, Safety Population, BRIGHTE Trial

	Randomized Cohort			Non-randomized Cohort
Characteristic	FTR 600 mg BID N=203	Placebo N=69	Total Randomized N=272	N=99
Baseline HIV-1 RNA viral load (log_{10} copies/mL)				
Mean (SE)	4.4 (0.1)	4.4 (0.1)	4.4 (0.1)	4.2 (0.1)
Median	4.7	4.5	4.7	4.3
Min, max	1.6, 6.4	1.6, 6.9	1.6, 6.9	1.6, 6.6
Baseline CD4 cell counts (cells/mm^3), n (%)				
<20	55 (27)	17 (25)	72 (26)	40 (40)
20 to <50	19 (9)	6 (9)	25 (9)	14 (14)
50 to <200	76 (37)	26 (38)	102 (38)	25 (25)
≥200	53 (26)	20 (29)	73 (27)	20 (20)

Characteristic	Randomized Cohort FTR 600 mg BID N=203	Placebo N=69	Total Randomized N=272	Non-randomized Cohort N=99
Baseline CD4 cell counts (cells/mm^3)				
Mean (SE)	147 (12)	170 (25)	153 (11)	99 (13)
Median	99	100	100	41
Min, max	0, 1160	0, 915	0, 1160	0, 641
Number of years treated for HIV, n (%)				
1-5	11 (5)	8 (12)	19 (6)	1 (1)
6-10	16 (8)	6 (9)	22 (8)	4 (4)
11-15	30 (15)	14 (20)	44 (16)	11 (11)
16-20	72 (35)	18 (26)	90 (33)	22 (22)
>20	70 (34)	22 (32)	92 (34)	58 (59)
Unknown	4 (2)	1 (1)	5 (2)	3 (3)
History of AIDS, n (%)	170 (84)	61 (88)	231 (85)	89 (90)
History of hepatitis B and/or C at baseline, n (%)	15 (7)	6 (9)	21 (8)	8 (8)
Number of prior antiviral regimens, n (%)				
2	7 (3)	3 (4)	10 (4)	1 (1)
3	8 (4)	5 (7)	13 (5)	2 (2)
4	16 (8)	4 (6)	20 (7)	5 (5)
5 or more	169 (83)	57 (83)	226 (83)	90 (91)
Unknown	3 (1)	0	3 (1)	1 (1)

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice daily; FTR, fostemsavir; SE, standard error.

The proportion of subjects with resistance to available ARVs in each group of the Randomized Cohort was evaluated for imbalances that could affect the primary endpoint. All subjects in the Randomized Cohort continued their baseline (failing) ARV regimen during the 8-day blinded period of the study. Subjects may have had suboptimal adherence to the baseline regimen prior to study entry for several reasons, including perceived lack of benefit. However, these agents may have been at least partially active if taken regularly. The review team hypothesized that subjects who were not consistently taking their baseline ARV regimen prior to the study may have had greater adherence in the setting of a clinical trial, thereby contributing to the antiviral effect otherwise attributable solely to the investigational agent (FTR or placebo). This hypothesis is more likely true for high potency ARVs such as DTG and boosted DRV.

As summarized in Table 13, more than 50% of subjects in each of the two Randomized Cohorts had resistance to 3 or more classes at baseline. In addition, the proportion of subjects with DTG and/or darunavir (DRV) resistance is comparable between the two groups. Consistent with eligibility criteria, a proportion of subjects in the Non-randomized Cohort had resistance to 4 or more classes and less than half retained susceptibility to DRV or DTG.

Table 13. Number of Class Phenotypic Resistance at Screening, BRIGHTE Trial

# Class Resistance	FTR Randomized N=202[a]	Placebo N=69	Non-randomized N=98[a]
0	19 (9)	8 (12)	1
1	23 (11)	9 (13)	2
2	37 (18)	14 (20)	4
3	66 (33)	15 (22)	17 (17)
4	40 (20)	16 (23)	50 (51)
5	16 (8)	5 (7)	21 (21)
6	0	1 (1)	3
NR	1 (0.5)	1 (1)	0
T20 resistant	34/191 (18)	16/68 (24)	31/94 (33)
DTG resistant	21/200 (11)	5/68 (7)	51/98 (52)
DRV resistant	91/200 (46)	32/68 (47)	83/98 (85)

Source: Clinical Virology Reviewer's analysis
[a] One subject in each of these groups did not have available data.
Abbreviations: DRV, darunavir; DTG, dolutegravir; FTR, fostemsavir; NR, not reported.

6.3.2. Primary and Key Secondary Efficacy Results

Primary Endpoint

The Applicant's primary efficacy results were confirmed by the statistical review team, and the results demonstrate superiority of FTR compared to placebo for decline in HIV-1 RNA $\log_{10}$ copies/mL from Day 1 to Day 8, as summarized in Table 14. Superiority was demonstrated in the primary efficacy analysis because the 95% CI for the mean difference between the two treatment groups excluded zero and the p-value was statistically significant. Note that the two-sided 95% confidence intervals for both treatment groups did not include zero indicating that there was also a statistically significant decrease from baseline in both treatment groups.

Table 14. Primary Analysis: Plasma HIV-1 RNA $\log_{10}$ (copies/mL) Change From Day 1 to Day 8 Using One-Way ANCOVA (Randomized Cohort)—ITT-E Population Using LOCF, BRIGHTE Trial

Analysis	FTR 600 mg BID	Placebo
n	201[b]	69
Adjusted mean (95% CI)	-0.79 (-0.88, -0.70)	-0.17 (-0.33, -0.01)
Difference[a] (95%CI)	-0.63 (-0.81, -0.44)	
p-value	<0.0001	

Source: Statistics Reviewer's analysis
[a] FTR compared to placebo
[b] Two subjects who received FTR with missing Day 1 HIV-1 RNA values were not included in the analysis.
Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; LOCF, last observation carried forward.

Table 15 displays mean $\log_{10}$ HIV-1 RNA values in each group of the Randomized Cohort at Screening, Baseline (Day 1), and Day 8 (excluding missing subjects and LOCF), as well as the unadjusted mean change in $\log_{10}$ HIV-1 RNA from Day 1 to Day 8. Of note, there was a small decline in HIV-1 RNA in both groups between the Screening and Baseline visit, which likely reflects either natural variation or increased adherence to the baseline ARV regimen. Given the short duration of the double-blind portion of the trial, there were only a few missing HIV-1 RNA values: 6 in the FTR arm and 4 in the placebo arm. Means calculated by excluding missing

subjects or using LOCF produced similar results. The unadjusted mean changes from Day 1 to Day 8 using LOCF were very similar to the results from the adjusted analysis in Table 14.

Table 15. HIV-1 RNA (log_{10} copies/mL) Results for Randomized Cohort—ITT-E Population, BRIGHTE Trial

Study Visit and Imputation Used (If Any)	FTR 600 mg BID (N=201)					Placebo (N=69)				
	n	Mean	SE	Upper 95% CL	Lower 95% CL	n	Mean	SE	Lower 95% CL	Upper 95% CL
Screening	201	4.533	0.06	4.41	4.65	68	4.656	0.112	4.43	4.88
Baseline (Day 1)	201	4.437	0.069	4.3	4.57	69	4.38	0.142	4.1	4.66
Day 8	195	3.646	0.074	3.5	3.79	65	4.161	0.147	3.87	4.45
Day 8 (LOCF)	201	3.643	0.073	3.5	3.79	69	4.222	0.143	3.94	4.51
Day 8-Day 1 (LOCF)	201	-0.794	0.051	-0.89	-0.69	69	-0.158	0.075	-0.31	-0.01

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice daily; CL, plasma clearance; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; LOCF, last observation carried forward; SE, standard error.

Secondary Endpoints

In two key secondary efficacy analyses, significantly more subjects in the FTR arm compared to the placebo arm had >0.5 log_{10} and >1.0 log_{10} decreases from Day 1 to Day 8, further supporting the efficacy of FTR (Table 16). Analysis of clinical endpoint trials (originally submitted to the FDA in support of approval) that showed that a difference of a 0.5 log_{10} HIV-RNA reduction from baseline between treatment arms was also associated with a reduction in clinical disease progression according to the FDA's guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015).

Table 16. Secondary Analysis: Proportion of Subjects With >0.5 log_{10} and >1.0 log_{10} Declines in Plasma HIV-1 RNA (copies/mL) From Day 1 to Day 8—ITT-E Population Using LOCF, BRIGHTE Trial

Decline in VL from Day 1 to Day 8	FTR 600 mg BID N=201 n (%)	Placebo N=69 n (%)	Risk Difference[a] (95% CI)	p-Value
>0.5 log_{10}	132 (66)	13 (19)	47 (36, 58)	<0.0001
>1.0 log_{10}	93 (46)	7 (10)	36 (26, 40)	<0.0001

Source: Statistics Reviewer's analysis
[a] FTR compared to placebo
Abbreviations: BID, twice daily; CI, confidence interval; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; LOCF, last observation carried forward; VL, viral load.

Durability of Virologic Response

The HTE population enrolled in this study had not been able to achieve virologic suppression with currently available therapy. Therefore, assessing the durability of virologic response in HTE subjects is an important component of understanding the overall efficacy of FTR.

From Day 8 onward, all subjects were transitioned from their initial (failing) background regimen to an optimized regimen in combination with open-label FTR 600 mg BID. The OBT

often included a combination of ARVs with full activity, partial activity, and sometimes no residual activity (e.g., lamivudine or emtricitabine). Since background drugs in the initial failing regimen were reoptimized after the end of the double-blind phase and all placebo subjects received open-label FTR, observed efficacy results at Weeks 24, 48 and 96 in the open-label phase should be interpreted in the context of FTR as a component of an OBT regimen with other active and potent drugs.

It is understood that components of the OBT affect the rates of virologic suppression and that the treatment effect cannot be attributed to FTR exclusively. This matter is not a concern in our overall interpretation of the efficacy of FTR, as the need for multiple drugs for effective treatment of HIV-1 infection is well established. Virologic suppression was achieved and maintained with FTR plus OBT through Week 96 in a majority of subjects previously unable to achieve virologic suppression. From a clinical perspective, this observation suggests the contribution of FTR, but the trial was not designed to demonstrate the contribution of FTR as an individual drug to the OBT after Day 8.

Some tables in this section include data from multiple treatment arms: placebo-randomized, FTR-randomized, and nonrandomized. The side-by-side presentation of the Randomized and Non-randomized Cohorts is not intended to make comparisons between groups. Furthermore, no statistical comparisons were made between groups. Outcomes in the two arms of the Randomized Cohort (FTR and placebo arms) were assessed separately to provide a general sense of whether the initial 8 days of functional monotherapy affected achievement of virologic suppression (e.g., rapid accumulation of resistance-associated substitutions[RASs]). The results for the Non-randomized Cohorts are presented in some tables to show trends in virologic suppression with FTR treatment in a population with limited to no treatment options, with the understanding that lower rates of virologic suppression are expected in this group relative to the Randomized Cohort.

Virologic Response – FDA Snapshot Algorithm

Virologic response was evaluated using the FDA Snapshot algorithm (November 2015) after the final subject in each cohort (Randomized and Non-randomized Cohort) completed the Week 24 visit (occurred on February 7, 2017 with a source data lock of July 21, 2017), Week 48 visit (occurred on July 26, 2017 with a source data lock of March 4, 2018) and Week 96 visit (occurred on June 22, 2018 with a source data lock of August 14, 2018).

Table 17 summarizes virologic suppression for subjects in the Randomized Cohort over time using the FDA Snapshot algorithm. The results through Week 96 suggest the initial 8 days of functional monotherapy in the FTR arm did not affect achievement of viral suppression. Please see Section III.16 for more detailed tables showing the percentage of subjects <200 and <400 copies/mL and tables showing each snapshot category.

Table 17. Virologic Outcomes (HIV-1 RNA <40 copies/mL) at Week 24, 48, and 96 for Randomized Cohort—ITT-E Population, BRIGHTE Trial

Timepoint HIV-1 RNA (Copies/mL)	FTR 600 mg BID N=203 n (%)	Placebo N=69 n (%)
Week 24 <40 copies/mL	113 (56)	31 (45)
Week 48 <40 copies/mL	115 (57)	31 (45)
Week 96 <40 copies/mL	124 (61)	39 (57)

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice daily; FTR, fostemsavir; ITT-E, intent-to-treat, exposed.

Table 18 presents the details of the Snapshot analysis for the Randomized Cohort and Table 19 presents the corresponding results for the Non-Randomized cohort. The placebo and FTR groups of the Randomized Cohort have been pooled for this analysis since all subjects were receiving OBT during the open-label phase of the trial. Please refer to Table 168, Table 169, and Table 170 in III.16.2 to see outcomes for the placebo and FTR groups presented separately. Because Week 24 and Week 48 results had very similar trends, findings only at Week 24 (a short-term evaluation) and Week 96 (a longer-term evaluation) were included in the label.

Table 18. Virologic Outcomes by FDA Snapshot Algorithm for the Randomized Cohort—ITT-E Population, BRIGHTE Trial

Virologic Outcome	Week 24 N=272 n (%)	Week 48 N=272 n (%)	Week 96 N=272 n (%)
HIV-1 RNA <40 copies/mL	144 (53)	146 (54)	163 (60)
HIV-1 RNA ≥40 copies/mL	108 (40)	104 (38)	81 (30)
Data in window not below threshold	88 (32)	71 (26)	33 (12)
Discontinued for lack of efficacy	1 (<1)	6 (2)	10 (4)
Discontinued for other reason while not below threshold	4 (1)	9 (3)	17 (6)
Change in ART	15 (6)	18 (7)	21 (8)
No virologic data	20 (7)	22 (8)	28 (10)
Discontinued study due to AE or death	11 (4)	13 (5)	15 (6)
Discontinued study for other reasons	5 (2)	7 (3)	8 (3)
Missing data during window but on study	4 (1)	2 (1)	5 (2)

Source: Statistics Reviewer's analysis
Abbreviations: AE, adverse event; ART, antiretroviral treatment.

Table 19. Virologic Outcomes by FDA Snapshot Algorithm for the Non-Randomized Cohort—ITT-E Population, BRIGHTE Trial

Virologic Outcome	Week 24 N=272 n (%)	Week 48 N=272 n (%)	Week 96 N=272 n (%)
HIV-1 RNA <40 copies/mL	37 (37)	38 (38)	37 (37)
HIV-1 RNA ≥40 copies/mL	54 (55)	52 (53)	43 (43)
Data in window not below threshold	44 (44)	33 (33)	15 (15)
Discontinued for lack of efficacy	0	2 (2)	3 (3)
Discontinued for other reason while not below threshold	2 (2)	3 (3)	6 (6)
Change in ART	8 (8)	14 (14)	19 (19)
No virologic data	8 (8)	9 (9)	19 (19)
Discontinued study due to AE or death	4 (4)	7 (7)	14 (14)
Discontinued study for other reasons	0	2 (2)	4 (4)
Missing data during window but on study	4 (4)	0	1 (1)

Source: Statistics Reviewer's analysis
Abbreviations: AE, adverse event; ART, antiretroviral treatment; ITT-E, intent-to-treat, exposed.

Table 20 summarizes the ARVs that were used in the OBT. For subjects in the Randomized Cohort, integrase strand transfer inhibitors (INSTIs, primarily DTG) were the most common class of drugs in the OBT, followed by protease inhibitors (PIs; primarily DRV) and NRTIs. CCR5 antagonist (maraviroc [MVC]) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) were used less frequently, while entry inhibitors (enfuvirtide [ENF] or ibalizumab [IBA]) were used least frequently. In the Non-randomized Cohort, NRTIs and PIs were the most common class of drugs in the OBT, followed by INSTIs (primarily DTG). Entry inhibitors and NNRTIs were used less frequently, and the CCR5 antagonist was used least frequently. The majority of subjects in the Randomized Cohort had one or two active drugs in their assigned OBT, while the majority of subjects in the Non-randomized Cohort had no active drugs.

Table 20. Summary of Components of Initial OBT—ITT-E Population, BRIGHTE Trial

Component	Placebo (N=69)	FTR 600 mg BID (N=203)	Total Randomized (N=272)	Total Non-randomized (N=99)
Initial drug class in OBT, n (%)				
CCR5 antagonist	17 (25)	35 (17)	52 (19)	8 (8)
Entry inhibitor	7 (10)	21 (10)	28 (10)	25 (25)
Ibalizumab	0	0	0	15 (15)
INSTI	59 (86)	180 (89)	239 (88)	75 (76)
Dolutegravir	55 (80)	174 (86)	229 (84)	74 (75)
NRTI	37 (54)	117 (58)	154 (57)	85 (86)
NNRTI	15 (22)	47 (23)	62 (23)	24 (24)
Etravirine	12 (17)	42 (21)	54 (20)	21 (21)
PI	43 (62)	114 (56)	157 (58)	84 (85)
Darunavir[a]	37 (54)	97 (48)	134 (49)	71 (72)
Total number of ARVs/subject in initial OBT				
n	68	199	267	99
mean	3.8 (0.2)	3.7 (0.1)	3.7 (0.1)	4.7 (0.1)
median	4.0	4.0	4.0	5.0
min, max	1, 8	1, 7	1, 8	1, 8
Number of active ARVs in initial OBT, n (%)				
0	1 (1)	15 (7)	16 (6)	80 (81)
1	34 (49)	108 (53)	142 (52)	19 (19)
2	34 (49)	80 (39)	114 (42)	0
>2	0	0	0	0

Source: Statistics Reviewer's analysis
[a] Darunavir was boosted with ritonavir or cobicistat
Abbreviations: ARV, antiretroviral drug; BID, twice daily; FTR, fostemsavir; INSTI, integrase strand transfer inhibitor; ITT-E, intent-to-treat, exposed; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background therapy; PI, protease inhibitor.

Immunologic Response

One of the ultimate goals of HIV-1 treatment is to restore immune function, primarily via restoration of CD4+ T cell count. Immune recovery may be delayed in the HTE population relative to a treatment-naïve population due to protracted immune destruction, particularly in patients with no treatment options. Therefore, the expectation was that immune recovery will

occur more quickly among subjects in the Randomized Cohort compared to the non-Randomized Cohort.

Consistent with expectation, baseline CD4+ T cell counts were lower in the non-Randomized Cohort compared to the Randomized Cohort. As shown in Table 21, CD4+ T cell counts steadily increased over time. However, it is important to note that the number of subjects continually decreased (e.g., dropouts due to death, AEs, lack of benefit), so the gains in CD4+ T cell counts largely reflect those with virologic success.

Table 21. Summary of Mean Change From Baseline in Absolute CD4+ T Cell Count (cells/mm^3) by Visit—Observed, ITT-E Population, BRIGHTE Trial

	Randomized Cohort FTR 600 mg BID N=272			Non-randomized Cohort FTR 600 mg BID N=99		
Timepoint	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Baseline	272	152.5	182.01	99	99.4	130.81
Day 8	255	19.8	60.98			
Week 24	247	90.4	112.10	87	41.0	78.56
Week 48	228	138.9	135.06	83	63.5	112.60
Week 96	213	204.7	191.28	65	119.1	201.76

Source: Sponsor's Analysis, Table 50 (modified) of the Clinical Study Report
Baseline is defined as the last nonmissing value on or before the date of first dose of study treatment. Baseline values are absolute values. Postbaseline values are changes from baseline.
Abbreviations: BID, twice daily; FTR, fostemsavir; ITT-E, intent-to-treat, exposed.

Similarly, in the Non-randomized Cohort mean changes in CD4+ T cell counts from baseline increased over time by 41, 63.5, and 119 cells/mm^3 at Weeks 24, 48, and 96 respectively.

6.3.3. Subgroup Analyses of the Primary Endpoint

Subgroup analyses were conducted to assess the potential for differences in the treatment effect for various demographic groups and are presented in Section III.16.1. Overall, the treatment effect of FTR 600 mg BID compared to placebo appeared consistent across demographic subgroups of age, gender, race, ethnicity, and geographic region. A statistically significant difference in HIV-1 RNA $\log_{10}$ change from Day 1 to Day 8 was not observed for women but trended in the same direction as men and the study group overall: 95% CI -0.45 (-0.92, +0.01), p-value 0.057. Of note, the sample sizes for some subgroups were small, which limits the ability to identify trends with certainty. In addition, conducting multiple subgroup analyses without any multiplicity adjustment could result in spurious findings due to chance, even if the observed result for one subgroup is seemingly very different from the other subgroups.

6.4. Review Issues Relevant to the Evaluation of Benefit

As described in Section 6.3, the BRIGHTE trial demonstrated that treatment with FTR is superior to placebo in reducing HIV-1 RNA during the 8-day blinded treatment period. Additionally, FTR in combination with OBT resulted in a durable virologic response in the majority of subjects in the Randomized Cohort. Virologic response rates were lower in the

Non-randomized Cohort due to lack of active ARVs in the OBT. Substantive increases in CD4+ T cell counts were observed in both cohorts.

Given the lack of therapeutic alternatives for HTE patients, there is a need to identify factors that can optimize successful treatment with FTR. The review team identified several questions aimed at determining factors associated with virologic success or failure.

- Issue 1: Assessing the impact of subjects who did not meet eligibility criteria for the BRIGHTE trial on efficacy results
- Issue 2: Identifying baseline predictors of response
- Issue 3: Assessing the adequacy of the proposed dose for patients with high baseline EC_{50} values
- Issue 4: Evaluating efficacy at Week 24 in subjects with DTG- and/or boosted DRV-containing OBT

The review team carefully reviewed how the results of these inquiries should be incorporated into the overall approval action, including the indicated population (e.g., whether there is a need to exclude populations, including those with certain baseline resistance-associated polymorphisms [RAPs]). The following sections outline the multidisciplinary approach taken by the review team to evaluate the issues.

6.4.1. Assessing the Impact of Subjects Who Do Not Meet Eligibility Criteria for the BRIGHTE Trial on Efficacy Results

Issue

A number of subjects did not meet important eligibility criteria for the BRIGHTE trial including evidence of heavy treatment experience or failure on current ARV. Inclusion of these subjects may impact the assessment of efficacy of FTR.

The entry criteria for the BRIGHTE trial included the following:

- Documented resistance, intolerability, and/or contraindication to ARV agents in at least 3 classes, AND
- Failing the current regimen with confirmed plasma HIV-1 RNA ≥400 copies/mL
- Randomized Cohort: Availability of at least 1 but no more than 2 fully-active ARV classes remaining that could be effectively combined to form a viable new regimen.

A number of subjects did not meet the above eligibility criteria.

- HIV-1 RNA <400 copies/mL at baseline (n=21), indicating these subjects were not failing their current ARV regimen. One of these subjects had HIV-1 RNA <50 copies/mL at Screening. Two subjects in each group had HIV-1 RNA <50 copies/mL at baseline.

- HIV-1 RNA decline >0.4 $\log_{10}$ copies/mL between Screening and Baseline (n=63), indicating these subjects were not truly failing their current ARV regimen and instead were likely nonadherent.
- Absence of 3-class resistance based on genotypic evidence, phenotypic evidence, evidence of historical resistance, or documented evidence of ineligibility or intolerance (n=19).

Assessment

Sensitivity analyses were performed to assess efficacy of FTR after removing subjects who were not eligible based on these different entry criteria.

Subjects With HIV-1 RNA <400 copies/mL at Baseline

Results after excluding seven subjects in the placebo group and 14 subjects in the FTR group with HIV-1 RNA <400 copies/mL at baseline were similar to the primary efficacy analysis, although there was a somewhat greater decline from Day 1 to Day 8 in the FTR treatment group (Table 22).

Table 22. Plasma HIV-1 RNA $\log_{10}$ (copies/mL) Change From Day 1 to Day 8 After Excluding Subjects With HIV-1 RNA <400 copies/mL at Baseline, BRIGHTE Trial

Analysis	FTR 600 mg BID	Placebo
n	187	62
Adjusted mean (95% CI)	-0.85 (-0.95, -0.75)	-0.16 (-0.33, +0.01)
Difference[a] (95%CI)	-0.69 (-0.89, -0.49)	
p-value	<0.0001	

Source: Statistics Reviewer's analysis
[a] FTR compared to placebo
Abbreviations: BID, twice daily; FTR, fostemsavir.

Subjects With HIV-1 RNA Decline >0.4 $\log_{10}$ copies/mL From Screening to Baseline

Including subjects who are not failing on their current ARV regimen may impact the primary endpoint assessment of FTR efficacy at Day 8 because the decline in HIV-1 RNA cannot be solely attributed to the activity of FTR. These subjects can be identified by a notable decline in HIV-1 RNA between Screening and Baseline.

The number of subjects with >0.4 $\log_{10}$ decline in HIV-1 RNA from Screening to Baseline was balanced between arms with 16 (23.5%) in the placebo arm and 47 (23.4%) in the FTR arm. Results after excluding these 63 subjects were similar to the primary efficacy analysis, although there were somewhat greater declines from Day 1 to Day 8 in both treatment arms (Table 23).

Table 23. Plasma HIV-1 RNA log_{10} (copies/mL) Change From Day 1 to Day 8 After Excluding Subjects With >0.4 log_{10} Decrease From Screening to Baseline, BRIGHTE Trial

Analysis	FTR 600 mg BID	Placebo
n	154	53
Adjusted mean (95% CI)	-0.90 (-1.00, -0.79)	-0.22 (-0.40, -0.04)
Difference[a] (95%CI)	-0.67 (-0.88, -0.46)	
p-value	<0.0001	

Source: Statistics Reviewer's analysis
[a] FTR compared to placebo
Abbreviations: BID, twice daily; FTR, fostemsavir.

In addition, results were similar when adjusting for Screening HIV-1 RNA instead of baseline (Day 1) HIV-1 RNA in all subjects with available Screening data (Table 24).

Table 24. Plasma HIV-1 RNA log_{10} (copies/mL) Change From Screening to Day 8, BRIGHTE Trial

Analysis	FTR 600 mg BID	Placebo
n	201	68
Adjusted mean (95% CI)	-0.80 (-0.89, -0.70)	-0.15 (-0.32, -0.01)
Difference[a] (95%CI)	-0.64 (-0.84, -0.45)	
p-value	<0.0001	

Source: Statistics Reviewer's analysis
[a] FTR compared to placebo
[b] One subject who received placebo with a missing Screening HIV-1 RNA value was not included in the analysis.
Abbreviations: BID, twice daily; FTR, fostemsavir.

Subjects Not Eligible by Resistance Criteria

The virology reviewer identified 19 subjects who did not have 3-class resistance at study entry; 13 (6%) subjects were randomized to the FTR group, and 6 (9%) were randomized to the placebo group (9%). A sensitivity analysis was performed to determine whether exclusion of these subjects affected the primary efficacy analysis. As summarized in Table 25, the results were essentially unchanged from the primary efficacy analysis.

Table 25. Plasma HIV-1 RNA log_{10} (copies/mL) Change From Day 1 to Day 8 After Excluding Subjects Who Were Not Eligible by Resistance Criteria or Evidence of Intolerance, BRIGHTE Trial

Analysis	FTR 600 mg BID	Placebo
n	188	63
Adjusted mean (95% CI)	-0.82 (-0.91, -0.72)	-0.14 (-0.31, +0.03)
Difference[a] (95%CI)	-0.68 (-0.87, -0.48)	
p-value	<0.0001	

Source: Statistics and Virology Reviewers' analysis
[a] FTR compared to placebo
Abbreviations: BID, twice daily; FTR, fostemsavir.

Conclusion

The proportion of subjects who did not meet eligibility criteria was balanced between the FTR and placebo groups, and sensitivity analyses demonstrated that excluding subjects who did not meet criteria did not substantially change the efficacy outcome. Therefore, the review team concludes that inclusion of subjects who were not truly failing their baseline ARV regimen in the BRIGHTE trial did not affect the overall efficacy assessment of FTR for treatment of MDR HIV-1 infection. Results from the Intent-to-Treat, Exposed population can be displayed in

product labeling because these results accurately convey the activity of FTR in the HTE population.

6.4.2. Identifying Baseline Predictors of FTR Response at Day 8

Issue

Identifying factors that impact response (e.g., susceptibility) in advance of treatment initiation can improve treatment outcomes. Since alternative ARV options are severely limited for HTE patients such as those enrolled in the BRIGHTE trial, it is important to identify factors that influence treatment success and understand their impact. This section summarizes the evaluation of key factors including the presence of screening envelope gp120 substitutions, Screening FTR phenotype, and viral tropism. The results of these analyses will be used to guide product labeling (e.g., limitations of use based on the presence of substitutions).

Assessment

Day 8 Analysis of Randomized FTR Arm

In the randomized FTR group of the BRIGHTE trial, HIV-1 RNA from Day 1 to Day 8 using observed data declined >0.5 $\log_{10}$ copies/mL in 132/197 subjects (67%) and <0.5 $\log_{10}$ copies/mL in 65/197 subjects (33%). The median decline in HIV-1 RNA at Day 8 was 0.009 $\log_{10}$ copies/mL in subjects who failed at Day 8 and 1.2 $\log_{10}$ copies/mL in subjects who succeeded at Day 8. Interestingly, of the 65 subjects with <0.5 $\log_{10}$ decline in HIV-1 RNA at Day 8, only 18 (28%) were virologic failures post-Day 8, which is evidence of the effectiveness and potency of the OBT.

Screening EN RAPs

Envelope (EN) RAPs, M427L, M434T, M475I, S375H or M were shown to decrease the activity of FTR in cell culture assays (see Table 223 and Table 224) and confer decreased susceptibility to FTR. Additionally, EN substitutions at these sites were selected in cell culture resistance selection experiments (see Section III.18).

The effect of the EN RAPs on Day 8 response (>0.5 $\log_{10}$ decline in HIV-1 RNA) was assessed in an as-treated analysis by censoring the subjects who had a >0.4 $\log_{10}$ decline in HIV-1 RNA from Screening to Baseline or less than 400 copies/mL at Screening. These subjects were censored because, given the decline in HIV-1 RNA from Screening to Baseline, they were less likely failing on their current ARV regimen and the assessment of FTR on antiviral decline would be confounded by other active drugs in the background regimen. Of the 198 subjects with available EN RAP data, 47 subjects were censored, leaving 151 subjects in the as-treated analysis.

The overall response at Day 8 in the as-treated analysis was 71%, similar to the Day 8 response in the primary endpoint analysis (see Table 16). The Day 8 response rate in subjects without any

change at the four envelope RAP amino acid sites (S375, M426, M434, or M475) in their virus was 81% compared to the reduced response rate of 64% for subjects who had changes at these RAPs in their virus (Table 26, Table 235). The Day 8 response rate was 54% for subjects with Applicant-predefined RAPs. Based on 25 subjects with two EN RAPs and one with three RAPs, the response rate at Day 8 was not decreased with the presence of more than one RAP. The presence of the specific polymorphisms S375M, M426L, M434I, or M475V showed a lower Day 8 response of 37% and a median $\log_{10}$ decline in HIV-1 RNA of 0.17 (Table 26, Table 235). Similarly, the median decline in HIV-1 RNA at Day 8 for subjects with predefined EN RAPs was lower compared to subjects with no EN RAPs (0.66 $\log_{10}$ copies/mL and 1.08 $\log_{10}$ copies/mL, respectively) (Table 26, Table 234). The presence of each polymorphism S375M, M426L and M475V at Screening showed lower declines in HIV-1 RNA at Day 8 with median $\log_{10}$ declines of 0.32, 0.19, and 0, respectively (Table 26). The M434I RAP had less of an effect with a median HIV-1 RNA decline of 0.66. The review team notes the numbers of subjects with S375H/M, M434I and M475V polymorphisms were small.

Table 26. Outcome of Randomized FTR Cohort (Response >0.5 Decline Day 8) by Presence of Screening EN RAPs (As-treated Analysis[a]) (FDA Analysis), BRIGHTE Trial

EN RAP	Response Rate at Day 8 (>0.5 Decline) N=151	Median $\log_{10}$ Decline in VL: Baseline to Day 8 N=151
Overall	107/151 (71%)	1.05
No EN RAPs (any change at S375, M426, M434 or M475)	51/63 (81%)	1.08
Any change at S375, M426, M434, or M475	56/88 (64%)[b]	1.03
No EN RAPs at predefined sites	70/83 (84%)	1.11
Predefined EN RAPs: S375I/M/N/T, M426L, M434I, or M475I/V	37/68 (54%)	0.66
S375M	1/5 (20%)	0.32
M426L	6/17 (35%)	0.19
M434I	3/6 (50%)	0.66
M475V	0/1 (0%)	0
S375M, M426L, M434I, or M475V	11/30 (37%)	0.17
1 EN RAP	38/62 (61%)	1.03
2 or 3 EN RAPs	18/26 (69%)	1.09
No change at L116, A204, V255, or A281[c]	66/87 (75%)	1.11
Any change at L116, A204, V255, or A281[c]	37/57 (65%)	0.85

Source: Clinical Virology Reviewer analysis
[a] Removed subjects who had <400 copies/mL at Screening or >0.4 $\log_{10}$ decline Screening to Baseline
[b] Statistically significant p-value at the two-sided 0.05 level (unadjusted for baseline)
[c] Subset of subjects with complete EN sequence and data for these sites n=144
Abbreviations: EN, envelope; FTR, fostemsavir; RAP, resistance-associated polymorphism VL, viral load.

For other EN RAPs, changes at sites L116 (n=1), A204 (n=6), V255 (n=8) or A281 (n=42) showed a response rate of 65% at Day 8, compared to the response rate of 75% for no changes at these sites (Table 26). The median decline in HIV-1 RNA at Day 8 for subjects with changes at EN RAPs L116, A204, V255 or A281 was 0.85 $\log_{10}$ copies/mL compared to 1.11 $\log_{10}$ copies/mL for no changes at these sites (Table 26). However, most (72%, 41/57) of the isolates with changes at L116, A204, V255 or A281 also had a change at one of the four main sites for EN RAPs (375, 426, 434, or 475). The response rate for the 16 subjects with changes at L116, A204, V255 or A281 but without changes at one of the four main sites for EN RAPs was 94%

(15/16). Thus, polymorphisms at L116, A204, V255 or A281 do not appear to directly contribute to reduced response to FTR but rather are found in combination with EN RAPs 375, 426, 434 and 475.

Screening FTR Phenotype

The FC in susceptibility to FTR at Screening was highly variable ranging from 0.06 to 6651. The median FTR FC at Screening for subjects who were successes at Day 8 (>0.5 $\log_{10}$ decline in HIV-1 RNA) was 0.73 (75% quartile =3.1) compared to a median FC of 1.6 (75% quartile =38) for subjects who were failures at Day 8 (less than 0.5 $\log_{10}$ decline in HIV-1 RNA).

The effect of screening FTR phenotype on response at Day 8 was assessed in an as-treated analysis (subjects who had a >0.4 $\log_{10}$ decline in HIV-1 RNA from Screening to Baseline or less than 400 copies/mL at Screening were censored). The majority of subjects (55%; 83/151) had a Screening phenotypic FC <2; the response rate for these subjects was 80% (66/83) (Table 27). The response rate for subjects with FTR phenotypic FCs of 2 to 200 were moderately decreased at 69% (29/42). Importantly, phenotypic FCs of >200 resulted in lower response rates to FTR of 29% (5/17) (Table 27).

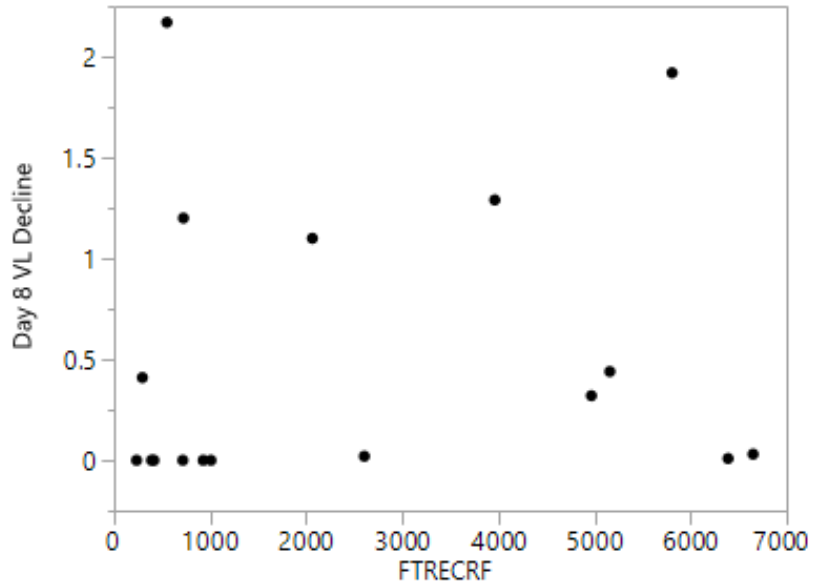
Table 27. Response Rate of Randomized FTR Cohort (>0.5 Decline Day 8) by Screening Phenotype, BRIGHTE Trial

FTR Phenotypic Fold Change in EC_{50} Value	Response Rate at Day 8 (>0.5 $\log_{10}$ Decline) As-treated Analysis[a] N=151
Not reported	9
0-2	66/83 (80%)
>2-10	17/25 (68%)
10-200 (range 11-104)	12/17 (71%)
>200 (range 234-6651)	5/17 (29%)

Source: Clinical Virology Reviewer analysis
[a] Removed subjects who had <400 copies/mL at Screening or >0.4 $\log_{10}$ decline Screening to Baseline
Abbreviations: EC_{50}, half maximal effective concentration; FTR, fostemsavir.

However, there were five subjects with >200-fold decreased susceptibility to FTR at Screening who still achieved a >0.5 $\log_{10}$ decline in HIV-1 RNA at Day 8 (Table 28). A bivariate fit of Day 8 HIV-1 RNA decline by FTR fold change at Screening in subjects who had >200-fold decrease in FTR susceptibility shows a nonlinear relationship and the five outlier subjects who had >1 $\log_{10}$ declines despite >200-fold decreased in FTR susceptibility (Figure 4).

Figure 4. Bivariate Fit of Day 8 HIV-1 RNA Decline by FTR FC at Screening (Subjects With >200-FC at Screening), BRIGHTE Trial



Source: Clinical Virology Reviewer analysis
Abbreviations: FC, fold change; FTR, fostemsavir; VL, viral load; FTRECRF, FTR EC_{50} fold change from reference.

All five of these subjects, despite having highly decreased FTR susceptibility and the presence of screening EN RAPS, had over 1 log_{10} declines in HIV-1 RNA at Day 8 (Table 28). The predose concentration of FTR at Day 8 varied for each of these five subjects but was low for two of these subjects (38 ng/mL and 166 ng/mL). Therefore, higher concentrations of FTR, which might possibly overcome the decreased susceptibility to FTR, do not explain why all these subjects responded better to FTR. Additionally, three of the five subjects had evidence of resistance to background ARV drugs, supporting failure of the background regimen and contribution of FTR to the HIV-1 RNA decline, despite evidence of FTR resistance. A clear interpretation of FTR response based on Screening phenotype and genotype is confounded by these data.

Table 28. Subjects With Screening FTR FC >200 Who Were Day 8 Successes, BRIGHTE Trial

PID	Predose Concentrations (ng/mL) on Day 8	log_{10} Decline at Day 8	Screening EN RAPs	FTR FC Screening	Background ARV Drugs[a]
AI438047.000201	1,060	1.2	S375S/N M426L	723	**DRV/r, FTC, TDF**
AI438047.000247	2,320	1.3	S375S/N/T M426L	3,963	DRV/r, RAL, FTC, TDF
AI438047.000393	166	1.92	S375T M426L	5,809	T20 and MVC
AI438047.000602	38.3	1.1	S375S/T M426L	2,064	RPV
AI438047.000708	1,150	2.2	S375I	550	DTG and DRV/r

Source: Clinical Virology Reviewer analysis
Of the 65 subjects with <0.5 log_{10} decline at Day 8, 18 (28%) were virologic failures (Table 29) post Day 8.
[a] Bolded = evidence of resistance or partial sensitivity
Abbreviations: ARV, antiretroviral; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EN, envelope; FC, fold change; FTR, fostemsavir; MVC, maraviroc; PID, patient identifier; RAP, resistance-associated polymorphism; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

Day 8 Response by Tropism

In cell culture assays, the median EC_{50} value of TMR against CXCR4-tropic strains was higher suggesting a possible tropism effect (see Section 5.1). The cell culture data suggest there may be overlap between tropism determinants of gp120 and the antiviral activity of TMR against gp120. Therefore, the response rate at Day 8 in the randomized FTR group was assessed in subjects who had CCR5, CXCR4 or dual-mixed tropic virus at baseline. In the as-treated analysis, response rates were lower for subjects with CXCR4-tropic virus than subjects who had CCR5- or dual-mixed-tropic virus (44% versus 77% or 70%) (Table 29). These clinical results showing decreased FTR activity against some CXCR4-tropic viruses support nonclinical findings.

Table 29. Outcome of Randomized FTR Cohort (Response >0.5 log_{10} Decline Day 8) by Baseline Tropism, BRIGHTE Trial

Baseline Tropism	Response Rate at Day 8 (>0.5 log_{10} Decline) As-treated Analysis[a] N=151
Not reported	9/12 (75%)
CCR5	34/44 (77%)
CXCR4	**4/9 (44%)** [b]
Dual-mixed	60/86 (70%)

Source: Clinical Virology Reviewer analysis
[a] Removed subjects who had <400 copies/mL at Screening or >0.4 log_{10} decline Screening to Baseline.
[b] Three of the four CXCR4 responder isolates also had S375S/N or S/T, one also had M426R. Of the five nonresponder CXCR4 isolates, one had had S375S/N, one had S375T plus M426R, one had M426L, and two had none of the 4 RAPs.
Abbreviation: FTR, fostemsavir.

Although the Day 8 response rates for subjects with CXCR4-tropic virus were lower, this result is based on a limited number of subjects (n=9). Moreover, three of the five CXCR4-isolates from nonresponders at Day 8 also had EN RAPs, and two of the isolates had phenotypic fold changes to FTR of 17-fold and 42-fold, respectively, which confounds the interpretation of a lower response based on CXCR4-tropism alone.

Conclusions

The key EN RAPs S375M, M426L, M434I or M475V are associated with decreased Day 8 response of 36% (10/28). Despite lower response rates in subjects with key EN RAPs, FTR may be an important agent in constructing an effective ARV regimen for patients with few therapeutic options. A phenotypic FC in FTR susceptibility at Screening of >200 was associated with lower response rates to FTR of 29%.

Given the low prevalence of these EN RAPs in the population and lack of readily available assays to assess presence of EN RAPs and FTR phenotype, the indication does not need to be restricted based on presence of EN RAPs or Screening FTR phenotype. However, this information will be provided in Section 12.4 of the package insert to inform providers about which patients may benefit most from using FTR as a component of an ARV regimen.

In addition, response rates were lower for subjects with CXCR4-tropic virus in BRIGHTE compared to subjects who had CCR5- or dual-mixed-tropic virus. However, given the limited number of CXCR4-isolates and presence of EN RAPs/high phenotypic TMR values, which confounds the interpretation, a determination of the response to FTR based on CXCR4-tropism cannot be fully elucidated from these trial data.

6.4.3. FTR Exposure-Response Relationship for Subjects With High Baseline FTR EC_{50} Values

Issue

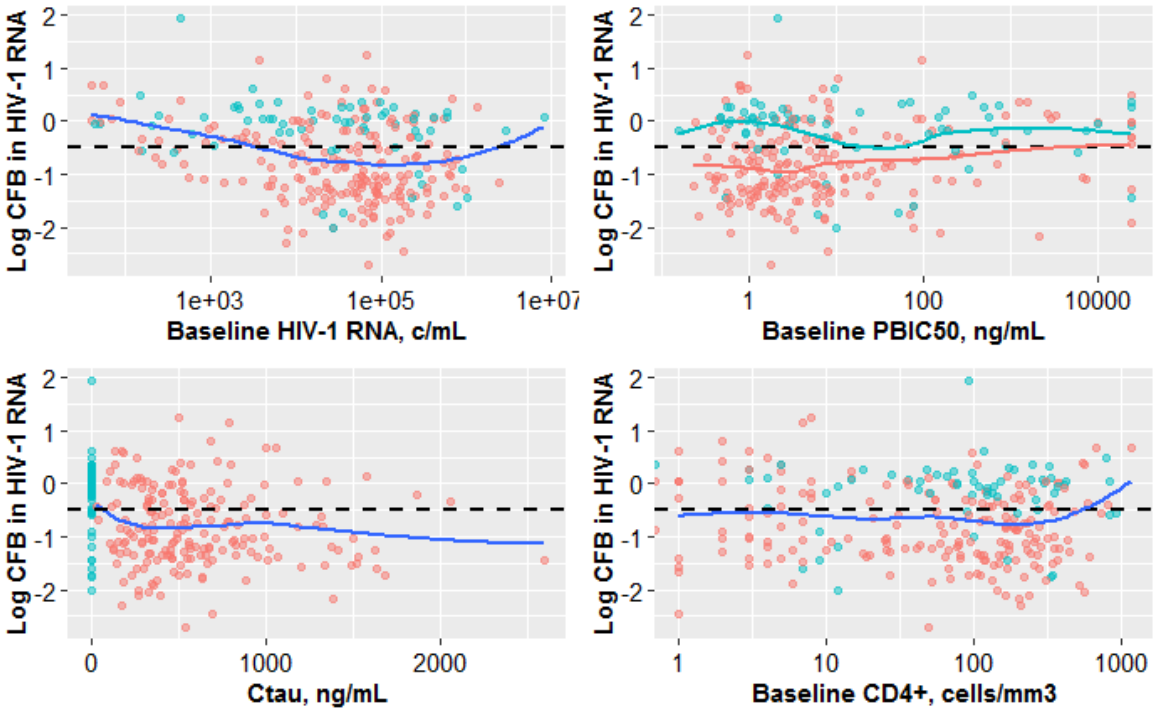
Fold changes in Screening/Baseline EC_{50} values were highly variable in the BRIGHTE trial, ranging from 0.06 to 6651. As shown above (6.4.2), subjects with baseline EC_{50} FC >200 had a response rate of 29%, which is significantly lower than the trial population at large. To assess whether higher concentrations of TMR by using a higher FTR dose might improve efficacy in patients with high baseline FTR EC50 values, the review team explored whether there is an FTR exposure-response relationship of HIV-1 RNA decline from Day 1 to Day 8.

Assessment

Exposure-Response (E-R) relationship for Day 8 virologic response was evaluated with two exposure metrics 1) predicted TMR C_{tau} and 2) inhibitory quotients (IQs, derived as TMR C_{tau}/EC_{50} adjusted for protein binding) based on the data from the 252 patients who had TMR C_{tau}, baseline EC_{50} values, and Day 8 response data in the Randomized Cohort of the BRIGHTE trial. Potential covariates (baseline EC_{50}, baseline HIV-1 RNA, and baseline CD4+) of HIV-1 RNA decline were also explored.

The univariate analyses (Figure 5) show that there is no apparent relationship between TMR C_{tau} and Day 8 response at the observed concentration range (bottom left). However, the lower baseline HIV-1 RNA (top left), and the higher baseline EC_{50} (top right) in the FTR-treated group appear to be associated with reduced response in Day 8 HIV-1 RNA decline.

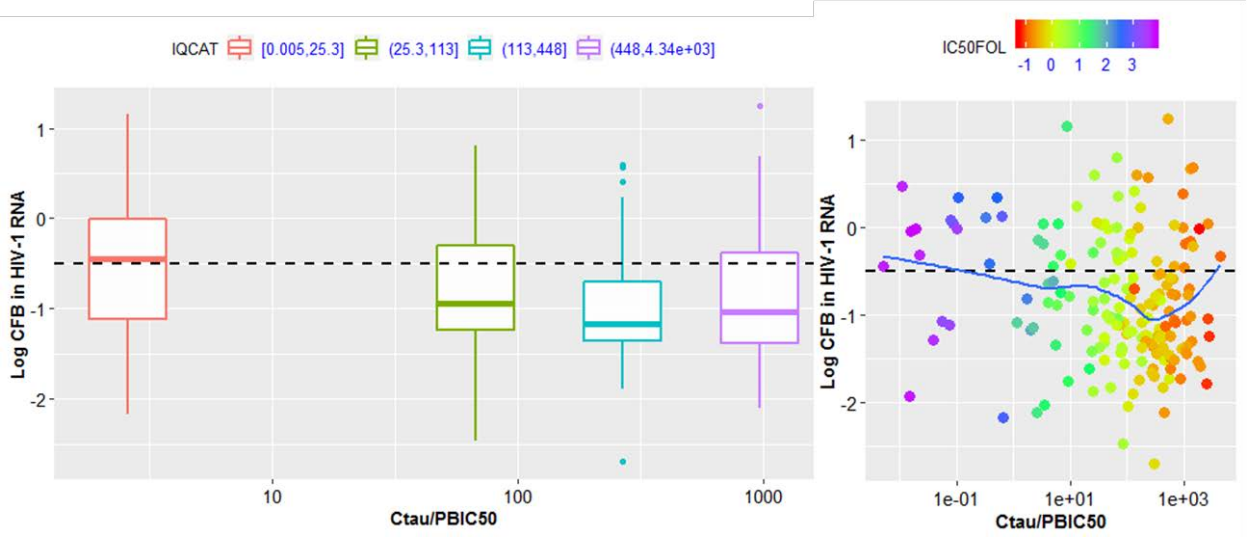
Figure 5. Graphical Exploration of Day 8 HIV-1 RNA Decline vs. Predictors of Interest, BRIGHTE Trial



Source: Pharmacometrics Reviewer's analysis.
IC_{50} represents EC50 in the figure. Green dots (placebo) and red dots (FTR 600 mg BID); $PBIC_{50}$: Baseline EC50 adjusted with protein binding (calculated as mw*EC_{50}/fu, where fu is the mean estimated unbound fraction of TMR in vivo (0.12), mw is the molecular weight of TMR free base (473.48 g/mole). Solid line is the loess smoother; blue-all data, green/red - placebo/FTR treatment group for Baseline EC50. Dotted lines present 0.5 log_{10} reduction in HIV-1 RNA from Day 1 to Day 8
Abbreviations: CFB, change from baseline; C_{tau}; plasma concentration during a dosing interval.

Because the EC_{50} and the derived IQ values are drug-specific, the IQ-Response relationship was explored with the data from the FTR-treated patients (N=187) excluding the placebo group (N=65). The lower IQs are associated with reduced response in Day 8 virologic decline. Presented by the quartile plot (Figure 6, the left panel), the lowest IQ quartile group had a lower median response in Day 8 decline compared to the rest of quartile groups. It is noted that the lowest IQ values are driven by the significantly high baseline IC_{50} values (Figure 6, right panel). Considering that no clear relationship was observed between C_{tau} and Day 8 response, the observed IQ-response relationship is reflective more of the EC_{50} - Day 8 response relationship. Furthermore, a large fold difference (>10) in median IQ values between the two lowest quartile groups is not expected to be overcome by any practical dose increase. Therefore, a dose adjustment is not recommended for patients with high baseline EC_{50} values.

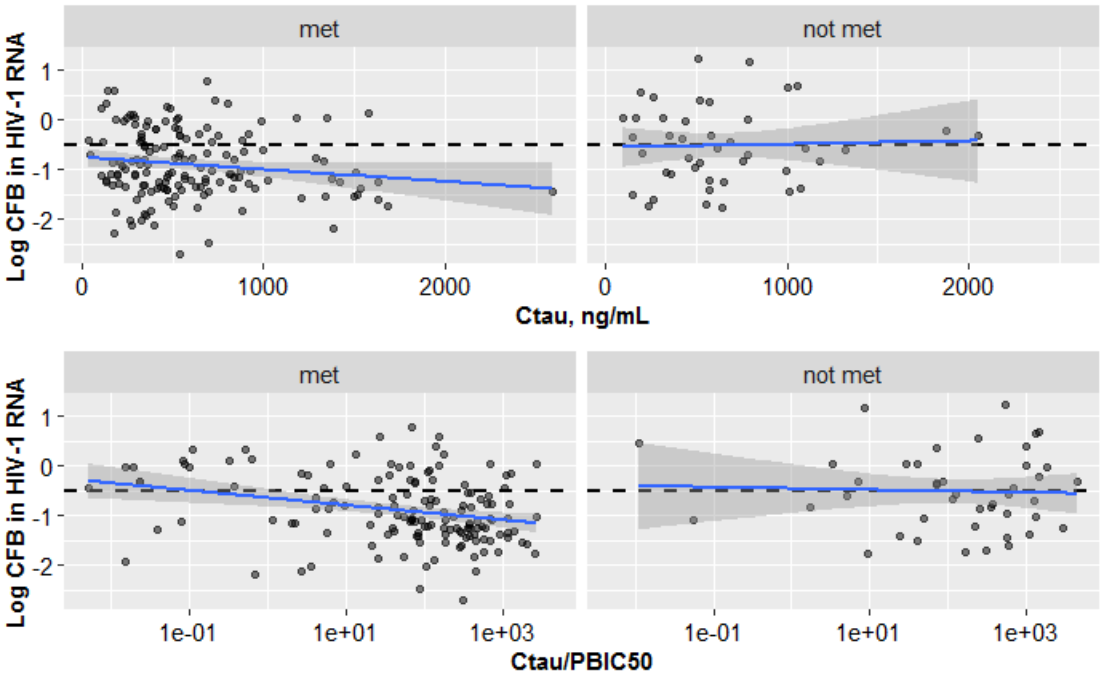
Figure 6. Inhibitory Quotient—Day 8 Response, BRIGHTE Trial



Source: Pharmacometrics Reviewer's analysis.
IC_{50} represents EC50 in the figure. The color scale in the left panel presents EC_{50} fold change in log-scale. EC_{50} fold change range from $<10^{-1}$ (red) to $>10^{3}$ (purple).
Abbreviations: CFB, change from baseline; C_{tau}, plasma concentration during a dosing interval; IQCAT: IQ categories by IQ quartiles.

A sensitivity analysis was performed to further assess the E-R relationship during functional monotherapy of FTR in the absence or presence of significant residual activity in the failing regimen. The E-R analysis subjects were grouped by meeting or not meeting a criterion (experienced <0.4 $\log_{10}$ decline from screen to baseline AND had the baseline HIV-1 RNA >400 copies/mL) which presumes a lack of residual activity from the failing regimen. In the subjects meeting the criterion (Figure 7, left panels), similar E-R relationships were observed: a shallow correlation between C_{tau} and Day 8 response and a positive trend between lower IQ and reduced Day 8 response. In the subjects not meeting the criterion, there was generally a reduced decline in Day 8 viral response and no E-R relationships were observed for C_{tau} nor IQ values. These results support that no dose adjustment needs to be recommended for patients with high baseline EC_{50} values, regardless of the baseline HIV-1 RNA levels or residual activity from the background regimen.

Figure 7. E-R Relationships in Subgroups by Based on Baseline HIV-1 RNA Criterion, BRIGHTE Trial



Source:Pharmacometrics Reviewer's analysis.
Met or not meeting a criterion (experienced <0.4 $\log_{10}$ decline from screen to baseline AND had the baseline HIV-1 RNA >400 copies/mL).
Abbreviations: CFB, change from baseline; C_{tau}, plasma concentration during a dosing interval; E-R, exposure-response.

Conclusions

There is no clear relationship between FTR concentration and HIV-1 RNA decline at Day 8. Therefore, no dose adjustment is recommended for patients with a high baseline EC_{50} FC.

6.4.4. Evaluating Efficacy at Week 24 in Subjects With DTG- and/or boosted DRV-Containing OBT

Issue

It is important to assess the durability of FTR as a component of an optimized ARV regimen; therefore, the response of open-label FTR 600 mg BID + OBT was evaluated at 24, 48 and 96 weeks. However, the impact of potent ARVs in the OBT can significantly impact virologic response at Weeks 24, 48 and 96, making it difficult to identify the contribution of FTR. Because two very potent drugs, DTG and boosted DRV, were included in the OBT in a high proportion of the subjects in the trial, the durability of the FTR + OBT response with and without these ARV background drugs was evaluated.

Assessment

In the placebo and randomized FTR groups combined, OBT initiated after Day 8 contained DTG for 84% (229/272) of subjects and DTG and boosted DRV for 43% (117/272) of subjects. A smaller proportion of subjects had an OBT that did not contain DTG; 6% (17/272) had boosted

DRV without DTG and 10% (26/272) had neither DTG nor boosted DRV in their OBT. Of the 134 subjects with DRV-containing OBT, 120 subjects received DRV/r and 13 subjects received DRV/c; no documentation of a boosting agent was available for one subject. Overall, DTG and boosted DRV were predominant and potent components of the OBT for most subjects in this trial.

Baseline HIV-1 RNA values were comparable by use of DTG and/or boosted DRV in the initial OBT (Table 30), as was improvement from baseline to Day 8 (as shown in the Appendix—Section III.16.3). Therefore, differences in response rates at Week 24 and beyond are unlikely to be related to imbalances in baseline HIV-1 RNA or observed improvements at the end of the double-blind phase of the trial.

Table 30. Baseline VL (log_{10} Copies/mL) by Use of DTG and/or boosted DRV[a] in the OBT—ITT-E Population, BRIGHTE Trial

OBT	Placebo (N=69)	FTR 600 mg BID (N=203)	Total Randomized (N=272)
DTG and DRV			
N	29	88	117
mean (se)	4.3 (0.2)	4.3 (0.1)	4.3 (0.1)
Median	4.2	4.5	4.4
min, max	1.7, 6.1	1.7, 6.1	1.7, 6.1
With DTG, without DRV			
N	26	86	112
mean (se)	4.3 (0.2)	4.6 (0.1)	4.5 (0.1)
Median	4.6	4.8	4.7
min, max	1.6, 6.9	1.6, 6.0	1.6, 6.9
Without DTG, with DRV			
n	8	9	17
mean (se)	4.5 (0.4)	4.6 (0.2)	4.5 (0.2)
median	4.9	4.6	4.8
min, max	2.3, 5.5	3.7, 5.4	2.3, 5.5
Without DTG or DRV			
n	6	20	26
mean (se)	4.8 (0.4)	4.3 (0.3)	4.4 (0.2)
median	4.8	4.3	4.5
min, max	3.7, 6.5	1.8, 6.4	1.8, 6.5

Source: Statistics Reviewer's analysis
[a] Darunavir boosted with ritonavir or cobicistat
Abbreviations: BID, twice daily; DTG, dolutegravir; DRV, darunavir; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy; VL, viral load.

As shown in Table 31, response rates were higher in subjects receiving DTG as part of their OBT compared to those not receiving DTG. The Week 24 virologic response rate for subjects receiving DTG in their OBT with or without boosted DRV was 56% (129/229) for both randomized groups combined compared to 35% (15/43) without DTG. The response rate for subjects receiving boosted DRV without DTG in their OBT was 29% (5/17). Additionally, the response rates for subjects not receiving DTG were similar to the response rate of 37% in the nonrandomized group where most subjects were resistant to DTG and did not have DTG as an option for use in the OBT. These results show that inclusion of DTG, a potent ARV, in the OBT substantially impacted the response rates post-Day 8 in the Randomized Cohort.

Table 31. Week 24 Efficacy: Randomized Cohort, ITT-E Population for Subjects Who Used DTG and/or boosted DRV[a] in OBT, BRIGHTE Trial

	Proportion with <40 HIV-1 RNA (copies/mL)		
OBT	**Placebo**	**FTR 600 mg BID**	**Randomized Arms Combined**
With DTG and DRV	14/29 (48%)	54/88 (61%)	68/117 (58%)
With DTG, without DRV	13/26 (50%)	48/86 (56%)	61/112 (54%)
Without DTG, with DRV	2/8 (25%)	3/9 (33%)	5/17 (29%)
Without DTG or DRV	2/6 (33%)	8/20 (40%)	10/26 (38%)

Source: Statistics Reviewer's analysis
[a] Darunavir boosted with ritonavir or cobicistat
Abbreviations: BID, twice daily; DTG, dolutegravir; DRV, darunavir; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy.

Conclusions

As previously noted, response rates of open-label FTR plus OBT were durable over 24, 48 and 96 weeks. The results of this subgroup analysis showed that including at least one highly potent ARV in the OBT, such as DTG if appropriate and available, increases the likelihood of a durable virologic response. This information is important to include in the FTR label so providers caring for HTE patients can set realistic expectations about the likelihood of achieving virologic suppression based on selection of OBT. However, even in cases where DTG is not a viable option, this patient population with limited options may still achieve virologic suppression, albeit at a lower rate.

7. Risk and Risk Management

The overall assessment of safety of FTR is informed by a variety of sources, including nonclinical toxicology, safety pharmacology studies, and early phase clinical studies. The safety assessment for the intended population of HTE subjects is based primarily on the BRIGHTE trial but is also heavily informed by the Phase 2b trial, which was conducted in a population that retained susceptibility to several ARVs. Prior to NDA submission, the clinical review team identified several potential risks based on the results of Phase 1-2 trials and interim clinical study reports of the BRIGHTE trial. These AEs of special interest included:

1. Clinical safety issues:
    - Prolongation of the QT interval
    - Immune reconstitution inflammatory syndrome (IRIS)
    - Rash and hypersensitivity reactions
    - Hepatobiliary AEs
    - Elevations in serum creatine kinase (CK) and reports of myalgia
    - Neuropsychiatric events
2. Issues relating to the presence of a beta-lactam containing photodegradant
    - Adequacy of controls to limit formation of the photodegradant during manufacturing
    - Sensitizing potential of the beta-lactam compound and risk to patients (e.g., hypersensitivity)
3. Emergence of resistance/cross-resistance to other ARVs

After completing the interdisciplinary analysis and review, the team resolved several of these risk issues and identified two that warranted additional discussion as review issues: resistance and the beta-lactam–containing photodegradant. These issues were selected because of their importance in contributing to the safe (and effective) use of the product. They are discussed in detail in Section 7.7.

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of FTR supporting this NDA has been extensively explored from (1) single and repeated dose toxicity studies in rats (up to 6-month) and dogs (up to 9-month), (2) in vitro and in vivo genotoxicity studies, (3) reproductive and developmental toxicity studies including fertility studies in male and female rats, embryo-fetal developmental studies in rats and rabbits, and a peri- and post-natal developmental study in rats, (4) carcinogenicity studies in transgenic mice (6-month) and rats (2-year bioassay), and (5) juvenile studies in rats. In addition, PKs/toxicokinetics were studied as part of the toxicity studies or in separate animal PK studies to support FTR and its active drug moiety TMR's exposures, and to compare PKs and pharmacodynamics in animals and humans. The target organs of toxicity or system pharmacology effects that may be relevant to human risks or cause of safety concerns are highlighted below. From the nonclinical perspective, the human risks should be manageable and margins of safety acceptable. The therapeutic benefits of FTR to the target HIV patient population should outweigh the potential risks that may emerge.

7.1.1. Safety Pharmacology-Related Functional Effects

The following reported pharmacological effects could be meaningful to risk management: (1) central nervous system (CNS) and behavioral effects: ataxia, decreased and/or labored breathing in mice (at 1,000 mg/kg single-dose), circling, tremors, abnormal gait, cage biting, lameness, head pressing against cage, and nausea/vomiting (from 1-month study at ≥100 mg/kg/day; safety factor [SF] >25); (2) Cardiac effects: potassium channels inhibition (hERG assay;15, 30, 53% at 3, 10, 30µM TMR, respectively), action potential duration prolongation (rabbit Purkinje fibers; 12% at 30µM TMR), electrocardiogram (ECG) QT prolongation in conscious dogs (QT_{80}, for ~8 to 18 msec, ~2.2 µg/ml), and heart rate increases (dogs, 75 mg/kg 2-week study or 60 mg/kg 9-month study). In humans, no similar CNS/behavioral effects, as mentioned above, were reported (except gastrointestinal [GI] indigestion) as AEs in FTR clinical trials. QT and heart rate findings may be associated with results observed in the human QT study (Section III.17.3), and tachycardia events reported in clinical trials. The SF mentioned above and throughout the document is expressed by using the ratio of drug exposures between the specific animal species and humans at the recommended daily dose (19.4 µg.h/ml at 600 mg bid).

7.1.2. Target Organs of Toxicity

Kidney

Tubular dilatation (multifocal, involving cortical tubules such as distal convoluted tubules) or increased kidney organ weight were reported in 2-week, 1-month, and 6-month rat studies (SF =31 male/47 female). Renal tubular hyperplasia was also seen in the 2-year rat carcinogenicity study. Renal AEs and laboratory abnormalities have been reported in FTR human clinical trials.

Liver

Increased bilirubin and multifocal canalicular pigment deposits in 9-month dog study (SF =2.6). Biliary chemistry findings such as increased bilirubin, alkaline phosphatase (ALP), or aspartate aminotransferase (AST) were reported in the 1-month range-finding and the 2-week dog studies. Hepatic AEs and laboratory abnormalities have been reported in FTR human clinical trials.

Testicular Tissues

In rats, decreased sperm count/dysmorphology and degenerative seminiferous tubule epithelium were reported in 2-week, 1-month, and 6-month studies (SF =31). In dogs, debris in epididymis and atrophy of seminiferous epithelium were reported in the 9-month study; SF =3.5).

Adrenal Gland

Increased organ weight and angiectasis were reported in multidose 6-month and single-dose 3-month rat studies (SF =33). Organ weight increases (early embryofetal and fertility study, at 600 mg/kg) and adrenal necrosis (2-yr carcinogenicity rat study, at 100 mg/kg) were also reported. Higher incidence of pheochromocytoma in females (at 100 mg/kg) was reported but was not statistically significant in the rat carcinogenicity study. In dogs, adrenal necrosis and inflammation occurred in both 1-month (at ≥100 mg/kg), and 2-week (moribund dose 300/200 mg/kg) studies. Adrenal toxicity has not been reported in FTR human clinical trials.

7.1.3. Reproductive and Developmental Toxicology

In rats, FTR caused maternal toxicity (decreased food consumption/weight gain and associated clinical chemistry changes such as decreased BUN eosinophil counts; SF =17), and fetal toxicity (low fetal weight; SF =198). Teratogenic effects occurred in rats at the maternally toxic dose of 1,000 mg/kg/day, such as cleft palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw, and protruding tongue (SF =144). Paternal toxicity in male rats was also reported (decreases in prostate gland/seminal vesicle weights, sperm density/motility/abnormality; SF =10). In rabbits, similar maternal toxicity occurred (decreased food consumption/weight gain; SF =17). In regard to neonatal toxicity, decreases in survival rate during postnatal Day 7 to 14 (SF =135) occurred. Fostemsavir showed no remarkable toxicity in the juvenile rat study (SF =70), except that slight cardiomyopathies were observed in males that were not dose-dependent and not seen in the recovery groups.

7.1.4. Mutagenesis and Carcinogenesis

Fostemsavir was not genotoxic in the bacterial reverse mutation assay (Ames test in Salmonella and *E. coli*), a chromosome aberration test in human lymphocytes, and rat bone marrow micronucleus test. Fostemsavir produced no statistically significant increases in tumors over controls in a 2-year carcinogenicity study conducted in rats and a 26-week carcinogenicity study conducted in transgenic mice.

7.1.5. Impurities

In regard to impurities, there is no safety concern from the nonclinical perspective based on the International Conference on Harmonisation (ICH) M7 approach. A beta-lactam photodegradant impurity (BMT-218946, formed under short wavelength visible light) had been thoroughly studied and reviewed by both the FDA and the Applicant's expert panel. It was concluded that systemic sensitizing potential of the photodegradant is orders-of-magnitude less than that of beta-lactam antibiotics (e.g., penicillins, cephalosporins), and trace quantities of BMT-218946 are judged very unlikely to produce acute allergic reaction in patients previously sensitized to a beta-lactam antibiotic.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Not applicable. FTR is a first-in-class drug.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable. This drug is not yet commercially available in any country.

7.4. FDA Approach to the Safety Review

7.4.1. Sources of Data for Clinical Safety Assessment

Data from two trials formed the basis of the clinical safety evaluation:

- Phase 3 BRIGHTE trial conducted in HTE subjects. A summary of the design of the BRIGHTE trial can be found in Section 6.2.1.
- Phase 2b trial (205889) conducted in subjects with varying degrees of prior ARV experience. A brief synopsis of the design of the Phase 2b trial will be provided here and additional details are available in Section III.17.1.

Phase 2b Trial (205889) Synopsis

Trial 205889 (AI438011) was a Phase 2b randomized, active-controlled, partially-blinded multicenter trial to investigate the safety, efficacy, and dose-response of FTR. To be eligible for the trial, subjects were required to have HIV-1 RNA ≥1,000 copies/mL despite prior ART experience, defined as current or previous exposure to at least 1 week of at least 1 ARV drug.

Subjects had to be susceptible to all study drugs, including the standardized OBT of raltegravir (RAL) and tenofovir disoproxil fumarate (TDF).

A total of 251 subjects participated in the study across 45 investigational sites. Subjects were randomized equally to one of 5 study cohorts: FTR 600 mg QD (n=51), FTR 400 mg BID (n=50), FTR 1,200 mg QD (n=50), FTR 800 mg BID (n=49), or ritonavir-boosted atazanavir (ATV/r) 300 mg/100 mg (ATV/r) (n=51). All subjects received study medication with RAL 400 mg BID and TDF 300 mg QD. A small number of subjects in each cohort were enrolled in a monotherapy substudy in which subjects received one of the 4 FTR doses for 7 days prior to adding RAL + TDF. The planned duration of treatment was 96 weeks + 24 weeks of follow-up. However, due to delays in the NDA submission related to manufacturing changes, study participants were provided access to FTR for much longer than 96 weeks.

7.4.2. Safety Analysis Plan and Definitions

The prespecified safety analysis plan and definitions were reviewed during protocol development and were acceptable to the clinical review team. Use of descriptive statistics was predefined in the protocol for summarizing the safety outcomes. The review team was in agreement with the proposed approach. The Applicant translated verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for the events reported in both trials. The translations were reviewed and found acceptable, unless specifically noted in this review.

As specified in the protocol, the severity of AEs was determined using the Division of Acquired Immunodeficiency Syndrome (DAIDS) toxicity scales. Version 1.0 of the DAIDS toxicity scale, which was used for the Phase 2b trials, was replaced by Version 2.0 while the BRIGHTE study was underway. In order to ensure a standardized approach, Version 2.0 was used to define the toxicity grade in the datasets for both trials. Causality of safety events was determined by the treating physician. A safety event was classified as related if there was reasonable evidence of a causal relationship between study drug and the event. The following definitions are being used for the purposes of this review:

- AEs were protocol-defined as: “any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment.”
- Treatment-emergent adverse events (TEAEs) are defined as any AE that occurred on or after the day of treatment initiation.
- Adverse drug reactions (ADRs) are defined as any TEAE considered by the investigator as related to the study drug within reasonable possibility.
- Adverse events of special interest (AESI) were classified based on preclinical and clinical experience
- Serious adverse events (SAEs) were protocol-defined as any untoward medical occurrence that, at any dose:
  - results in death
  - is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization.) Potential drug-induced liver injury (DILI) is also considered an important medical event. (see Section 7.6.6 for the definition of potential DILI.)

7.4.3. Reviewer's Approach to the Safety Evaluation

Clinical trial data were independently analyzed using JReview, JMP, and Python software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review. No major issues were identified with respect to recording, coding, and categorizing AEs.

All analyses represent events that occurred through Week 96. Events of interest that occurred after 96 weeks were included in the datasets and the Safety Update Report. These late-onset events will be described in text (as needed) but are not included in tables unless otherwise specified.

Pooling of Data Within and Across Trials

Data from the BRIGHTE trial and the Phase 2b trial were not pooled because there are significant differences in the trial populations. The BRIGHTE trial was used primarily to inform the safety profile of the drug in the intended population of HTE patients, which is a population that suffers from significant comorbid illness relating to advanced HIV/AIDS. This includes not only increased risk for severe manifestations of infectious diseases, but also direct end-organ damage (e.g., AIDS nephropathy), chronic inflammation, cardiovascular disease, and a propensity for malignancies.

The Phase 2b trial, in contrast, enrolled a population with better overall health status. Adjudication of causality between FTR and AEs was less confounded in this population because there is less contribution from underlying illness. In addition, this study had a control group and all subjects received the same OBT. For these reasons, the Phase 2b trial serves as an excellent source for signal detection and aids in the interpretation of Phase 3 BRIGHTE trial results.

Within the BRIGHTE trial, data from the two groups of the Randomized Cohort (placebo and FTR) were pooled because the brief 8-day randomized period is not anticipated to change the safety profile over 96 weeks. Randomized and Non-randomized Cohorts were not pooled because subjects in the Non-randomized Cohort had more advanced HIV infection and the

majority had very low baseline CD4+ T cell counts. In many of the tables in this review, the results from the Randomized and Non-randomized Cohort are presented side-by-side for ease of presentation but no formal statistical analyses were performed to determine differences in safety outcomes within the BRIGHTE trial.

In the Phase 2b trial, the four FTR groups are consolidated into two groups based on how the total daily dose compares to the Phase 3 dose of 600 mg BID. The two lower dose groups (600 mg QD and 400 mg BID) are pooled, as are the two higher dose groups (1,200 mg QD and 800 mg BID). This approach allows for assessment of dose-related safety concerns and a general comparison of FTR relative to the ATV/r control group.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of FTR for the proposed indication, patient population, dosage regimen, and duration. The data meet the minimum recommended sample size of 300 to 500, as outlined by FDA's guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015). A total of 1,465 subjects have been exposed to at least 1 dose of FTR across the clinical development program: 624 subjects with HIV-1 infection and 841 healthy subjects. Of the 624 subjects with HIV-1 infection, 570 were enrolled in the Phase 2b and Phase 3 trials which offered treatment for >96 weeks. An additional 54 subjects with HIV-1 infection were treated with FTR in a Phase 2a trial (8 days of exposure) or via expanded access. The mean FTR exposure for the 841 healthy subjects who participated in Phase 1 clinical pharmacology trials was 6.8 days.

Table 32 summarizes the exposure periods for the BRIGHTE trial, which remains ongoing. The mean (SD) duration of exposure in the Phase 2b trial was 158.0 (102.8) weeks for the higher dose cohort, 189.9 (91.5) weeks for the lower dose cohort, and 153.6 (102.6) weeks for the ATV/r control cohort. Please see Table 181 in Section III.17 for details. This period of exposure enabled the review team to identify both early and late onset AEs.

Table 32. Duration of Exposure, BRIGHTE Trial

Variable	Randomized Cohort N=272	Non-randomized Cohort N=99	Overall N=371
Duration of exposure (weeks)			
Mean (SD)	111.5 (43.4)	105.4 (44.9)	109.9 (43.8)
Median (min, max)	119.8 (0.1, 175.9)	116.3 (3.9, 175.9)	119.0 (0.1, 175.9)
Subjects treated, by duration, n (%)			
Any duration (at least 1 dose)			
<24 weeks	23 (8.5)	8 (8.1)	31 (8.4)
≥24 - <48 weeks	13 (4.8)	7 (7.1)	20 (5.4)
≥48 - <96 weeks	17 (6.2)	17 (17.2)	34 (9.2)
≥96 - <144 weeks	161 (59.2)	48 (48.5)	209 (56.3)
≥144 weeks	58 (21.3)	19 (19.2)	77 (20.8)

Source: adsl.xpt; Software: Python
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation.

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The demonstrated safety profile of FTR in HTE subjects with MDR HIV-1 infection is acceptable at the indicated dose. Overall, there is no clear pattern of high-grade FTR-related safety issues, but the causality assessment is complicated by lack of comparator group and confounding from poor health status and concomitant medications.

In the BRIGHTE trial, infections and malignancies were the leading causes of death and events requiring hospitalization, which is consistent with expectations for this population. Infections and GI events were reported most commonly, but rarely resulted in discontinuation.

No safety concerns emerged in the Phase 2b trial that were not apparent in the BRIGHTE trial. Overall, safety events, particularly high-grade events, occurred with much less frequency in the Phase 2b population. Deaths were uncommon and there was no pattern observed among SAEs or AEs resulting in discontinuation of FTR. Similar to the BRIGHTE trial, the most commonly reported AEs were infections or GI events.

The Safety Update Report described AEs that occurred during the 60 days following the Week 96 data cut. The reported AEs were similar to those that occurred through Week 96 and no new safety signals were identified. There were no events that changed the reviewer's opinion about the benefit/risk assessment of FTR for treatment of MDR HIV-1 infection in HTE subjects.

7.6.1. Overall Adverse Event Summary

Table 33 and Table 34 provide a summary of TEAEs reported through Week 96 in the BRIGHTE trial and the Phase 2b trial, respectively. A significant proportion of subjects in the BRIGHTE trial had high-grade safety events, including death, in contrast to the Phase 2b trial in which high grade safety events were much less common. This trend indicates that much of the morbidity observed in the BRIGHTE trial is related to underlying illness rather than FTR exposure.

Table 33. Overview of Treatment-Emergent Adverse Events, Safety Population, BRIGHTE Trial, 96 Weeks

Event Category	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Any AE	249 (91.5)	98 (99.0)	347 (93.5)
FTR-related AE	105 (38.6)	34 (34.3)	139 (37.5)
Moderate or severe AEs (Grade 3-4)	79 (29.0)	49 (49.5)	128 (34.5)
Death[a]	10 (3.7)	14 (14.1)	24 (6.5)
SAE	92 (33.8)	48 (48.5)	140 (37.7)
FTR-related SAE	9 (3.3)	3 (3.0)	12 (3.2)
SAEs with fatal outcome	10 (3.7)	14 (14.1)	24 (6.5)
AE leading to discontinuation of study drug	14 (5.1)	12 (12.1)	26 (7.0)

Event Category	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
AE leading to dose modification of study drug	35 (12.9)	11 (11.1)	46 (12.4)
AE leading to interruption of study drug	33 (12.1)	11 (11.1)	44 (11.9)
AE leading to reduction of study drug	2 (0.7)	0 (0.0)	2 (0.5)
AE leading to dose delay of study drug	0 (0.0)	0 (0.0)	0 (0.0)

Source: adae.xpt; Software: Python
[a] Limited to treatment-emergent deaths
Abbreviations: AE, adverse event; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with at least one event; SAE, serious adverse event.

Table 34. Overview of TEAEs, Safety Population, Phase 2b Trial

Event Category	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Any AE	92 (92.9)	94 (93.1)	50 (98.0)
FTR-related AE	33 (33.3)	35 (34.7)	31 (60.8)
Moderate or severe AEs (grade 3-4)	19 (19.2)	17 (16.8)	17 (33.3)
Death	1 (1.0)	2 (2.0)	0 (0.0)
SAE	20 (20.2)	15 (14.9)	8 (15.7)
FTR-related SAE	0 (0.0)	1 (0.9)	2 (3.9)
SAEs with fatal outcome	1 (1.0)	2 (2.0)	0 (0.0)
AE leading to discontinuation of study drug	5 (5.1)	2 (2.0)	6 (11.8)
AE leading to dose modification of study drug	11 (11.1)	10 (9.9)	9 (17.6)
AE leading to interruption of study drug	11 (11.1)	10 (9.9)	9 (17.6)
AE leading to reduction of study drug	1 (1.0)	0 (0.0)	0 (0.0)
AE leading to dose delay of study drug	0 (0.0)	0 (0.0)	0 (0.0)

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Additional analyses were performed to determine whether the safety profile differed between demographic subgroups. Older, white, male, North American subjects had numerically higher proportions of AEs but are also the most heavily represented population in the trial. Please see Section III.17.2.1 for additional details (Table 182 and Table 183).

7.6.2. Deaths

A total of 29 subjects died during the BRIGHTE trial, of which 28 received FTR. One subject randomized to receive placebo died before starting open-label FTR. Seventeen of the 28 deaths in FTR-exposed subjects occurred in the Non-randomized Cohort and 11 occurred in the Randomized Cohort. Twenty-four of the subjects had fatal on-treatment SAEs, and four subjects died after withdrawing from the study. The majority of all subjects who died had advanced HIV disease: 20/28 had baseline CD4+ T cell count <50 cells/mm^3 (15 nonrandomized, 5 randomized).

The causes of death for the 28 subjects who received FTR are summarized in Table 184 (Section III.17.2.2). The majority of deaths were caused by infections/sepsis (n=13) or malignancy (n=8).

Five subjects died from organ failure (cardiovascular disorder, hepatic failure, renal failure, or stroke). One subject died from progressive multifocal leukoencephalopathy (PML), and one subject died from IRIS. The IRIS event was considered a treatment-related SAE; the remaining fatal events were classified as unrelated to FTR by the investigator. The clinical reviewer independently reviewed the narratives for all subjects who died during the trial and agrees with the causality assessment.

Three subjects died in the Phase 2b trial. One subject in the high dose FTR group died of sepsis. Two deaths occurred in the low dose FTR group: one of completed suicide and one of gunshot wound. There were no deaths in the ATV/r control group. None of the events were considered drug-related by investigators, and the clinical reviewer agrees with this assessment. Additional details are available in Table 185 located in Section III.17.2.2.

Medical Officer's Assessment: *Overall, the analysis of fatal events does not reveal any serious risks attributable to FTR. The majority of events are likely a consequence of advanced HIV infection.*

7.6.3. Serious Adverse Events

As observed with the analysis of fatal events, the majority of SAEs reported in the BRIGTHE trial were related to advanced HIV infection and occurred more often in the Non-randomized Cohort (49% of subjects) than the Randomized Cohort (34%). Infections were the most frequently reported events (16% of subjects overall), followed by neoplasms (8%) and GI disorders (6%). A small proportion of SAEs were considered FTR-related by the study investigators, as summarized in Table 35. After reviewing the narratives for these events, the clinical reviewer agrees with the investigators' causality assessment. Please see Section 7.6.6 for a more detailed discussion of AEs of special interest, which include many of the events included here. A more comprehensive list of SAEs is provided in Table 186, located in Section III.17.2.3.

Table 35. FTR-related SAEs, All Grade, Safety Population, BRIGHTE Trial

Adverse Event by PT	Randomized N=272 n (%)	Non-randomized N=99 n (%)	Total N=371 n (%)
Immune reconstitution inflammatory syndrome[a,b]	2 (0.7)	1 (1.0)	3 (0.8)
Nephrolithiasis	1 (0.4)	1 (1.0)	2 (0.5)
Renal impairment	1 (0.4)	0 (0.0)	1 (0.3)
Acute kidney injury	1 (0.4)	0 (0.0)	1 (0.3)
Rhabdomyolysis	1 (0.4)	0 (0.0)	1 (0.3)
Hyperkalaemia	0 (0.0)	1 (1.0)	1 (0.3)
Hyperglycaemia	1 (0.4)	0 (0.0)	1 (0.3)
Hepatocellular injury	1 (0.4)	0 (0.0)	1 (0.3)
Disorientation	1 (0.4)	0 (0.0)	1 (0.3)
Loss of consciousness	1 (0.4)	0 (0.0)	1 (0.3)
Myocarditis	0 (0.0)	1 (1.0)	1 (0.3)

Adverse Event by PT	Randomized N=272 n (%)	Non-randomized N=99 n (%)	Total N=371 n (%)
Rash generalised	1 (0.4)	0 (0.0)	1 (0.3)
Foetal growth restriction	1 (0.4)	0 (0.0)	1 (0.3)

Source: adae.xpt; Software: Python
[a] Immune reconstitution inflammatory syndrome = PTs Immune reconstitution inflammatory syndrome and central nervous system immune reconstitution inflammatory response
[b] IRIS was a fatal SAE in one subject (subject ID AI43847.000694)
Abbreviations: FTR, fostemsavir; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term; SAE, serious adverse event.

SAEs were reported in substantially fewer subjects in the Phase 2b trial: 20% of high-dose FTR subjects, 15% of low-dose FTR subjects, and 16% of ATV/r control subjects. The most commonly reported events were in the following System Organ Class (SOC): Infections and Infestations; Injury, poisoning and procedural complications; and GI disorders. Additional details are available in Section III.17.2.3, Table 188.

Medical Officer's Assessment: *Evaluation of the Phase 3 and Phase 2b SAEs did not reveal patterns to suggest a serious safety risk attributable to FTR treatment.*

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Seven percent of subjects discontinued from the BRIGHTE trial overall. Of note, discontinuation of FTR was mandated in the study protocol for subjects with the following ECG abnormalities: QT value >500 msec; confirmed QTcF value >470 msec for women and >450 msec for men; confirmed PR Interval >260 msec (severe first degree AV block); confirmed second or third degree heart block (see please Section 7.6.6 for a discussion on the risk for QT prolongation).

Most events leading to discontinuation occurred in a single subject with the exception of the following: Electrocardiogram QT prolonged (n=3); Abdominal pain (n=2); Non-cardiac chest pain (n=2); Hepatic failure (n=2). FTR-related events leading to discontinuation included QT prolonged (n=3), abdominal pain (n=2), and the following events that were reported in one subject each: hepatic enzyme increased, hepatocellular injury, tachycardia, dyspepsia, flatulence, nausea, rhabdomyolysis, mycobacterial infection, rash, noncardiac chest pain, neck pain, asthenia, fatigue, and dizziness. There was no pattern in time-to-onset of events leading to discontinuation. For additional details, see Table 189 in Section III.17.2.4, which provides a complete list of AEs leading to discontinuation, grouped by unique subject ID number.

Given the lack of therapeutic alternatives for the HTE population enrolled in the BRIGHTE trial, not many discontinuations for AEs were expected for tolerability issues unless they were severe. Analysis of the Phase 2b events allows for a broader assessment of FTR tolerability in a population that has more ARV choices, and is therefore less obligated to continue FTR.

A full listing of AEs leading to discontinuation in the Phase 2b trial is available in Section III.17, Table 190. Discontinuations due to AEs were rare among FTR recipients in the Phase 2b trial and more frequent among ATV/r recipients (4% versus 12%, respectively); there was no overlap

of reported events leading to discontinuations between the FTR and ATV/r cohorts. Events leading to discontinuation in the FTR cohorts include completed suicide, tuberculosis, acute kidney injury, and ischemia. GI and hepatobiliary events led to discontinuation in the ATV/r cohort, which is consistent with the known safety profile of atazanavir (ATV).

Medical Officer's Assessment: *GI events were the leading tolerability issue associated with FTR based on the BRIGHTE trial; this trend was not observed in the Phase 2b trial, in which no tolerability issues were evident. No new patterns were identified to suggest a serious toxicity concern associated with FTR.*

7.6.5. Treatment-Emergent Adverse Events

A combination of data from the BRIGHTE trial and the Phase 2b trial were used to assess the general AE profile of FTR. Although it will not be presented in labeling, the Phase 2b trial was important in this assessment because 1) it contained a control group and 2) there was less confounding from comorbid illness. Please refer to Section III.17.2.5 for incidence of TEAEs. In this section, TEAEs considered possibly related to study drug (ADR) are discussed.

Given the lack of a control group for safety in the BRIGHTE trial, the Sponsor's assessment of causality was used to classify the relationship between AEs and FTR exposure. Although this approach may result in some misclassification of events, no alternative approach was available. The clinical review team felt that causality assessment was even more challenging in the Non-randomized Cohort compared to the Randomized Cohort due to the poor health status of the population. Therefore, only ADRs from the Randomized Cohort will be presented in tabular format in product labeling; additional information about ADRs in the Non-randomized Cohort will be provided in text. Table 36 summarizes ADRs occurring in at least 2% of subjects in the BRIGHTE trial and Table 37 summarizes ADRs in the Phase 2 trial. Of note, the clinical reviewer pooled several similar PTs to improve signal detection.

Table 36. Adverse Drug Reactions Occurring in at Least 2% of Subjects, All Grade, BRIGHTE Trial

Adverse Event by PT	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Nausea	27 (9.9)	6 (6.1)	33 (8.9)
Diarrhoea	12 (4.4)	6 (6.1)	18 (4.9)
Rash[a]	9 (3.3)	4 (4.0)	13 (3.5)
Fatigue[b]	9 (3.3)	7 (7.1)	16 (4.3)
Headache	12 (4.4)	1 (1.0)	13 (3.5)
Sleep Disturbance[c]	9 (3.3)	0 (0.0)	9 (2.4)
Dyspepsia[d]	8 (2.9)	0 (0.0)	8 (2.2)

Adverse Event by PT	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Abdominal pain	8 (2.9)	0 (0.0)	8 (2.2)
Vomiting	5 (1.8)	3 (3.0)	8 (2.2)
IRIS[e]	6 (2.2)	1 (1.0)	7 (1.9)
Somnolence	6 (2.2)	1 (1.0)	7 (1.9)

Source: adae.xpt; Software: Python
Pooled terms:
[a] Rash (rash, rash pruritic, dermatitis allergic, rash generalized, rash maculo-papular, rash erythematous, rash macular, rash papular)
[b] Fatigue (fatigue + asthenia)
[c] Sleep Disturbance (insomnia, sleep deficit, sleep disorder, abnormal dreams)
[d] Abdominal pain (pain, pain upper, discomfort)
[e] IRIS (IRIS + CNS IRIS)
Abbreviations: IRIS, immune reconstitution inflammatory syndrome; N, number of subjects in treatment group; n, number of subjects with adverse event; PT, preferred term.

Table 37. Adverse Drug Reactions Occurring in at Least 2% of FTR Subjects, All Grade, Phase 2b Trial

Adverse Event	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r Control N=51 n (%)
Nausea	7 (7.1)	3 (3.0)	4 (7.8)
Headache	5 (5.1)	6 (5.9)	3 (5.9)
Rash[a]	5 (5.1)	5 (5.0)	0 (0.0)
Dyspepsia	3 (3.0)	0 (0.0)	2 (3.9)
Vomiting	3 (3.0)	1 (1.0)	2 (3.9)
Diarrhoea	2 (2.0)	4 (4.0)	2 (3.9)
Flatulence	2 (2.0)	4 (4.0)	1 (2.0)
Gastritis	2 (2.0)	0 (0.0)	1 (2.0)
Insomnia	2 (2.0)	0 (0.0)	0 (0.0)
Paraesthesia	1 (1.0)	2 (2.0)	0 (0.0)

Source: adae.xpt; Software: Python
Pooled terms:
[a]Rash: Rash, Rash generalized, Rash maculo-papular, Rash popular, Urticaria, Drug eruption, Erythema, Rash pruritic, Skin irritation
Laboratory AEs excluded
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with adverse event; PT, preferred term.

Medical Officer's Assessment: *Infections were the most commonly reported events in both trials, which is reflective of the patient population rather than the safety profile of the drug. GI symptoms, headache, and rash were commonly noted as FTR-related events across both trials. For the reasons previously discussed, ADRs reported in the Randomized Cohort will be presented in labeling, as these are the most reflective of the population for whom FTR will be indicated.*

7.6.6. Adverse Events of Special Interest

The purpose of this section is to provide a more detailed discussion regarding safety signals that occur at a high frequency and/or are associated with serious outcomes. An organ-based review of renal and pancreatic labs and AEs will be presented in Section III.17, along with a review of cardiac AEs. They are not discussed here because there were no significant concerns for these organ systems based on clinical events and laboratory abnormalities.

7.6.6.1. Prolongation of the QT Interval

As previously noted in Table 5, the thorough QT study revealed a mean (upper 90% confidence interval) QTcF increase of 11.2 milliseconds (13.3 milliseconds) at four times the recommended dose (2,400 mg BID). The observed increase in QTcF was TMR concentration-dependent (additional details available in Section III.17.3). Consequently, the BRIGHTE trial mandated discontinuation of study participation of subjects with significant QT prolongation. ECGs were obtained on Day 1, Weeks 4, 8, 12, 16, 24, 36, 48, and every 48 weeks thereafter.

The datasets, narratives, and clinical study report were reviewed for subjects with QT prolongation to determine whether these subjects had associated cardiac arrhythmias. Nineteen percent of subjects experienced an increase in the QTcF of ≥30 msec. Seven subjects (2%) discontinued the BRIGHTE trial due to prolonged QT interval, which are described in the Sponsor's summary table (Table 38). All subjects had other ECG abnormalities at baseline and/or other points during the study. Notably, none had clinical symptoms at the time of QT prolongation and time to onset and discontinuation was quite variable, ranging from Day 23 to 628. The subjects did not appear to have higher plasma TMR C_{max}. There were no subjects in the Phase 2b trial who discontinued study due to an AE of QT prolongation.

Table 38. Listing of Subjects Withdrawn for Meeting Protocol-Specified QTc Stopping Criteria

Subject ID Age Gender	Details for AE of "ECG QT Prolongation" (where reported)				Study Day Withdrawn	Baseline (Day 1) / Maximum QTcF (msec)/ Study Day	Comments
	Onset Study Day[a]	Maximum Grade	Serious	Related to Study Drug			
Randomized Cohort, FTR 600 mg BID							
AI438047.000706 60 years Male	120	3	No	Yes	Study Day 120	448 / 461 Day 120	AE of ventricular extrasystoles also reported (Study Day 90, not related to study drug); study drug was not interrupted due to the Day 90 event. Abnormal ECG at Baseline of Sinus Bradycardia.
AI438047.000166 53 years Male	1	2	No	No	Study Day 23	451 / 456 Day 8	No other CV-related events were reported. Abnormal ECG at Baseline of LBB Block and QTc interval prolongation.
AI438047.000476 66 years Male	92	1	No	No	Study Day 153	436 / 482 Day 99	AEs of diastolic dysfunction (Day 58) and hypocalcemia and hypokalemia (Study Day 95 for both) also reported; all 4 AEs were not related to study drug, and study drug was not interrupted for any of the events. Abnormal ECG at Baseline of Sinus Bradycardia, RBB Block, Left Axis Deviation; Left Ventricular Hypertrophy recorded at Screening and post-baseline.
Non-Randomized Cohort, FTR 600 mg BID							
AI438047.000753 72 years Male	69	2	No	Yes	Study Day 244	428 / 462 Day 147	Confirmed QTc value >450 msec; AE of palpitations reported (Study Day 150, not related to study drug). Abnormal ECG findings at Baseline and Day 147 of Sinus Bradycardia, RBB Block, Other Intraventricular Conduction Defect and Left Axis Deviation

Subject ID Age Gender	Details for AE of "ECG QT Prolongation" (where reported)				Study Day Withdrawn	Baseline (Day 1) / Maximum QTcF (msec)/ Study Day	Comments
	Onset Study Day[a]	Maximum Grade	Serious	Related to Study Drug			
AI438047.000042 50 years Male	Not applicable (ECG QT prolongation was not required to be reported as an AE)				Study Day 43	461 / 463 Day 29	Initial onset: Day 1. Confirmed QTc value >450 msec; no related AEs were reported. Abnormal ECG findings at Baseline of RBB Block and QTcF Interval Prolonged.
AI438047.000096 53 years Male	Not applicable (ECG QT prolongation was not required to be reported as an AE)				Study Day 510	445 / 469 Day 343	Initial onset: Day 343. Confirmed QTc value >450 msec; no related AEs were reported. Medical history of Right Bundle Block. Abnormal ECG findings at Baseline and Study day 33 of RBB Block, Other Intraventricular Conduction Defect: Left Anterior Fasicular Block and Left Axis Deviation.
AI438047.000785 54 years Male	Not applicable (ECG QT prolongation was not required to be reported as an AE)				Study Day 628	448 / 470 Day 336	Initial onset: Day 28 Confirmed QTc value >450 msec; AE of pulmonary hypertension (Study Day 82) and AE of hypokalemia (Study Day 172) were reported; study drug was not interrupted due to either event. Abnormal ECG finding of Sinus Bradycardia at Baseline and Day 336; First degree A-V Block also reported at Day 336.

Source: Applicant's Clinical Study Report for Trial 205888, Table 76 (Data source: Listing 3, Listing 21, Listing 37, Listing 104, Listing 329)
[a] Relative to first dose of study drug
Abbreviations: AE, adverse event; A-V, atrial-ventricular; BID, twice daily; CV, cardiovascular; ECG, electrocardiogram; FTR, fostemsavir; LBB, left bundle branch; RBB, right bundle branch.

Among the seven subjects who discontinued the BRIGHTE trial, six resumed treatment with FTR through the expanded access program (EAP). Only one of these subjects had a cardiac AE while receiving treatment through the EAP. Approximately 7 weeks after resuming FTR treatment in the EAP, the subject reported dyspnea on exertion and fatigue. He was hospitalized and found to have complete heart block requiring pacemaker placement. The subject continued FTR without changes. The treating physician reported the event as a Grade 2 SAE (atrioventricular block complete) that was unrelated to FTR. The clinical reviewer agrees with the assessment.

The study cohort was also evaluated more broadly to assess the arrhythmogenic potential of FTR. An analysis was conducted to identify AEs in the following MedDRA Standardized Medical Query (SMQ) categories: Cardiac Arrhythmias (broad and narrow); Torsade de pointes/QT prolongation (broad and narrow). The same analyses were conducted for the Phase 2b trial for additional signal detection (Table 195). These analyses did not identify any new cases of concern.

Medical Officer's Assessment: *The risk of QT prolongation has been documented at supratherapeutic doses (4x the indicated dose), and the Applicant proposed inclusion of a Warning and Precaution to communicate the risk for QT prolongation with FTR. The clinical team agrees that providers should be aware of this risk. Of note, FDA's QT-IRT team felt that a Warning and Precaution was not necessary because it is unlikely that clinical exposures will reach those observed with supratherapeutic dosing (see III.17.3 for additional details). Although there is no evidence from the clinical trials that treatment with FTR causes serious arrhythmias at doses up to 1,600 mg per day, the total sample size across the two studies remains limited to detect low-frequency events, and it is unknown whether the risk is additive. Therefore, providers*

should be particularly cautious for patients taking other medications that can prolong the QT interval (e.g., subjects taking macrolide antibiotics for MAI prophylaxis). This information will be communicated in product labeling as a Warning and Precaution in Section 5, as proposed by the Applicant.

7.6.6.2. IRIS

IRIS is a phenomenon characterized by an exaggerated inflammatory reaction to a pre-existing infectious disease causing a paradoxical worsening in the patient's condition. IRIS typically occurs when the immune system experiences a rapid recovery following initiation of ART. There are no universal definitions, but there is general agreement that a diagnosis of IRIS requires clinical deterioration from either 1) a known infection that has been treated (paradoxical IRIS) or 2) an undiagnosed infection (unmasking IRIS). Many pathogens have been associated with IRIS in people living with HIV, including mycobacteria, cryptococcus, and herpes group viruses. There is a wide spectrum of IRIS severity ranging from mild to life-threatening. Risk for IRIS increases for patients with more severe immune suppression and higher HIV-1 viral loads prior to ART initiation. Hence, the HTE population enrolled in the BRIGHTE trial is at higher risk for these reactions than the HIV population overall.

A total of eight subjects experienced an IRIS event in the BRIGHTE trial: 6 in the Randomized Cohort and 2 in the Non-randomized Cohort. Median time to onset was 4.3 weeks. Three of the events were SAEs, of which one was fatal (atypical mycobacterial infection). Five of the subjects had a notable rise in CD4 count from baseline to the time of onset. The cases are summarized in Table 39. No IRIS events were reported in the Phase 2b trial.

Table 39. Summary of IRIS Events, Safety Population, BRIGHTE Trial

Subject ID	IRIS Event/ Pathogen	Event Onset (Study Day)	Severity	CD4 Cell Count (BL/Max Near IRIS Event)	FTR- Related: Investigator Assessment	FTR- Related: Clinical Reviewer Assessment
Randomized Cohort						
AI438047.000232	History of HCV and cryptococcal meningitis	87	Grade 2	BL: 3 cells/μL Max: 57 cells/μL	Yes	Yes
AI438047.000429	Cerebral toxoplasmosis	26	Grade 3	BL: 281 cells/μL Max: 364 cells/μL	Yes	Yes
AI438047.000486	PML	42	Grade 2	BL: 3 cells/μL Max: 397 cells/μL	Yes	Yes
AI438047.000607	Folliculitis	4	Grade 2	BL: 5 cells/μL Max: 9 cells/μL	Yes	Possible – there is no evidence of immune reconstitution; other causes of folliculitis (besides IRIS) are plausible
AI438047.000655	PML, pneumococcal pneumonia	109	Grade 3	BL: 55 cells/μL Max: 194 cells/μL	Yes	Yes
AI438047.000694	Atypical mycobacterial infection	32	Grade 4 (fatal)	BL: 1 cells/μL Max: 5 cells/μL	Yes	Yes
Non-randomized Cohort						
AI438047.000338	History of CMV colitis/retinitis and cerebral toxoplasmosis	44	Grade 2	BL: 13 cells/μL Max: 90 cells/μL	No	Yes – given the notable rise in CD4 count at the time of the event, this is consistent with IRIS related to FTR treatment
AI438047.000705	CNS lesion with history of JC virus	3	Grade 3	BL: 73 cells/μL Max: 70 cells/μL	Yes	Possible – there is no evidence of immune reconstitution 3 days into treatment course.

Source: Adapted from Table 38 of the Summary of Clinical Safety, with additional information from analysis datasets (adsl, adae, adcm) and case narratives.
Abbreviations; BL, baseline; CNS, central nervous system; CMV, cytomegalovirus; FTR, fostemsavir; HCV, hepatitis C virus; ID, identifier; IRIS, immune reconstitution inflammatory syndrome; JC, John Cunningham; PML, progressive multifocal leukoencephalopathy.

Medical Officer's Assessment: *The occurrence of IRIS events was anticipated in the HTE population. The clinical review team agrees with the Applicant's proposal to include IRIS as a Warning and Precaution. Of note, IRIS is included in Warnings and Precautions as class labeling for ARVs.*

7.6.6.3. Rash and Hypersensitivity Reactions

Many ARVs across classes are associated with hypersensitivity reactions (HSRs) or severe rashes including erythema multiforme, Stevens-Johnson syndrome, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Concomitantly administered ARVs confound the causality assessment for FTR, which is particularly an issue in the BRIGHTE trial, which lacks a control group and in which OBT is not standardized. Hence, the Phase 2b trial again serves an important role in enabling detection of FTR-related rash and HSR events.

The evaluation of rash and HSRs have notable overlap and are therefore presented together. Both rash and HSR were identified as potential safety signals during the early stages of FTR development. A Phase 1 drug-drug interaction (DDI) study (Study 206268) evaluating DRV and FTR in healthy volunteers was terminated early due to rash and hypersensitivity-related safety events: one subject had an SAE of anaphylaxis (Grade 3 rash and Grade 1 pharyngeal edema), one subject had blood-tinged stool with lower abdominal pain, and three subjects developed a rash. Upon further review, the SAE of anaphylaxis was considered unlikely to be a true Type I HSR because symptoms presented after 5 days of dosing, which is an uncharacteristic timeline for anaphylactic reactions.

Rash

In pooled Phase 1 trials, the PT "rash" was reported in 1% of FTR-exposed subjects and 0 placebo subjects. In the Phase 2a study that evaluated 8 days of FTR, 10% of subjects had a rash, which increased to a total of 16% when events in the follow-up period were included.

The analyses presented in Table 40 and Table 41 captured PTs containing the word "rash" in the BRIGHTE trial and Phase 2b trial, respectively. Most events were Grade 1 or 2 in severity. There were no serious rash events in either trial. One event of Grade 3 rash led to study discontinuation in the Randomized Cohort of the BRIGHTE trial (rash onset on FTR Day 8 lasting 13 days; subject withdrew from the trial). There was no pattern with respect to rash morphology for related events compared to unrelated events. Additional analyses are presented in Section III.17, which follow a similar trend (see Table 196 and Table 197).

Table 40. Pooled Rash Events, All Cause, All Grade, Safety Population, BRIGHTE Trial

Grouped Query PT	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Rash	20 (7.4)	16 (16.2)	36 (9.7)
Rash	7 (2.6)	3 (3.0)	10 (2.7)
Rash pruritic	5 (1.8)	4 (4.0)	9 (2.4)
Rash maculo-papular	4 (1.5)	1 (1.0)	5 (1.3)
Rash papular	4 (1.5)	5 (5.1)	9 (2.4)
Rash generalised	3 (1.1)	4 (4.0)	7 (1.9)
Rash macular	1 (0.4)	2 (2.0)	3 (0.8)
Rash erythematous	0 (0)	1 (1.0)	1 (0.3)

Source: adae.xpt; Software: Python
Abbreviations: N, number of subjects in treatment group; n, number of subjects with adverse event; PT, preferred term.

Table 41. Pooled Rash Events, All Cause, All Grade, Safety Population, Phase 2b Trial

Grouped Query PT	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Rash	11 (11.1)	15 (14.9)	1 (2.0)
Rash	6 (6.1)	9 (8.9)	0 (0)
Rash generalised	1 (1.0)	0 (0)	0 (0)
Rash macular	1 (1.0)	0 (0)	0 (0)
Rash maculo-papular	1 (1.0)	0 (0)	0 (0)
Rash papular	1 (1.0)	3 (3.0)	1 (2.0)
Rash pruritic	1 (1.0)	5 (5.0)	0 (0)

Source: adae.xpt; Software: Python
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with adverse event; PT, preferred term.

Interestingly, the frequency of FTR-related rash was comparable in both trials at 3%: 11 subjects in the BRIGHTE trial and six subjects in the Phase 2b trial. In addition, Table 41 demonstrates a clear imbalance in rash events between the FTR and ATV/r groups. In total, this analysis is supportive of a relationship between FTR exposure and mild to moderate rash events. There is no evidence of serious cutaneous events.

Medical Officer Assessment: *Related rash events will be included in Section 6 of FTR labeling. Given the generally benign nature of these events, no additional labeling is warranted. The term "rash" will include the pooled terms used in Table 40 and Table 41 in addition to the term "dermatitis allergic" from the broader HLGT Epidermal and dermal conditions.*

Hypersensitivity Reactions (HSRs)

Allergic reactions became a topic of increased scrutiny in 2016 when the presence of a beta-lactam–containing photodegradant was noted. This finding raised new concerns about the risk for allergic reactions including anaphylaxis. For patients taking FTR for treatment of HIV-1 infection, there were concerns that the beta-lactam photodegradant could trigger allergic reactions in patients with known beta-lactam allergies or sensitize patients without a history of beta-lactam allergies. In addition, there were concerns that other drugs manufactured in the same

site could be contaminated with the beta-lactam impurity, thereby putting a much larger population at risk of allergic reactions.

Evaluation of the sensitizing potential of FTR and changes to manufacturing are covered in detail in Section 7.7.2 and the product quality review. In brief, changes to the manufacturing process were successful in reducing the quantity of the photodegradant to levels that are unlikely to cause reactions. In addition, the beta-lactam moiety was found to have low sensitizing potential.

This section will summarize the clinical review of HSR reactions that were observed in trials utilizing FTR that was manufactured without the additional controls that will be employed for commercial manufacturing. Events that were identified cannot be attributed to any particular moiety of the FTR molecule, but assuming that all events were caused by the beta-lactam photodegradant, this would represent a "worst case scenario" of HSR risk.

The clinical review team used the Anaphylaxis and Hypersensitivity MedDRA SMQs to capture AEs that could be suggestive of HSR reactions. Both broad and narrow search results were obtained and reviewed, but only the narrow results will be discussed, as they are more likely to represent true allergic events. All available narratives were reviewed. The events will be summarized in this section and can be viewed in tabular format in Section III.17 (Table 198).

No subjects in the BRIGHTE or Phase 2b trial had AEs in the Anaphylaxis SMQ. The Hypersensitivity SMQ captured 73 subjects (20%) with events, with an even distribution between the Randomized and Non-randomized Cohorts. Rash and other cutaneous AEs were predominant. Many of the skin events were considered unrelated to FTR by the investigator, but the temporal relationship between FTR initiation and event onset made it difficult for the clinical reviewer to definitively rule out an association.

There were 3 SAEs. A 54-year-old male subject had Grade 3 generalized rash that was attributed to ENF; FTR was continued without interruption (Subject ID AI438047.000016). A 49-year-old male subject undergoing treatment for pharyngeal cancer had Grade 3 pharyngeal edema that led to a 19-day interruption of FTR treatment (Subject ID AI438047.000249). A 60-year-old subject had Grade 2 HSR (lip swelling) attributed to treatment with an ACE inhibitor; treatment with FTR was suspended for 1 day (Subject ID AI438047.000323, also shown in Table 42).

Characteristics of nine subjects who had an AE of "hypersensitivity" (PTs of hypersensitivity, drug hypersensitivity, or injection site hypersensitivity) are summarized in Table 42. Time to onset was highly variable and all events were Grade 1 or 2. One event was considered an SAE (Subject ID AI438047.000323, discussed in the previous paragraph) for which FTR treatment was interrupted. Three of the subjects had a history of allergies to beta-lactam antibiotics, and several subjects had allergies to more than one medication.

Table 42. Summaries of HSR Cases, BRIGHTE Trial

Subject ID	Onset of Event (FTR Day)	Event	FTR Discontinued (Yes/No)	FTR- Related by Investigator Assessment (Yes/No)	Additional Details
Randomized Cohort					
AI438047.000004	956	Grade 1 HSR	No	No	Investigator term “intermittent environmental allergy” was mapped to MedDRA term “hypersensitivity.”
AI438047.000027	5	Grade 1 HSR (Rash)	No	No	Event occurred 5 days after starting amoxicillin/clavulanic acid and resolved in 18 days
AI438047.000104	112	Grade 2 HSR (Rash)	No	No	Event resolved in 18 days
AI438047.000152	674	Grade 2 HSR	No	No	The subject discontinued DRV and the event resolved in 7 days. Subject has a history of PCN allergy.
AI438047.000297	28	Grade 1 facial erythema, Grade 1 thigh erythema	No	No	Event attributed to fluconazole which was taken 1-2 days prior to symptom onset. Subject has a history of cephalosporin allergy.
AI438047.000323	717	Grade 2 HSR with lip swelling	Yes, temporarily	No	Event attributed to ACE inhibitor and resolved in 2 days.
AI438047.000432	557	Grade 1 HSR	No	No	Event resolved in 3 days
Non-randomized Cohort					
AI438047.000149	484	Grade 2 HSR	No	No	Event attributed to doxycycline and resolved in 4 days.
AI438047.000368	443	Grade 2 HSR	No	No	Event attributed to TMP-SMX and resolved in 6 days. Subject has history of PCN allergy.

Source: Adapted from Table 42 of the Summary of Clinical Safety, with additional information from datasets (adsl, adae, adcm) and case narratives.
Abbreviations: ACE, angiotensin-converting enzyme; DRV, darunavir; FTR, fostemsavir; HSR, hypersensitivity reaction; MedDRA, Medical Dictionary for Regulatory Activities; PCN, penicillin; TMP-SMX, trimethoprim-sulfamethoxazole.

In the Phase 2b trial, 43 FTR subjects (22%) and 3 ATV/r subjects (6%) had AEs in the HSR SMQ. Similar to the BRIGHTE trial, the majority of AEs were rash events. The only case of HSR was in the ATV/r group (see Table 199).

Medical Officer's Assessment: *None of the HSR events were considered FTR-related; although attribution of causality is challenging due to multiple concomitant medications, including ARVs known to cause rash and HSR, the events overall were mild to moderate in severity and resolved despite ongoing treatment with FTR. No labeling is needed for HSR, as there were no compelling cases of serious drug-related reactions.*

7.6.6.4. Hepatobiliary Events

Early in the NDA review cycle, the clinical reviewer noted cases of hepatic impairment leading to death or discontinuation of FTR, as well as a significant number of subjects with elevations in hepatic transaminases. Review of clinical trials in HTE subjects for other ARVs revealed a generally higher rate of hepatic events compared to trials in treatment-naïve subjects, suggesting that underlying disease is contributing to this trend. See (TaiMed 2018), (Tibotec 2011), and (ViiV 2014) for prescribing information for IBA, etravirine (ETR), and DTG, respectively. A series of analyses were conducted to ascertain the contribution of FTR in these events and to identify subjects who might be at highest risk. Subjects with viral hepatitis coinfection were evaluated with additional scrutiny.

Clinical AEs were identified using the Hepatobiliary SOC, as summarized in Table 43. A total of 24 subjects had hepatobiliary events, 7 of which had SAEs (PTs cholecystitis, acute cholecystitis, cholelithiasis, hepatic failure, and hepatic injury). The subject with hepatocellular injury also had cholecystitis. Three events occurred in subjects with viral hepatitis coinfection, including the two hepatic failure SAEs; one had a history of hepatitis C virus (HCV) infection (treated) with decompensated cirrhosis as well as hepatorenal syndrome; the other had HBV reactivation.

Table 43. Hepatobiliary AEs, All Cause, All Grade, Safety Population, BRIGHTE Trial

Adverse Event by PT	Toxicity Grade	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Cholelithiasis[a]	G1 n=1 G2 n=5 G3 n=1	4 (1.5)	3 (3.1)	7 (1.9)
Hepatic steatosis	G1 n=3 G2 n=2	4 (1.5)	1 (1.0)	5 (1.3)
Hepatomegaly	G1 n=2 G2 n=2	3 (1.1)	1 (1.0)	4 (1.1)
Hepatic cirrhosis[a]	G1 n=1 G3 n=1	2 (0.7)	0 (0.0)	2 (0.5)
Hepatic failure	G3 n=1 G4 n=1	0 (0.0)	2 (2.0)	2 (0.5)
Biliary colic	G2 n=1	0 (0.0)	1 (1.0)	1 (0.3)
Cholecystitis	G2 n=1	1 (0.5)	0 (0.0)	1 (0.3)
Cholecystitis acute[a]	G3 n=1	0 (0.0)	1 (1.0)	1 (0.3)

Adverse Event by PT	Toxicity Grade	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Chronic hepatitis	G2 n=1	1 (0.4)	0 (0.0)	1 (0.3)
Hepatic function abnormal[a]	G1 n=1	1 (0.4)	0 (0.0)	1 (0.3)
Hepatocellular injury[a]	G3 n=1	1 (0.4)	0 (0.0)	1 (0.3)
Hepatorenal syndrome	G4 n=1	0 (0.0)	1 (1.0)	1 (0.3)
Hyperbilirubinaemia	G3 n=1	0 (0.0)	1 (1.0)	1 (0.3)
Ocular icterus	G1 n=1	0 (0.0)	1 (1.0)	1 (0.3)

Source: adae.xpt; Software: JReview
[a] At least one event occurred in a subject with HBV or HCV co-infection
Abbreviations: AE, adverse event; N, number of subjects in treatment group; n, number of subjects with adverse event; PT, preferred term.

Hepatobiliary events were infrequent among FTR subjects in the Phase 2b trial (see Table 200 in Section III.17). One subject interrupted FTR treatment due to an SAE of chronic cholecystitis. More events were reported in the ATV/r control group, primarily relating to hyperbilirubinemia and jaundice, which is consistent with the known safety profile of ATV. This analysis supports the conclusion that the events seen in the BRIGHTE trial are related, at least in part, to comorbid illness.

Table 44 summarizes hepatic lab abnormalities in the BRIGHTE trial. Grade 3 and 4 elevations in bilirubin or hepatic transaminases occurred in 3 to 4% of the study population, which will be included in labeling. Grade 3 or 4 elevations among subjects in the FTR cohorts of the Phase 2b trial occurred in 1% for alanine aminotransferase (ALT), 3.5% for AST 0% for bilirubin and <1% for ALP (see Table 201).

Table 44. Maximum Postbaseline Serum Liver Biochemistry Abnormalities, Safety Population, BRIGHTE Trial

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Alanine aminotransferase (U/L), sum	71 (26)	20 (20)	91 (25)
Grade 1 (<3 × ULN)	39 (14)	14 (14)	53 (14)
Grade 2 (≥3 to <5 × ULN)	18 (7)	5 (5)	23 (6)
Grade 3 (≥5 to <10 × ULN)	10 (4)	1 (1)	11 (3)
Grade 4 (≥10 × ULN)	4 (1)	0 (0)	4 (1)
Aspartate aminotransferase (U/L), sum	63 (23)	24 (24)	87 (23)
Grade 1 (<3 × ULN)	37 (14)	16 (16)	53 (14)
Grade 2 (≥3 to <5 × ULN)	16 (6)	6 (6)	22 (6)
Grade 3 (≥5 to <10 × ULN)	6 (2)	1 (1)	7 (2)
Grade 4 (≥10 × ULN)	4 (1)	1 (1)	5 (1)
Bilirubin (umol/L), sum	21 (8)	14 (14)	35 (9)
Grade 1 (1.1 to <1.6 × ULN)	7 (3)	8 (8)	15 (4)
Grade 2 (1.6 to <2.6 × ULN)	7 (3)	0 (0)	7 (2)
Grade 3 (2.6 to <5.0 × ULN)	7 (3)	4 (4)	11 (3)
Grade 4 (≥5.0 × ULN)	0 (0)	2 (2)	2 (1)

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Alkaline phosphatase (U/L), sum	73 (27)	21 (21)	94 (25)
Grade 1 (1.25 to 2.5 x ULN)	61 (22)	16 (16)	77 (21)
Grade 2 (2.6 to 5.0 x ULN)	9 (3)	4 (4)	13 (4)
Grade 3 (5.1 to 10.0 x ULN)	1 (0)	1 (1)	2 (1)
Grade 4 (>10.0 x ULN)	2 (1)	0 (0)	2 (1)

Source: adlb.xpt; Software: Python
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; ULN, upper limit of normal.

Evaluation for DILI

Subjects with marked elevations in hepatic transaminases and/or bilirubin were evaluated for potential DILI. The clinical review team used the eDISH approach to classify subjects into one of four categories, shown below. The narratives for subjects who met any of the lower three categories were reviewed to determine the etiology of the biochemistry elevations. If no other causes could be found, the case would be attributed to FTR.

- Normal: ALT <3x upper limit of normal (ULN) and bilirubin <2x ULN
- Hyperbilirubinemia: bilirubin >2x ULN, ALT <3x ULN
- Temple's Corollary: ALT >3x ULN, bilirubin <2x ULN
- Hy's Law: ALT >3x ULN and bilirubin >2x ULN

To improve signal detection, the FDA review team used a broad definition of Hy's Law. Typically, ALT and bilirubin elevations must both reach the specified threshold within 28 days. The FDA analysis examined all subjects who had elevations in both parameters, even if they were separated in time. Seven subjects were identified using this approach, of which 6 were further evaluated. The six subjects are summarized in Table 45. The 7th subject (AI438047.000676) had peak ALT/AST elevation at Week 8 and peak bilirubin elevation at Week 36. These were felt to be discrete events unrelated to FTR.

Table 45. Subjects With Postbaseline ALT >3x ULN and Bilirubin >2x ULN, Safety Population, BRIGHTE Trial

Subject ID	Summary of Clinical Events	Reviewer Assessment: Etiology of ALT/Bilirubin Elevation	Reviewer Assessment: FTR-associated DILI (Yes/No)
AI438047.000117[a] (randomized)	26 y/o male was diagnosed with metastatic cholangiocarcinoma. Hepatic enzymes remained elevated from diagnosis through time of death.	Cholangiocarcinoma	No
AI438047.000201[a] (randomized)	48 y/o female with history of HBV had a Grade 4 HBV flare and discontinued from the study. Her ARVs, including TDF, had been paused during an exacerbation of chronic depression	HBV Flare	No

Subject ID	Summary of Clinical Events	Reviewer Assessment: Etiology of ALT/Bilirubin Elevation	Reviewer Assessment: FTR-associated DILI (Yes/No)
AI438047.000413[b] (randomized)	33 y/o male with history of HBV infection but was HBsAg negative at Screening. OBT not active against HBV. Subject had + HBsAg when AST/ALT elevation began and TDF added to OBT.	Acute HBV or HBV reactivation	No
AI438047.000428[c] (randomized)	51 y/o male diagnosed with liver tuberculosis and hepatic abscess. ALT/AST peaked Week 18, bilirubin peaked Week 25	Tuberculosis with hepatic involvement, liver abscess	No
AI438047.000477[b] (nonrandomized)	52 y/o male with normal LFTs at baseline. OBT contains ATV/r. Subject had persistent elevation of bilirubin (attributed to ATV/r) and ALT/AST, which peaked at Week 48 but remained elevated.	Unclear, ATV/r likely contributing to persistently elevated bilirubin	Cannot exclude contribution of FTR
AI438047.000626[a] (randomized)	33 y/o male had acute Hepatitis A Virus infection. Hepatic labs were normal before and after the event.	Acute Hepatitis A	No

Source: adsl, adae, adcm, adlb, narratives, summary of clinical safety
[a] Identified as Hy's Law case by Applicant
[b] Identified by Applicant as having ALT and Bilirubin elevation but not meeting Hy's Law criteria
[c] Identified in FDA analysis
Abbreviations: ALT, alanine aminotransferase; ARV, antiretroviral; AST, aspartate aminotransferase; ATV/r, ritonavir-boosted atazanavir; DILI, drug-induced liver injury; FTR, fostemsavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ID, identifier; LTF, lost to follow-up; OBT, optimized background therapy; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

Thirty-four subjects were identified with ALT >3x ULN (Temple's Corollary subjects): 29 in the Randomized Cohort and 5 in the Non-randomized Cohort. Median (range) time to peak ALT elevation was 91 days (36 to 273) in the Randomized Cohort and 212 days (44 to 426) in the Non-randomized Cohort. These subjects were divided into subgroups to look for trends (normal versus abnormal ALT at baseline, viral hepatitis coinfection at baseline), but no clear patterns emerged.

Ten subjects were noted to have elevated bilirubin. Seven of these subjects were receiving ATV as a component of OBT and had elevations in indirect bilirubin. Of the remaining three, one subject had a contemporaneous acute GI illness and one had nonspecific abdominal symptoms and a surge in CD4+ T cell count at the time of the bilirubin elevation. The third subject had a persistent elevation with no clear etiology. All subjects continued FTR despite the elevations.

Pharmacometric analyses were performed to determine whether FTR exposure was related to risk for hepatic laboratory abnormalities. As shown in Figure 15, no relationship was found. Please see Section III.14.3 for more details of this analysis.

Viral Hepatitis Coinfection

Subjects with HBV or HCV coinfection are at increased risk for hepatic events. As noted in Table 43, several of the hepatobiliary AEs occurred in coinfected subjects, including two cases

of liver failure (AI438047.0093 and AI438047.000094). Subgroup analyses were performed to compare subjects with and without viral hepatitis. A total of 29 coinfected subjects were identified at baseline: 14 with HBV, 14 with HCV, and 1 with both HBV and HCV. Grade 3 or 4 elevations in hepatic labs occurred more frequently in coinfected subjects compared to subjects with HIV monoinfection: 14% versus 3% for ALT and AST, and 7% versus 4% for bilirubin for co-infected and monoinfected, respectively. As previously noted, there were several cases of HBV flares, which could potentially reflect an IRIS-type response to FTR treatment. In some instances of HBV flares, subjects had an interruption in HBV antiviral therapy, perhaps related to optimization of their background regimen based on HIV susceptibility. The total number of subjects with coinfection is small in this cohort, and definitive trends in risk are therefore difficult to establish.

Medical Officer's Assessment: *There is no clear evidence of FTR-induced DILI. The majority of subjects with hepatobiliary events and/or laboratory abnormalities had a clear or plausible alternate etiology. Among the cases that remain unclear, no unifying trends were noted. However, the clinical events and laboratory trends suggest that patients with HBV or HCV co-infection are at higher risk of hepatic events. Therefore, additional monitoring is likely warranted in this population. Labeling will include a Warning and Precaution regarding the risk for transaminase elevations in patients with HBV or HCV co-infection.*

7.6.6.5. Elevations in Serum Creatine Kinase and Correlation With Myalgia

The review team evaluated the correlation between laboratory and clinical muscle disorder events to determine whether FTR has a deleterious effect on muscle health. Myalgia was the most frequently reported AE in the MedDRA High Level Group Term (HLGT) Muscle Disorders. One event of Grade 4 rhabdomyolysis was reported as an SAE in a 61-year-old male. The event occurred on study Day 91, was deemed related to FTR, and led to discontinuation of FTR treatment. All remaining muscle AEs were grade 1 or 2, were nonserious, and did not result in FTR treatment interruption. Events deemed related to FTR included muscle spasm in three subjects, myalgia in two subjects, and the event of rhabdomyolysis noted above. Laboratory abnormalities occurred more commonly than clinical AEs. The majority of laboratory abnormalities were grade 1; no grade 4 elevations were reported. Tabular listings of clinical AEs and laboratory abnormalities are available in Section III.17 (Table 202 and Table 203).

The relationship between clinical symptoms and laboratory abnormalities was evaluated in the Randomized Cohort, as shown in Table 46. Given the minimal overlap between clinical symptoms and CK elevations, it seems most muscular events did not result in elevation of CK, and most CK elevations were asymptomatic.

Table 46. Relationship between HLGT Muscle Disorder Adverse Events and Graded Elevations in Creatine Kinase, Safety Population in Randomized Cohort (N=272), BRIGHTE Trial

	HLGT Muscle Disorders	
Graded Postbaseline Elevation in Creatine Kinase (grade 1-4)	**Yes N=23 n (%)**	**No N=249 n (%)**
Yes, N=22	3 (0)	19 (8)
No, N=250	20 (100)	230 (92)

Source: adlb.xpt, adae.xpt; Software: Python
Abbreviations: HLGT, high level group term; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality.

The trend in the Phase 2b trial was similar to the BRIGHTE trial (see Table 204 and Table 205 in Section III.17.2.7). Fourteen subjects (7%) in the FTR cohorts and two subjects (4%) in the ATV/r cohort reported an AE in the Muscle Disorders HLGT. Myalgia was reported in 10 subjects: 6 in the lower dose FTR group and 4 in the high dose FTR group. Three of these events were Grade 3 and one was an SAE. Six of the 10 subjects with myalgia also had graded CK elevations, all in the low-dose FTR cohort: 4 were grade 1 and 1 each were grade 2 and 3. Two subjects each reported muscle spasms and muscular weakness, both in the low-dose FTR cohort. In the ATV/r group, there were two subjects with muscle spasms, which was the only muscular AE reported. The imbalance in events between the FTR and ATV/r group suggests a relationship to FTR.

Use With Statins

The effect of statins on risk for AEs (e.g., rhabdomyolysis) was also examined. The proportion of subjects taking statins during this trial was small. However, many more HTE patients are likely to be taking statins in clinical practice, as HIV infection is a risk factor for cardiovascular disease and some ARVs have been associated with deleterious changes in lipid profile. Therefore, understanding possible relationships is important to guide providers about the safety of concomitant use.

As shown in Table 47, no relationship was found between statin use and clinical AEs or CK elevations. The two subjects who had AEs on statins + FTR reported a total of three events, which were not severe and deemed not related. One subject had muscle spasm and myalgia and the other had myalgia.

Table 47. Relationship between Statin Use and Graded Elevations in Creatine Kinase or Muscle Disorder Adverse Events, Safety Population in Randomized Cohort (N=272), BRIGHTE Trial

	Statin, Concomitant Use	
Graded Postbaseline Elevation in Creatine Kinase (grade 1-4)	**Yes N=20 n (%)**	**No N=252 n (%)**
Yes, N=22	0 (0)	22 (9)
No, N=250	20 (100)	230 (91)
HLGT muscle disorders		
Yes, N=23	2 (10)	21 (8)
No, N=249	18 (90)	231 (92)

Source: ADSL, ADAE, ADLB. ADCM. Software: Python.
Numbers in parentheses are column percentages.
Statin drugs are specified as concomitant use (postbaseline) of HMG CoA reductase inhibitors, including atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.
Abbreviations: HLGT, high level grouped term; N, number of subjects in treatment group; n, number of subjects with adverse event.

There was extensive discussion among the review team regarding the safety of FTR with high-dose statins, which are recommended in current treatment guidelines for patients at high risk of CV disease (Grundy et al. 2019). No clinically relevant drug interactions are anticipated between statins and FTR. Pharmacometric analyses were performed to determine whether FTR exposure was related to risk for adverse effects on muscle. As shown in Figure 15, no relationship was found. Please see Section III.14.3 for more details of this analysis. However, given the small number of subjects in this trial with statins, risk cannot be fully ruled out. Please see Section 8.2.2 for more discussion from the clinical pharmacology perspective.

Medical Officer's Assessment: *Myalgia may be associated with FTR but is most often mild and not associated with significant increase in CK. CK abnormalities were observed frequently but were mostly mild. No dose relationship was found between FTR exposure and serious muscular AEs. CK elevations and myalgia will be noted in Section 6 of product labeling and Section 7 will advise providers to start with the lowest statin dose possible when administered with FTR.*

7.6.6.6. Neuropsychiatric Events

Many ARVs have been associated with neuropsychiatric AEs, notably integrase inhibitors and efavirenz. Establishing a causal relationship between neuropsychiatric events and particular ARVs is challenging because of the prevalence of neuropsychiatric illness among people living with HIV (Treisman and Kaplin 2002). In many prior HIV trials, a significant proportion of the neuropsychiatric AEs reported in the trial have occurred in subjects with a prior history of illness, making the contribution of the drug unclear. Despite the challenges, it is important to be vigilant for potentially causal relationships, given the potentially serious outcomes associated with these events.

Neuropsychiatric events from the BRIGHTE trial and Phase 2b trial, respectively, are shown in Table 48 and Table 49. For the purpose of this analysis, events were pooled from several HLGTs from both the neurologic disorders and psychiatric disorders SOCs, as described in Section III.17.2.6. In addition, individual PTs were merged by the clinical reviewer, as shown in the table footnotes. The full analyses with unmerged PTs are also available in Section III.17 (Table 206 and Table 207).

Depression and anxiety were the most frequently reported conditions in both the BRIGHTE and Phase 2b trial. Neuropsychiatric events occurred somewhat more frequently in the FTR groups compared to the ATV/r group in the Phase 2b trial, but given the small number of events overall, this observation may be due to chance.

SAEs in the BRIGHTE trial included suicidal ideation in two subjects and the following events reported in one subject each: depression, psychotic disorder, and suicide attempt. FTR was interrupted for the subject with suicide attempt, who also had an AE of schizophrenia. Two additional subjects also interrupted FTR treatment for AEs—one for depression and one for disturbance in attention. One subject had several related AEs: amnesia, depression, disturbance in attention, and memory impairment. Another subject had a related AE of mood altered. In the Phase 2b trial, one subject had SAEs of depression and acute stress disorder. Another had a fatal SAE of suicide. FTR was interrupted for one subject with an AE of depression. Related AEs included anxiety, memory impairment, and amnesia, each occurring in a single subject.

Table 48. Pooled Neuropsychiatric AEs Reported in at Least 2 Subjects, All Cause, All Grade, Safety Population, BRIGHTE Trial

Adverse Event by PT	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Depression[a]	20 (7.4)	3 (3.0)	23 (6.2)
Anxiety[b]	6 (2.2)	4 (4.0)	10 (2.7)
Suicidality[c]	3 (1.1)	1 (1.0)	4 (1.1)
Memory impairment	3 (1.1)	0 (0.0)	3 (0.8)
Disturbance in attention	2 (0.7)	0 (0.0)	2 (0.5)
Irritability	2 (0.7)	0 (0.0)	2 (0.5)
Psychotic disorder	2 (0.7)	0 (0.0)	2 (0.5)
Affect disorder[d]	2 (0.7)	0 (0.0)	2 (0.5)
Mood change[e]	2 (0.7)	0 (0.0)	2 (0.5)

Source: adae.xpt; Software: JReview
[a]Depression = depression, major depression, and depressive syndrome
[b]Anxiety = anxiety and anxiety disorder
[b]Suicidality = suicidal ideation and suicide attempt
[d]Affect Disorder = affect lability and affective disorder
[e]Mood change = mood altered and mood swings
Abbreviations: AE, adverse event; N, number of subjects in treatment group; n, number of subjects with adverse event; PT, preferred term.

Table 49. Pooled Neuropsychiatric AEs Reported in at Least 2 FTR Subjects, All Cause, All Grade, Safety Population, Phase 2b Trial

Adverse Event by PT	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Depression	3 (3.0)	3 (2.9)	2 (3.9)
Anxiety[a]	2 (2.0)	3 (2.9)	3 (5.9)
Memory impairment	0 (0.0)	2 (2.0)	0 (0.0)
Amnesia	0 (0.0)	2 (2.0)	0 (0.0)

Source: adae.xpt; Software: JReview
[a]Anxiety = anxiety and anxiety disorder
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with adverse event; PT, preferred term.

Sleep Disorders

Sleep disorders were reported with similar frequency among FTR subjects in the BRIGHTE trial and Phase 2b trial. These events were reported more frequently among FTR subjects compared to ATV/r subjects in the Phase 2b trial. The analyses are available in Section III.17, Table 206 and Table 207. In short, 18 subjects reported insomnia in the BRIGHTE trial; the events were considered FTR-related in 7/18 subjects, one of whom had a Grade 3 event. Other FTR-related events reported in one subject each included sleep disorder, nightmare, and sleep deficit. None of the sleep events were SAEs and none led to FTR discontinuation. In the Phase 2b trial, 7% of FTR subjects and 4% of ATV/r subjects had insomnia. FTR-related events included two cases of insomnia, one case of hypersomnia, and one case of nightmare.

Medical Officer's Assessment: *Neuropsychiatric events are common, especially depression, but the association to FTR is difficult to adjudicate. Sleep disturbance does appear to be associated with FTR exposure, and the frequency of sleep disturbance events suggests that the drug is active in the brain. FDA proposed and the Applicant agreed to include sleep disturbance as a pooled term in labeling. FDA proposed inclusion of depression under Less Common Reactions, but the Applicant felt it was not warranted given the heavily confounded causality assessment. The clinical review team accepted that the relationship between FTR and depression has not been clearly characterized.*

7.6.7. Laboratory Findings

The majority of laboratory information is presented in sections pertaining to the safety analysis of the respective organ system. Liver biochemistries and CK are presented in Section 7.6.6, while renal and pancreatic labs are presented in Section III.17.2.8. The laboratory findings in those sections are discussed in the context of the associated clinical events to help with interpretation of the significance of the clinical events.

The events included in this section reflect other laboratory abnormalities that will be included in labeling. The Applicant proposed inclusion of a narrower list of laboratory abnormalities that they considered more likely attributable to FTR. The list was expanded by the clinical review team because in the absence of a control group, the relationship between FTR and laboratory abnormalities cannot be reliably judged, which necessitates use of a uniform standard for

inclusion. The review team proposed, and the Applicant agreed, to include all Grade 3 or 4 events reported in at least 2% of the Randomized Cohort. Please refer to Section III.17.2.8 for other laboratory results that did not meet this threshold, which are primarily serum chemistries but also include hematology labs.

Table 50. Chemistry Postbaseline Laboratory Abnormalities, Safety Population, BRIGHTE Trial

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Glucose (mmol/L)/hyperglycaemia, sum	90 (33)	40 (40)	130 (35)
Grade 1 (110 to 125 mg/dL)	41 (15)	24 (24)	65 (18)
Grade 2 (>125 to 250 mg/dL)	39 (14)	13 (13)	52 (14)
Grade 3 (>250 to 500 mg/dL)	10 (4)	2 (2)	12 (3)
Grade 4 (>500 mg/dL)	0 (0)	1 (1)	1 (0)
Urate (mmol/L), Sum	82 (30)	26 (26)	108 (29)
Grade 1 (0.45 to <0.59 mmol/L)	64 (24)	18 (18)	82 (22)
Grade 2 (0.59 to <0.71 mmol/L)	9 (3)	4 (4)	13 (4)
Grade 3 (0.71 to <0.89 mmol/L)	7 (3)	3 (3)	10 (3)
Grade 4 (≥0.89 mmol/L)	2 (1)	1 (1)	3 (1)

Source: adlb.xpt; Software: Python
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality.

Table 51. Hematology Postbaseline Laboratory Abnormalities, Safety Population, BRIGHTE Trial

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Hemoglobin (g/dL), sum	44 (16)	24 (24)	68 (18)
Grade 1 (male: 10.0 -10.9 g/dL; female: 9.5 to 10.4 g/dL)	20 (7)	8 (8)	28 (8)
Grade 2 (male: 9.0 -9.9 g/dL; female: 8.5 to <9.5 g/dL)	8 (3)	7 (7)	15 (4)
Grade 3 (male: 7.0 -8.9 g/dL; female: 6.5 to <8.5 g/dL)	13 (5)	6 (6)	19 (5)
Grade 4 (male: <7.0 g/dL; female: <6.5 g/dL)	3 (1)	3 (3)	6 (2)
Neutrophils (cells/mm^3), sum	29 (11)	14 (14)	43 (12)
Grade 1: (800 to 1,000 cells/mm^3)	15 (6)	5 (5)	20 (5)
Grade 2: (600 to 799 cells/mm^3)	4 (1)	2 (2)	6 (2)
Grade 3: (400 to 599 cells/mm^3)	6 (2)	4 (4)	10 (3)
Grade 4: (<400 cells/mm^3)	4 (1)	3 (3)	7 (2)

Source: adlb.xpt; Software: Python
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality.

Table 52. Postbaseline Changes in Lipid Profile, Safety Population, BRIGHTE Trial

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Cholesterol (mmol/L), sum	82 (30)	29 (29)	111 (30)
Grade 1 (5.18 -6.19 mmol/L)	46 (17)	20 (20)	66 (18)
Grade 2 (6.20 – 7.77 mmol/L)	25 (9)	8 (8)	33 (9)
Grade 3 (>7.77 mmol/L)	11 (4)	1 (1)	12 (3)

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
LDL cholesterol calculation (mmol/L), sum	57 (21)	18 (18)	75 (20)
Grade 1 (3.37 -4.12 mmol/L)	31 (11)	10 (10)	41 (11)
Grade 2 (4.13 – 4.90 mmol/L)	17 (6)	7 (7)	24 (6)
Grade 3 (>4.91 mmol/L)	9 (3)	1 (1)	10 (3)
Triglycerides (mmol/L), sum	86 (32)	34 (34)	120 (32)
Grade 1 (1.71 to 3.42 mmol/L)	44 (16)	19 (19)	63 (17)
Grade 2 (>3.42 to 5.7 mmol/L)	31 (11)	8 (8)	39 (11)
Grade 3 (5.7 – 11.4 mmol/L)	10 (4)	7 (7)	17 (5)
Grade 4 (>11.4 mmol/L)	1 (0)	0 (0)	1 (0)

Source: adlipid.xpt; Software: Python
Abbreviations: LDL, low density lipoprotein; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality.

7.7. Review Issues Relevant to the Evaluation of Risk

7.7.1. FTR Resistance

Issue

The assessment of resistance emergence in virologic failures of an FTR-containing ARV regimen is critical to interpreting the overall risk-benefit of FTR and understanding the durability of FTR as a component of an ARV regimen in a highly treatment-experienced patient population. Further, since FTR may be used in combination with or subsequent to the other ARVs that target the entry process (i.e., IBA, MVC, or ENF), assessing cross-resistance of FTR with these drugs is important.

Assessment

Resistance Selection in Cell Culture

TMR-resistant viruses (both CCR5 and CXCR4-tropic strains) were selected following 14 to 49 days in cell culture passage in the presence of increasing concentrations of TMR. Breakthrough viruses exhibited 18-fold to 159-fold decreases in TMR susceptibility, and genotypic analysis identified amino acid substitutions (L116P/Q, L175P, A204D, V255I, A281V, M426L, M434I and M475I) within gp120. In general, most substitutions mapped to the conserved regions (C1, C2, C4 & C5) of the gp120 EN, confirming that TMR targets the viral EN protein during infection. Viruses containing site-directed substitutions S375M, M426L, or M475I showed decreased susceptibility to TMR of 318-fold, 208-fold, and 5-fold, respectively. Dual substitutions M426L/M475I or S375M/M434I showed decreased susceptibility to TMR of >50,000-fold and >20,000-fold, respectively.

Clinical Resistance Emergence in Virologic Failures From BRIGHTE Trial

In the randomized FTR group of the BRIGHTE trial, a decline in HIV-1 RNA <0.5 $\log_{10}$ copies/mL at Day 8 occurred in 65 subjects (32%, 65/203) of whom only 18 (28%, 18/65) were

virologic failures post-Day 8. Virologic success after Day 8 in a relatively high percentage of subjects despite a suboptimal response to 8 days of FTR functional monotherapy is a testament to the strong OBT started on Day 8, most of which included the potent anchor drugs, DTG and boosted DRV.

In the randomized FTR group, 25% (51/203) were virologic failures at Weeks 24, 48, and 96 combined, of whom 35% (18/51) had <0.5 log_{10} decline in HIV-1 RNA at Day 8 (Table 53). Of the virologic failures in the randomized FTR group with Screening data (or Baseline data for those without Screening data), 56% (28/50) had at least one pretreatment EN RAPs at EN amino acid sites 375, 426, 434, and/or 475, and 22% (11/50) showed >10-fold reduced phenotypic susceptibility to FTR at Screening. EN RASs (S375N, M426L or I, M434I or L, and M475I or V or L) emerged in 61% (23/38) of the virologic failures with postbaseline data in the randomized FTR group, consistent with 51% (22/43) of the virologic failures having emergent phenotypic resistance to FTR.

In the randomized placebo group where subjects started FTR+OBT after Day 8, the rate of virologic failure post-Day 8 of 26% (18/69) was similar to the randomized FTR group (Table 53). Interestingly, the proportion of virologic failures with EN RAPs at Screening was higher in this group at 78% (14/18). In addition, the proportion of virologic failures with >10-fold FTR phenotypic resistance at Screening was higher at 44% (8/18). However, the proportion of virologic failures with emergent EN RASs (27%; 4/15) and emergent FTR phenotypic resistance (25%; 4/16) was lower compared to the randomized FTR group.

Possible explanations for the higher rate of FTR resistance emergence in the virologic failures of the randomized FTR group are 1) 8 days of FTR monotherapy resulted in more selective pressure on the virus and the development of FTR resistance subsequently became apparent at virologic failure or 2) the higher rate of EN RAPs and FTR phenotypic resistance at Screening in the randomized placebo group might have resulted in lower rates of substitutions at these sites since they were already mutated.

Importantly, 30% (21/69) of the virologic failures in both randomized groups had genotypic and/or phenotypic resistance at Screening to at least one drug in the OBT initiated after Day 8. A high proportion of virologic failures with postbaseline data developed further resistance to optimized background drugs; 48% (23/48) and 50% (8/16) of the FTR and placebo randomized groups, respectively, developed emergent genotypic and/or phenotypic resistance to at least one drug in the OBT (Table 53).

Not surprisingly, rates of virologic failure were higher in the nonrandomized group at 51% (50/99) (Table 53). While the proportion of virologic failures with screening EN RAPs and FTR phenotypic resistance was similar to that observed in the randomized FTR group, the proportion of virologic failures with emergent FTR EN RASs and phenotypic resistance in the nonrandomized group was higher at 73% (33/45) and 72% (34/47), respectively, which most likely reflects less effective optimized background drugs. Consistent with the nonrandomized group of subjects having fewer ARV options, 90% (45/50) of these subjects had genotypic or

phenotypic resistance to at least one drug in their OBT at Screening. Emergence of additional genotypic and/or phenotypic resistance to a background drug occurred in 55% (27/49) of the nonrandomized virologic failure isolates with postbaseline data.

Table 53. Numbers of Subjects Experiencing Virologic Failure/Resistance, BRIGHTE Trial

Parameter	FTR Randomized	Placebo Randomized	Total Randomized	Non-randomized
Weeks 24, 48, and 96 combined	51/203 (25%)	18/69 (26%)	69/272 (25%)	50/99 (51%)
With <0.5 log_{10} decline at Day 8	18/51 (35%)	--		--
With Screening/Baseline data	50	18	68	48
With screening EN RAPs	28/50 (56%)	14/18 (78%)	42/68 (62%)	26/48 (54%)
With postbaseline data	38	15	53	45
With emergent EN RASs	23/38 (61%)	4/15 (27%)	27/53 (51%)	33/45 (73%)
S375N	16/38 (42%)	2/15 (13%)	18/53 (34%)	21/45 (47%)
M426L/I	14/38 (37%)	3/15 (20%)	17/53 (32%)	23/45 (51%)
M434I/L	4/38(11%)	1/15 (7%)	5/53 (9%)	5/45 (11%)
M475I/V/L	5/38 (13%)	3/15 (20%)	8/53 (15%)	5/45 (11%)
With FTR phenotypic resistance at Screening (>10-fold)	11/50 (22%)	8/18 (44%)	19/68 (28%)	13/48 (27%)
With FTR-emergent phenotypic resistance[a]	22/43 (51%)	4/16 (25%)	26/59 (44%)	34/47 (72%)
With genotypic or phenotypic resistance to OBT at Screening	16/51 (31%)	5/18 (28%)	21/69 (30%)	45/50 (90%)
With emergent genotypic or phenotypic resistance to OBT[b]	23/48 (48%)	8/16 (50%)	31/64 (48%)	27/49 (55%)

Source: Clinical Virology Reviewer analysis
[a] Of those with post BL phenotypic data
[b] Of those with post BL data
Abbreviations: EN, envelope; FTR, fostemsavir; OBT, optimized background therapy; RAP, resistance-associated polymorphism; RAS, resistance-associated substitution.

Phenotypic Resistance

The median FC in FTR susceptibility at Screening for the virologic failures from all groups was 1.3 (Table 54). However, the phenotypic susceptibility to FTR at virologic failure was greatly decreased with a median 595-fold decrease for all groups combined. Thus, virologic failure on an FTR-containing regimen results in emergence of EN RASs and high phenotypic resistance to FTR. The emergence of gp120 substitutions at positions 375, 426, 434, or 475 was associated with a decreased susceptibility to FTR at failure. In the Randomized Cohort, subjects with emergent gp120 substitutions at positions 375, 434, 426, 475 (n=26) had a median change in FTR EC_{50} of 1755-fold. In contrast, randomized subjects without emergent gp120 substitutions at these positions (n=27) had a median change in FTR EC_{50} of 3.6-fold. In the Non-randomized Cohort, subjects with (n=33) and without (n=12) emergent substitutions had a median change in FTR EC_{50} of 4216-fold and 767-fold, respectively.

Table 54. Median Phenotypic FTR Resistance of Virologic Failures at Screening and Virologic Failure in BRIGHTE Trial (FC From Reference) FDA-Derived

Timepoint	Randomized FTR	Randomized Placebo	Non-randomized	All
Screening	1.3	0.73	1.4	1.3
Virologic failure	142	495	2989	595

Source: Clinical Virology Reviewer analysis
Abbreviation: FC, fold change; FTR, fostemsavir.

Cross-Resistance: Cell Culture Nonclinical Data

FTR, MVC, ENF and IBA all target the entry process and resistance to each of these drug maps to amino acids within gp120 or gp41, so the potential for cross-resistance exists. Four functional EN clones with known FTR RASs (M426L (CXCR4), M426L(CCR5) M426L/M475I or S375M/M434I) were examined in a cell-cell fusion assay for susceptibility to MVC, ENF and IBA. The four EN clones exhibited susceptibility to ENF and IBA. Against MVC, 3 of 4 EN clones exhibited susceptibility, while the CXCR4-tropic EN clone, as expected, was not inhibited by MVC. Functional EN clones from FTR-resistant clinical samples with EN RASs retain susceptibility to ENF and IBA. FTR-resistant viruses are also susceptible to MVC unless the EN is CXCR4-tropic. The data provided also showed no correlation between FTR susceptibility and the number of N-linked glycosylation sites in V5 of gp160 (loss of these sites have been shown to correlate with IBA resistance). Envelopes with large differences in susceptibility to FTR (EC_{50} values of 1 to >20,000nM) did not have noteworthy changes in susceptibility to IBA, regardless of the number of N-linked glycosylation sites in V5.

Conversely, viruses resistant to IBA, ENF, and MVC were examined for susceptibility to TMR. The findings are as follows.

- Decreased susceptibility to IBA has been shown to be primarily due to the loss of potential N-linked glycosylation sites (PNGSs) in the V5 region of gp120. Two IBA-resistant viruses with EN substitutions that destroyed potential glycosylation sites retained susceptibility to FTR. Moreover, 5 of 7 additional viruses resistant to the CD4-directed postattachment inhibitor IBA retained susceptibility to FTR, while the other 2 viruses had reduced susceptibility to both FTR (>1,400-fold decreased susceptibility) and IBA.
- Six clinical ENs with single amino acid changes in the gp41 known to result in resistance to ENF were all susceptible to FTR.
- In the cell culture antiviral activity assessments, some CXCR4-tropic viruses, which are intrinsically resistant to MVC (a CCR5 coreceptor inhibitor), were shown to also have decreased susceptibility to FTR. Additionally, four CCR5-tropic MVC-resistant viruses were assessed for FTR susceptibility; one was sensitive to FTR while the other three were resistant with >5,000-fold decreased susceptibility to FTR. The data indicate that some ENs do exhibit cross-resistance to both FTR and MVC, but not all resistance to MVC confers cross-resistance to FTR. It appears that EN components which determine tropism may also contribute to resistance to FTR, but a definitive determination is difficult given the high variability of gp120 (EN).

Clinical Cross-Resistance With Ibalizumab: BRIGHTE Trial

In the BRIGHTE trial, 15 subjects were treated with IBA as part of their initial OBT along with FTR. Five of these subjects subsequently failed therapy. One subject without a sample at virologic failure was susceptible to both FTR and IBA at Screening, although there was an M426M/L mixture at Screening. The other four subjects exhibited reduced susceptibility to both FTR and IBA at virologic failure. Three of four subjects also had fewer PNGSs between amino acids 460 to 464 in the virologic failure sample compared to their Screening sample. One of the subjects exhibited 100-fold reduced susceptibility to TMR at baseline and an M426L polymorphism, but this subject was susceptible to IBA at baseline, indicating that susceptibility to FTR and IBA are not linked in this subject.

Clinical Cross-Resistance With MVC: BRIGHTE Trial

As shown above, subjects who had CXCR4-tropic virus had lower response rates to FTR; response rates were lower for subjects with CXCR4-tropic virus than subjects who had CCR5- or dual-mixed-tropic virus (44% versus 77% or 70%) (Table 29). In the BRIGHTE trial, there were 19 subjects in the randomized FTR arm (as-treated analysis) who were failing on MVC when they started the trial. Of these 19 subjects, 2 had CXCR4-tropic virus, 8 had dual-mixed virus, and 9 had CCR5-tropic virus (Table 55). Of the nine subjects with CCR5-tropic virus who were failing on MVC, eight (89%) were successes on FTR at Day 8 with a median 0.94 $\log_{10}$ decline in HIV-1 RNA. Of the 10 subjects with dual-mixed or CXCR4-tropic virus, 7/10 (70%) were successes at Day 8 with a median 1.3 $\log_{10}$ decline in HIV-1 RNA. Interestingly, both subjects with CXCR4-tropic virus who were not successes at Day 8 had changes in FTR susceptibility of 17-fold and 42-fold, respectively. Therefore, if failure on an MVC-containing regimen is used as a marker for MVC resistance, then MVC resistance does not preclude success with FTR, because

these subjects overall had a favorable response rate at Day 8. However, the two subjects with CXCR4-tropic virus failing on MVC had lower response rates to FTR at Day 8.

Table 55. Response to FTR at Day 8 for Subjects Failing on MVC at BRIGHTE Trial Entry

Subjects Failing on MVC at Trial Entry	Tropism	Subtype	Day 8 Success	Day 8 HIV-1 RNA Decline	EN RAPs at Screening	FTR FC
AI438047.000116[a]	CCR5	B	N	0.41	M426L	294
AI438047.000139	CCR5	C	Y	2	M434I	22
AI438047.000150	CCR5	B	Y	1.24		0.43
AI438047.000203	CCR5	B	Y	0.78	M434T	9.27
AI438047.000238	CCR5	B	Y	0.75		0.21
AI438047.000393	CCR5	B	Y	1.92	S375T M426L	5,809
AI438047.000529[a]	CCR5	F1	Y	0.94		
AI438047.000588	CCR5	BF1	Y	0.7		2.02
AI438047.000794[a]	CCR5	B	Y	1.78		0.07
AI438047.000008	DM	B	N	0		0.18
AI438047.000080	DM	B	Y	2.7		0.62
AI438047.000082	CXCR4	B	N	0.19	M426L	42
AI438047.000086	DM	B	Y	1.1		0.72
AI438047.000130	DM	B	Y	1.3	S375N	26
AI438047.000152	DM	B	Y	1.31	S375T M434I	2.54
AI438047.000163	DM	B	Y	1.25		1.72
AI438047.000169	DM	B	Y	1.4	M426R	0.46
AI438047.000483	CXCR4	B	N	0.43		17
AI438047.000674	DM	B	Y	1.51		0.26

Source: Clinical Virology Reviewer analysis
[a] Indicated resistant to MVC while also CCR5-tropic in ADPFSCR dataset
Abbreviations: DM, dual/mixed tropic; EN, envelope; FC, fold change; FTR, fostemsavir; MVC, maraviroc; RAP, resistance-associated polymorphism;

Clinical Cross-Resistance With ENF: BRIGHTE Trial

There were 28 subjects who had evidence of resistance to ENF at Screening with >4-FC in ENF susceptibility. The response rates to FTR at Day 8 were comparable between subjects with and without ENF resistance (Table 56). Therefore, ENF resistance does not affect response to FTR at Day 8, and these data support lack of cross-resistance between these two drugs.

Table 56. Response Rates to FTR at Day 8 for Subjects Failing on ENF at BRIGHTE Trial Entry

Fold Change at Screening	Response at Day 8	Median log_{10} Decline in HIV-1 RNA
<4-fold ENF susceptibility	77/110 (70%)	1.0
>4-fold ENF susceptibility	20/28 (71%)	1.1

Source: Clinical Virology Reviewer analysis
Abbreviations: ENF, enfuvirtide; FTR, fostemsavir.

Conclusions

The key points of FTR resistance analyses include the following:

- The selection of resistance in cell culture provided data on key amino acids of interest in the EN to explore in the clinical trial and confirmed the mechanism of action of FTR interaction with the EN.
- The virologic failure rate of FTR in combination with OBT in the randomized FTR group of the BRIGHTE trial was 25%.

- The majority of virologic failures had screening EN RAPS.
- Emergence of both genotypic and phenotypic resistance to FTR was predominant in the virologic failures.
- Resistance substitutions at S375, M426, M434 and M475 emerged in subjects who failed treatment on FTR in combination with OBT (in both randomized groups and the nonrandomized group).
- FTR virologic failures also developed resistance to other drugs in the OBT.
- FTR resistance substitutions do not confer cross-resistance to the postattachment inhibitor, IBA, or the fusion inhibitor, ENF, but in some cases may confer cross-resistance to the CCR5 inhibitor, MVC.
- Cell culture results show some viruses resistant to MVC (either CCR5-tropic or CXCR4-tropic) may exhibit cross-resistance with FTR. In the BRIGHTE trial, however, only CXCR4-tropic viruses showed lower response rates to FTR. The patients with CCR5-tropic virus who were failing on MVC did not show lower FTR response rates.
- Some IBA-resistant viruses may have cross-resistance to FTR; however, the data are too limited to make a definitive determination.

The emergence of FTR resistance does not preclude approval. Inclusion of clinical resistance data in labeling, including the presence of pre-treatment EN RAPs which may affect FTR response and the emergence of EN RASs and phenotypic changes, relays important information needed to use FTR effectively in combination with other active ARVs.

7.7.2. Safety Implications of a Photodegradant Product Containing a Beta-lactam Structure (BMT-218946)

Issue

In May 2016, ViiV discovered that FTR drug substance and BMS-698584 penultimate have the potential to form a photodegradant (BMT-218946) that contains a single beta-lactam ring. This discovery generated concern as the beta-lactam photodegradant could have sensitizing properties and/or antigenic properties thereby increasing the risk of allergic reactions in those exposed to the photodegradant. There are two populations at potential risk in this regard: 1) patients receiving FTR; and 2) patients receiving a drug product(s) from multiuse manufacturing facilities in which FTR is also produced. This section focuses on the potential risk to patients receiving FTR to determine whether risk mitigation via labeling is necessary. The potential risk of cross-contamination of other drug products and the steps taken to mitigate that risk are provided in the product quality review.

Background

To help assess the risk of allergic reactions in those exposed to the photodegradant, the Division requested that the Sponsor provide a white paper, authored by experts in the field of drug allergy, to comment on the relative systemic sensitizing potential of the photodegradant as compared to beta-lactam antibiotics (e.g., penicillins, cephalosporins) and whether additional studies would be helpful in making this determination. The in silico and in vitro assessments summarized below

were performed by the Sponsor and/or members of the white paper panel to assess the immunogenicity and antigenicity of the photodegradant.

Immunogenicity Assessment

Immunogenicity is the ability to induce an immune response in an individual who is not already sensitized. Beta-lactam antibiotics are structurally too small to act as complete antigens and therefore cannot independently elicit an immune response. Instead, they covalently bind to a larger carrier molecule, such as tissue or serum proteins, to form a multivalent antigen that can stimulate the immune system. This process is known as haptenation. Upon first exposure, the conjugated drug is taken up by antigen presenting cells (e.g., dendritic cells), and processed and presented to T and B-cells within the context of a T_h2 response. Specific IgE is produced by the B-cells and bound to high affinity receptors on the surface of mast cells and basophils. This process is referred to as sensitization.

An initial step in haptenation of beta-lactam antibiotics is attack and cleavage of the beta-lactam ring by nucleophiles present in proteins. Susceptibility to this attack is dependent, among other factors, on the stability of the beta-lactam ring in the molecule of interest. The potential immunogenicity of the photodegradant was investigated in-silico and in vitro by assessing the stability of its beta-lactam ring and its likelihood of reacting with nucleophiles.

- A high-level Structure-Activity Relationship analysis was performed to assess the potential for reactivity of the photodegradant with protein peptides as compared to beta-lactam structures with a known propensity to cause sensitization. The review team agrees with the Sponsor's conclusion that the beta-lactam bicyclic ring structure of the photodegradant is more stable than that found in penicillins, cephalosporins, or monobactams and therefore less likely to cause sensitization.
- An in silico chemical hazard assessment was performed, and the photodegradant was classified as either a weak dermal sensitizer or nonsensitizer depending on the computer program employed. However, this software was developed to predict dermal, not systemic, sensitization.
- A Direct Peptide Reactive Assay, which was developed and validated as a predictor of dermal sensitization, did not yield fully interpretable results due to technical limitations of the assay.
- Spectral data (IR and NMR) relevant to the stability of the beta-lactam ring in the photodegradant was assessed as well as hydrolysis rates at pH 3 and pH 9. IR and hydrolysis data indicated decreased reactivity (i.e., increased stability) of the beta-lactam ring compared to beta-lactam antibiotics; NMR data were inconclusive.
- Reactivity of the photodegradant (and positive controls) was assessed with butylamine (a low molecular weight nucleophile), amino acid nucleophiles (lysine and cysteine), and human serum albumin. In all cases, reaction was demonstrated with the positive controls but not with the photodegradant.

Antigenicity Assessment

Antigenicity is the ability of a chemical structure to elicit an immune response in a previously sensitized individual by combining with the final products of the adaptive immune response, in this case the specific IgE bound to mast cells and basophils. Cross-linking of the IgE by the antigen leads to activation of the mast cells and basophils and the release of histamine and other inflammatory mediators. This can manifest clinically as urticarial rash, hypotension, rhinitis, bronchospasm, angioedema, and anaphylactic shock.

Antigenicity was assessed via radioallergosorbent test inhibition studies (RAST-inhibition) and Basophil Activation Test (BATs).

- RAST-inhibition testing demonstrated that the photodegradant can be recognized by preexisting specific IgE to benzylpencillin and amoxicillin from some patients; however, higher concentrations (1 to 2 $\log_{10}$) of photodegradant are needed to generate a positive test result (i.e., >50% inhibition) compared to the culprit drug (i.e., benzylpenicillin or amoxicillin).
- BATs yielded positive results in 2 of 14 patient samples (one with direct BATs and one with indirect BATs). The reactivity in direct and indirect BATs with the photodegradant was marginal (+) and lower than the cross-reactivity with beta-lactam antibiotics. It was detectable in direct BATs only when basophils were primed with IL-3.

Quantitative Considerations

The above assessments of immunogenicity and antigenicity do not consider how risk may be impacted by the magnitude of photodegradant exposure. However, the expert panel commented on risk as relates to the potential blood concentrations of the photodegradant in patients receiving FTR (1,200 mg/day) based on the concentration of photodegradant detected prior to the initiation of enhanced manufacturing controls (i.e., at photodegradant levels of 30 ppm).

Based on a photodegradant level of 30 ppm, the maximum blood photodegradant concentration of patients receiving FTR would be 8.6 ng/mL. The panel noted that this concentration is just at the starting level for desensitization with oral penicillin, and that this dose is neither able to sensitize nor to elicit reactions in already sensitized patients. However, the Agency is aware that penicillin desensitization is performed in a monitored environment, and that there are reports in the literature of individuals with beta-lactam allergies who are exquisitely sensitive to re-exposure to minute quantities of beta-lactam antibiotics. The panel also noted that this concentration of photodegradant is >2,000-fold lower than the concentration used to observe marginal basophil reactivity in BAT testing (see Antigenicity Assessment). It is also notable that current manufacturing controls have yielded an undetectable photodegradant level (using an assay with a limit of detection of 5 ppm and limit of quantification of 10 ppm) on the last 6 batches of FTR manufactured. These assay thresholds are consistent with those agreed upon by the Agency.

There is Agency precedent in considering quantitative factors when making risk assessments related to beta-lactam exposure. The FDA's Center for Veterinary Medicine issued guidance for

tolerance or safe levels of penicillins and cephalosporins, both known sensitizers, in milk (August 2016). Acceptable levels range from 5 ppb to 20 ppb depending on the specific antibiotic. For someone drinking ½ liter (approximately two 8-ounce glasses) of milk per day at the maximum allowable level, the exposures would be 2.5 to 10 µg per day. For comparison, with current manufacturing controls achieving photodegradant levels <10 ppm, the exposure to the photodegradant at the anticipated 1,200 mg/day dose of FTR would be <14 µg/day.

Clinical Experience

Rash and hypersensitivity events were identified as a potential safety signal in early clinical development. An association between FTR and HSR, if found, could not be attributed to any specific moiety within the molecule; however, a "worst case scenario" analysis would attribute all potential HSR events to the beta-lactam moiety of the photodegradant,

The analysis of rash and hypersensitivity events is presented in Section 7.6.6 with supplementary information in Section III.17. An association was found between rash and FTR exposure but the majority of events were mild to moderate in intensity. No serious cutaneous events (e.g., Stevens-Johnson Syndrome, DRESS) have occurred in the FTR development program. None of the suspected HSR events were considered FTR-related, and symptoms resolved despite ongoing treatment with FTR (one subject paused FTR treatment but symptoms did not recur when FTR was restarted).

Based on review of the totality of the data, the clinical review team concludes that there is no evidence of an elevated risk of serious HSRs among FTR-treated patients.

Labeling Considerations

Per FDA's guidance for industry on *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011), warnings for anticipated adverse reactions (i.e., adverse reactions that have not been observed with a drug) are advised when "it appears likely that the adverse reaction will occur with the drug based on what is known about pharmacology, chemistry or class of the drug."

Based on the totality of available data including in silico and in vitro assessments, anticipated exposure levels, and clinical safety data, we have concluded that adverse reactions related to the beta-lactam moiety of the photodegradant are unlikely and that a warning in labeling is not warranted. Furthermore, we are concerned that including a warning in labeling may dissuade patients with limited treatment options from using the drug.

The Agency has precedent for demonstrating flexibility in labeling for nonantibiotic drug products that contain a beta-lactam ring. Ezetimibe (Zetia®), a drug approved in 2002 for the treatment of hypercholesterolemia, has a beta-lactam moiety, and no labeling specific to this issue was required.

Conclusions

- The totality of the data from the in silico and in vitro studies indicate that the photodegradant has very low potential for haptenation and therefore very low potential to induce an immune response in an individual who is not already sensitized.
- The relative antigenicity of the photodegradant is likely less than beta-lactam antibiotics, given the greater concentrations of the photodegradant required to demonstrate cross-reactivity in RAST-inhibition testing and weaker reactions in basophil activation tests.
- The extremely low levels of photodegradant produced with current manufacturing controls should greatly reduce the risk of sensitizing patients or eliciting reactions in patients already sensitized to beta-lactam antibiotics.
- There is no suggestion of an elevated risk of HSRs among FTR-treated patients
- Adverse reactions related to the beta-lactam photodegradant are unlikely, and a Warning in labeling is not warranted.

These conclusions are consistent with those of the Sponsor and the Sponsor's expert panel.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

In a renal impairment study (206217), TMR area under the curve (AUC) was higher by 48%, 36%, and 43% in subjects with mild, moderate, and severe renal impairment, respectively, as compared to subjects with normal renal function. Similarly, a less than a 40% difference was observed with C_{max} between subjects with normal and impaired renal function. No difference in TMR PK was observed between subjects with end-stage renal disease (ESRD) and subjects with normal renal function. Similar results were observed for unbound TMR PK parameters in all renal impairment groups, including subjects with ESRD. The effects of renal impairment on TMR PK are not considered clinically significant.

No clinically relevant differences in TMR PK were observed in subjects with ESRD on hemodialysis compared with the same subjects with ESRD off hemodialysis. TMR was not readily cleared by hemodialysis with approximately 12.3% of the administered dose removed during the 4-hour hemodialysis session. The review team agrees with the proposed labeling that no dose adjustment of FTR is required in patients with mild, moderate, or severe renal impairment or ESRD patients on dialysis (see Appendix Section III.14.2).

Hepatic Impairment

In a hepatic impairment study (206280), TMR C_{max} and AUC were higher by approximately 72% and 73%, respectively, in subjects with severe hepatic impairment as compared to subjects with normal hepatic function. A lesser magnitude of increase in TMR C_{max} and AUC was

observed for mild and moderate hepatic impairment. Similar results were observed for unbound TMR PK parameters in all hepatic impairment groups.

The review team agrees with the proposed labeling that no dose adjustment of FTR is required in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment (see Appendix Section III.14.2).

Other Intrinsic Factors

The population PK analysis indicated that sex, race, age (within adults), and body weight do not have a clinically significant effect on TMR PK. TMR PK data in subjects ≥65 years old were limited (see Appendix Section III.14.3).

8.2. Extrinsic Factors

8.2.1. Food Effect

Study 206283 evaluated the impact of a standard meal (423 kcal, 36% fat, 47% carbohydrates, and 17% protein), and Study 206295 evaluated the impact of a high-fat meal (985 kcal, 60% fat, 28% carbohydrates, and 12% protein) on TMR PK following administration of FTR. TMR AUC was increased by 81% with a high-fat meal but TMR AUC was not impacted by a standard meal. Regardless of the calorie and fat content of the meal, food had no significant effect on plasma TMR C_{max}. FTR was given without regard to food in the Phase 3 BRIGHTE trial. The review team agrees with the Applicant's proposed labeling that FTR can be administered with or without food (see Appendix Section III.14.2).

8.2.2. Drug Interactions

Strong CYP3A4 inducers decrease TMR exposure significantly. Therefore, FTR coadministration is contraindicated with strong CYP3A4 inducers. FTR coadministration with oral contraceptive containing ethinyl estradiol (EE) increases the EE AUC significantly. Therefore, total EE daily dose should be limited to ≤30 mcg. FTR may increase the exposure of grazoprevir (GZR) and voxilaprevir (VOX). Therefore, an alternative HCV regimen that does not contain GZR or VOX is recommended with FTR.

Effects of Other Drugs on FTR

TMR is metabolized by unidentified esterases (36.1%) and by CYP3A4 (21.2%), to metabolites BMS-646915 and BMS-930644, respectively. TMR is a substrate of P-gp and breast cancer resistance protein (BCRP).

The Applicant evaluated the effects of strong and moderate CYP3A4 inducers on TMR PK in clinical DDI studies (Table 57).

Table 57. Magnitude of Reduction in TMR Exposure With CYP3A Inducers

CYP3A Inducer	Inducer Category	Geometric Mean Ratio (90% CI) TMR C_{max}	TMR AUC_{tau}	TMR C_{tau}
Rifampin	Strong	0.241	0.181	-
600 mg QID	Strong	(0.208, 0.279)	(0.163, 0.200)	-
Etravirine	Moderate	0.516	0.502	0.483
200 mg BID	Moderate	(0.454, 0.587)	(0.442, 0.571)	(0.324, 0.720)
Rifabutin	Moderate	0.732	0.698	0.594
300 mg QID	Moderate	(0.647, 0.829)	(0.642, 0.760)	(0.461, 0.766)

Source: Table 76, Table 63, Table 70, Summary of Clinical Pharmacology Studies
Abbreviations: AUC_{tau}, area under the curve during a dosing interval; BID, twice daily; C_{max}, maximum plasma concentration; C_{tau}, plasma concentration during a dosing interval; TMR, temsavir; QID, four times a day.

Strong Inducers of CYP3A

In study 206277, when FTR was coadministered with rifampin, a strong CYP3A4 inducer, a significant reduction (an approximately 80% reduction in AUC_{tau}) in TMR plasma concentrations was observed (Table 146, see Appendix Section III.14.2). The review team agrees with the Applicant's proposed labeling that the use of FTR is contraindicated with strong CYP3A inducers such as rifampin, carbamazepine, phenytoin, enzalutamide, mitotane, and St. John's Wort because plasma TMR concentrations may be reduced to a clinically significant extent, which may result in loss of virologic response.

Moderate Inducers of CYP3A

In study 206281, coadministration of ETR, a moderate CYP3A inducer, with FTR decreased TMR exposure by approximately 50%. Coadministration of rifabutin, which is another moderate CYP3A inducer, with FTR decreased mean TMR exposure to a similar extent (Table 57). DRV and ritonavir (RTV) are both strong CYP3A inhibitors. When boosted DRV and ETR were coadministered with FTR, the effect of ETR was nullified and TMR mean plasma C_{max}, AUC_{tau}, and C_{tau} were increased by 53%, 34%, and 33%, respectively.

To determine the effects of coadministration of moderate CYP3A inducers on efficacy of FTR, the review team compared Week 24 efficacy of the BRIGHTE trial by the following background regimens; no ETR, ETR without PI, and ETR with PI. As summarized in Table 58, there was no clear efficacy difference among the three groups. Please refer to Section III.16.4 for additional details.

Table 58. HIV-1 RNA Response Rates (<40 copies/mL) at Week 24 for Randomized Cohort—ITT-E Population, BRIGHTE Trial

Treatment	<40 HIV-1 RNA (copies/mL) Placebo	FTR 600 mg BID
Without etravirine	28/57 (49%)	88/161 (55%)
Etravirine without PI	0/1	7/12 (58%)
Etravirine and PI	3/11 (27%)	18/30 (60%)

Source: Review team's analysis
Abbreviations: BID, twice daily; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; PI, protease inhibitor.

Further, the Applicant's exposure-response analysis for efficacy indicated that decreased plasma TMR C_{tau} values observed with moderate CYP3A inducers do not result in clinically relevant changes in Day 8 virologic response (see Appendix Section III.14.3).

Based on all the evidence, we agree with the Applicant's conclusion that FTR may be coadministered with moderate CYP3A inducers (e.g., efavirenz, ETR, nevirapine, rifabutin).

CYP3A4 Inhibitors

FTR can be coadministered with strong CYP3A4 inhibitors without dose adjustment, based on the results of clinical drug interaction studies 206269 and 206285 with cobicistat (COBI) and RTV, respectively. Following coadministration of COBI and RTV, plasma TMR concentrations are increased by 1.5- to 2-fold, which are expected to remain below the threshold defined by the QTc safety. Further, RTV- and COBI-containing regimens were coadministered to a significant portion of subjects (approximately 60% subjects) in the BRIGHTE trial, which supports the safety with coadministration of CYP3A4 inhibitors (see Appendix Section III.14.2).

Other HIV Drugs (as Perpetrator)

The HTE population is expected to be taking various background ARV regimens. Therefore, the Applicant conducted drug interaction studies with commonly coadministered HIV drugs in this population. In drug interaction studies with TDF (206266), MVC (206278), or RAL+TDF (205889), there was no clinically relevant impact on TMR C_{max} or AUC (see Appendix Section III.14.2).

In drug interaction studies with RTV (206269), COBI (206285), ATV/r (206269), boosted DRV with or without ETR (206281), or DRV/COBI (206285), TMR C_{max} was increased by 1.5- to 1.8-fold, and AUC was increased by 1.3- to 2-fold. These changes were not considered to have a clinically relevant impact (see the above section titled CYP3A4 inhibitors).

A clinical drug interaction study with DTG was not conducted. However, a clinically significant drug interaction between DTG and FTR is not expected based on the in vitro DDI profiles of both drugs and Population PK covariate analysis. In the Phase 3 trial, 84% (229/272) of the subjects had received DTG as part of their OBT (see Section 6.4.4). DTG was not a significant covariate for PK per the Population PK analysis. Therefore, DTG can be coadministered with FTR.

It is difficult to predict the net effect of tipranavir (TPV)/r on plasma concentrations of drugs that are dual substrates of CYP3A and P-gp. TPV/r is a mixed inhibitor and inducer of CYP3A and intestinal P-gp. In the Randomized Cohort of the BRIGHTE trial, seven participants received TPV/r. TMR exposures were comparable between subjects who received TPV/r and the overall BRIGHTE trial population based on individual post hoc estimates from the final Population PK model. A clinically significant interaction following TPV/r coadministration with FTR is

unlikely, although this conclusion is based on the limited data available from post hoc estimates in seven subjects.

Drugs That Increase Gastric pH

TMR exposure was not altered when coadministered with famotidine. Therefore, FTR can be coadministered with drugs that increase gastric pH.

Effects of FTR on Other Drugs

Combined Oral Contraceptive

When a combined oral contraceptive containing EE and norethindrone acetate (NEA) was coadministered with FTR in a clinical drug interaction study (206279), EE C_{max} was increased by 39% and EE AUC was increased by 40%. No significant changes in plasma norethindrone (NE) exposure were observed. EE AUC increase by 40% or more increases the risk of serious adverse reactions, including venous thromboembolism. Therefore, the Applicant's proposal that the total EE daily dose should be ≤30 mcg when coadministered with FTR is acceptable.

Methadone

In a drug interaction study (206216) utilizing stable doses of methadone (40 to 120 mg QD), FTR had no impact on the plasma R-methadone (active), S-methadone, and total methadone concentrations.

Statins

TMR is an inhibitor of BCRP and organic anion transporting polypeptide (OATP)1B1/3. Coadministration of FTR increased plasma rosuvastatin C_{max} by 78% and AUC by 69% in study 206276. The Applicant initially proposed to limit daily doses of the following statins in the label: rosuvastatin (≤20 mg); atorvastatin (≤20 mg QD), fluvastatin (≤40 mg QD), pitavastatin (≤2 mg QD), and simvastatin (≤40 mg QD). After consultation with the cardiometabolic and endocrinology clinical pharmacology team, it was concluded that no clinically significant drug interaction is expected between FTR and any statins including rosuvastatin.

The review team recommended the Applicant delete the dose cap and clinical comments related to statins. The Applicant agreed to remove dose cap for statins but proposed to retain a general recommendation to use the lowest possible starting dose for statins and monitor for statin associated AEs. Per the Applicant, proposed clinical recommendation for statins will help the health care practitioner with benefit versus risk assessment associated with statins.

The review team agrees that FTR is not a potent OATP1B1/3 and or BCRP inhibitor and a clinically significant drug interaction is unlikely between FTR and any statins, based on rosuvastatin drug interaction data. However, current treatment guidelines for statins recommend prescribing high statin doses in some patients with high risk of cardiovascular events (Grundy et al. 2019), and initiation of a high-dose, high-potency statin without titration may lead to AEs such as rhabdomyolysis in a subset of patients. Therefore, the review team accepted the

Applicant's conservative proposal to recommend the lowest possible starting dose for statins (rosuvastatin, atorvastatin, fluvastatin, simvastatin, pitavastatin) and monitor for statin-associated AEs.

HCV-Direct Acting Antivirals

The effect of FTR on HCV DAA exposure has not been studied in a clinical DDI study. The Applicant initially proposed contraindication only for GZR, due to potential for increased risk of ALT elevations. To determine the potential for drug interactions between FTR and HCV drugs, the review team estimated the effects of FTR on HCV NS3/4A PIs [glecaprevir, GZR, VOX, paritaprevir], which are known to have significant DDI with known BCRP/OATP1B inhibitors.

The review team used drug interaction data of FTR and rosuvastatin (a substrate of BCRP and OATP1B) and other available drug interaction data of HCV PIs (i.e., interactions with cyclosporine and rifampin, which are potent inhibitors of BCRP/OATP1B) from US Prescribing Information and publications. First, the review team determined the relative potency of FTR to inhibit BCRP/OATP1B compared to cyclosporine and single dose rifampin based on their effects on rosuvastatin C_{max} and AUC; the magnitude of inhibitory effects of FTR on BCRP/OATP1B is approximately 20 to 40% of that of cyclosporine and single dose rifampin. Then, the review team predicted the effects of FTR on the AUC and C_{max} of HCV PIs by applying the relative potency factors to the effects of cyclosporine and single-dose rifampin on the AUC and C_{max} of HCV PIs. The review team's assessment indicated that FTR may increase the exposures of GZR or VOX by 3-fold when coadministered. In contrast, the Applicant proposed that no drug interaction is expected between TMR and VOX based on their extrapolation approach, which is mainly based on the R values calculated based on reported in vitro results for known BCRP/OATP1B inhibitors. While the Applicant's approach is also reasonable, in the absence of empirical data, predicting the magnitude of interaction based on in vitro or other available data has inherent limitations and uncertainties. Overall, the review team agrees that FTR is not a potent OATP/BCRP inhibitor, but the effects of FTR on VOX could potentially be significant if a conservative extrapolation method is used. Therefore, the review team recommends alternative regimens that do not contain VOX or GZR, if possible. However, the review team concludes that coadministration should not be restricted for patients who do not have any other alternative options for their HCV treatment.

Other HIV Drugs

In drug interaction studies, there was no clinically relevant impact of FTR on C_{max} and AUC of following HIV drugs: TDF, MVC, RAL+TDF, ATV/r, DRV/r with or without ETR, and DRV/c.

8.3. Pediatric Labeling / Plans for Pediatric Drug Development

The initial approval of FTR for treatment of MDR HIV-1 infection will be limited to adults. Pediatric subjects were not included in the Phase 3 BRIGHTE trial for several reasons, including availability of drug product (related to manufacturing changes to control formation of the beta-

lactam photodegradant) and uncertainty about the minimum weight required for a patient to safely receive FTR 600 mg BID without reaching exposures that increase the risk of QT prolongation.

Fostemsavir was developed to address the needs of patients living with MDR HIV-1 infection who have few to no remaining active ARVs. This population is small among adults and exceedingly small among children for several reasons. First, the total number of children living with HIV infection has dropped substantially due to the increasingly effective measures to prevent mother to child transmission. A 2016 report from the Centers for Disease Control and Prevention identified 2,334 children under 13 years of age living with HIV in the United States. Second, the wide availability of highly potent and convenient ART options for children has made it easier to achieve and maintain virologic suppression. Third, extensive drug resistance is generated after many years of suboptimal ARV exposure; the majority of subjects in the BRIGHTE trial had failed 5 to 6 previous regimens. Such extensive drug exposure is unlikely to occur during childhood, especially in the era of highly effective ARV regimens with convenient dosing.

Given all these factors, Division of Antivirals concludes that the need for FTR in the pediatric population is limited to older adolescents. Discussions between the Applicant and FDA regarding the pediatric protocol are underway. A Pediatric Research Equity Act (PREA) postmarketing requirement will be issued at the time of approval for a study evaluating FTR in pediatric subjects weighing at least 40 kg. Please see Section III.22 for additional details.

8.4. Pregnancy and Lactation

Animal Data

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Appendix Section III.13.

Table 59. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	• No adverse maternal or embryo-fetal effects occurred in rats at clinically relevant exposures. However, at very high maternally toxic exposures (>200 times those in humans at the MRHD) fetal abnormalities (cleft palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw, and protruding tongue) and reductions in fetal body weights were observed. • In rabbits, reduced fetal body weight owing to maternal toxicity was observed at exposures 32 times those in humans at the MRHD. • In pre- and postnatal development study performed in the rat, fostemsavir caused reduced neonatal survival in the absence of other adverse fetal or neonatal effects at exposures up to 131 times those in humans at the MRHD. No adverse fetal effects were observed at exposures 35 times those in humans at the MRHD.
8.2 Lactation	Fostemsavir and related drug materials (i.e., temsavir and metabolites) were excreted in rat milk as shown in a single dose of fostemsavir administered to lactating rats 7 - 9 days postpartum.

Source: Primary Reviewer's assessment
Abbreviations: MRHD, maximum recommended human dose.

Details of above information are derived from a list of fertility and reproductive toxicology studies provided below. All safety factors shown are based on systemic exposures compared between animals and humans. Further details are available in Appendix Section III.13.1.

Table 60. Fostemsavir Reproductive Toxicity Safety Factors

Study	NOAEL (mg/kg)	Systemic Exposure (ug.h/ml)	Safety Factors
EEFT rat male	10	189	10
EEFT rat female	600	3610	186
EFT rat maternal & fetal	600	3840	198
EFT rabbit maternal	25	315	9
EFT rabbit fetal	50	328	17
PPNT rat maternal	300	2550	131
PPNT rat developmental	100	679	35

Source: Primary Reviewer's assessment
Safety factors are ratios of systemic exposure between animals and humans (recommended human dose, 600 mg bid with $AUC_{0\text{-}24h}$ =19.4 µg.h/ml).
Abbreviations: EEFT, early embryo-fetal toxicity study; EFT, embryo-fetal toxicity study; NOAEL, no observed adverse effect level; PPNT, peri- and postnatal toxicity study.

Clinical Experience

Clinical experience with FTR among pregnant and breast-feeding individuals is limited. Pregnancy and breast-feeding were exclusion criteria in the BRIGHTE and Phase 2b trials. The Applicant collected outcomes data for the eight pregnancies that occurred among FTR-exposed subjects and one pregnancy in the partner of a subject in the BRIGHTE trial. No congenital anomalies were reported among live-born infants.

Pregnancies Resulting in Live Births

Two subjects in the BRIGHTE trial were treated with FTR 600 mg BID from the time of conception through all three trimesters and gave birth to live infants at term (39 weeks). One subject had no maternal or fetal/infant complications. The other had an SAE of intrauterine

growth restriction (IUGR) at 31 weeks. Her concomitant ARVs included DTG and DRV/r; her comorbidities included toxoplasmosis with Grade 3 IRIS (preconception) and chronic smoking. The baby was born with low birthweight by World Health Organization standards at 2.2 kg but was otherwise healthy.

One subject in the Phase 2b trial and one subject in the BRIGHTE trial received FTR at conception through the first trimester. The Phase 2b subject was receiving FTR 1,200 mg QD with RAL and TDF. She discontinued from the study due to pregnancy approximately 6 weeks after her last menstrual period. Her pregnancy was uncomplicated, and she gave birth to a healthy term infant. The BRIGHTE subject was receiving FTR 600 mg BID plus DTG, DRV/r, MVC, and lamivudine. She withdrew from the study due to pregnancy at approximately 8 weeks gestation. She had no complications and gave birth to a healthy term infant.

A partner of a BRIGHTE trial subject gave birth to a healthy infant. Data are limited but no concerns were conveyed to the study Sponsor.

Pregnancies Ending in Induced or Spontaneous Abortion

One subject in the Phase 2b trial had an SAE of spontaneous abortion at approximately 7 gestational weeks. She was receiving FTR 400 mg BID plus TDF and RAL at the time of conception. She had one prior pregnancy resulting in live birth but the child subsequently died due to congenital heart disease (additional information is not available). The investigator concluded that the spontaneous abortion was unrelated to study medication.

Two subjects in the Phase 2b trial and one subject in the BRIGHTE trial had induced abortions in the first trimester. No information was available about fetal anomalies in these cases.

Conclusion

No risks for maternal or fetal toxicity have been identified in nonclinical studies at the recommended FTR dose. There are insufficient human data on the use of FTR during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage.

9. Product Quality

The Office of Pharmaceutical Quality review team has assessed NDA 212950 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. This includes suitable manufacturing controls and monitoring to mitigate potential risks from a photodegradant that contains a beta-lactam substructure. As such, OPQ recommends approval of this NDA from a quality perspective.

10. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

The results of the clinical site inspections and Sponsor inspection support the conclusion that the studies were conducted adequately, and the data generated support the proposed indication. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section III.20 for a summary of inspection findings and Section III.23 for financial disclosures.

11. Advisory Committee Summary

Not applicable. An Advisory Committee meeting was not held because no unexpected significant safety or efficacy issues were identified, and no controversial or challenging issues arose that would benefit from advisory committee discussion.

III. Appendices

12. Table Summary of Regulatory History

Table 61. Summary of Regulatory History

Date	Activity	Outcome
November 8, 2005	IND 73916 BMS-663068 was submitted in the United States for the treatment of HIV-1 infection	Safe to Proceed
October 1, 2010	Type B, End of Phase 1 meeting	Discussion centered around the patient population for the Phase 2 trial and ultimately the target population of the development program (treatment-naïve versus treatment-experienced)
January 10, 2011	Fast Track Designation Request	FDA granted Fast Track Designation on February 16, 2011
May 6, 2014	Type B, End of Phase 2 meeting	FDA agreed the marketing application would be supported by completed Phase 1 trials, Phase 2a trial, a Phase 2b trial and a single Phase 3 trial.
April 30, 2015	Request for Breakthrough Therapy Designation	FDA granted Breakthrough Therapy Designation on June 24, 2015
August 10, 2015	Type B, Breakthrough Therapy-Initial Comprehensive meeting request to discuss the overall clinical development program	Sponsor meeting scheduled for November 6, 2015 was canceled because preliminary comments sent by FDA were sufficiently clear and complete.
September 8, 2016	Change of Sponsor	Sponsor changed from Bristol-Myers Squibb to ViiV Healthcare
December 13, 2016	Type A, CMC meeting to discuss acceptability of manufacturing changes to address the βlactam-containing photodegradant	FDA indicated additional information is needed to make a determination
June 29, 2017	Type B, Breakthrough Therapy meeting to discuss evidence and conclusion regarding the systemic sensitization of a photodegradant formed during fostemsavir manufacture.	Sponsor meeting canceled because preliminary comments sent by the FDA were sufficiently clear and complete.
August 2, 2017	Type B, CMC meeting to discuss the proposed In Vitro/In Vivo Correlation (IVIVR) approach for fostemsavir	FDA communicated in order for a final decision on the acceptability of PBPK model/mechanistic IVIVR, a thorough review of the proposed model is required.
November 27, 2017	Type A, CMC meeting to discuss a bridging approach to support a required manufacturing site transfer for fostemsavir	Sponsor meeting canceled because preliminary comments sent by the FDA were sufficiently clear and complete.

Date	Activity	Outcome
December 18, 2017	Type B, Pre-NDA meeting request to discuss Sponsor's plan to submit an NDA and seek agreement on the scheduled and elements for a rolling review.	Sponsor meeting scheduled for February 28, 2018 was canceled because preliminary comments sent by the FDA were sufficiently clear and complete. Agreement was reached regarding submission of NDA and rolling review.
April 17, 2019	Request for Rolling Review	FDA granted Rolling Review May 17, 2019.

Source: Regulatory Project Manager and Clinical Reviewer
Abbreviations: CMC, chemistry, manufacturing, and controls; PBPK, physiologically based pharmacokinetics.

13. Pharmacology Toxicology Assessments and Additional Information

13.1. Summary Review of Studies Submitted Under IND

Nonclinical safety profile of fostemsavir (FTR) supporting this NDA has been extensively explored from (1) single and repeated dose toxicity studies in rats (up to 6-month) and dogs (up to 9-month), (2) in vitro and in vivo genotoxicity studies, (3) reproductive and developmental toxicity studies including fertility studies in male and female rats, embryo-fetal developmental studies in rats and rabbits, and a peri- and postnatal developmental study in rats, (4) carcinogenicity studies in transgenic mice (6-month) and rats (2-year bioassay), and (4) juvenile studies in rats. In addition, pharmacokinetics (PKs)/toxicokinetics were studied along with the toxicity studies or in separate animal PK studies to support BMS-663068 with its active drug moiety (BMS-626529)'s exposures in toxicity studies, and to compare PKs and pharmacodynamics in animals to humans. Note that because all of the Sponsor's nonclinical study reports had used code names BMS-663068 and BMS-626529 for FTR and temsavir (TMR), respectively, code names—instead of generic names—are adopted for the following nonclinical summary section.

Nonclinical ADME Profile of BMS-663068

BMS-663068 has a high bioavailability in animals as compared to humans (~80% in rats, ~100% in dogs and monkeys; versus ~27% in humans). BMS-663068 rapidly converts to active drug BMS-626529 in systemic circulation. BMS-626529 has a high plasma protein binding property, with approximately 70 (dog) to 99% (rabbit) in all the animal species studied (human: 92%), and the steady state volume of distribution of BMS-626529 ranged between 0.36 (rat) and 0.93 (dog), suggesting it is widely distributed in tissue intravascularly and extravascularly. Radioactive BMS-663068 studies showed drug-derived radioactivities of BMS-663068, BMS-626529 and metabolite BMS-646915 widely distributed to all tissues (esp. small intestine, kidney, adrenal gland and lung), plus placenta, all fetal tissues including brain, and lactating milk. BMS-626529 metabolized extensively in animals, with ≤5% recoverable in intact BMS-626529 from urine, bile or feces. Two major metabolites BMS-646915 (via hydrolysis) and BMS-930644 (via N-dealkylation) were identified in plasma. BMS-626529 has an elimination half-life of approximately 3.2 to 4.6 hr in rats or dogs (po or iv); and 3.2 (po) or 0.9 (iv) hrs in

monkeys compared to 11 hrs in humans. BMS-663068, BMS-626529 and the major metabolite BMS-646915 do not have inhibitory or inductive activities on cytochromes P450 or p-glycoprotein at any clinical meaningful concentrations under in vitro conditions. BMS-646915 is the primary drug-related material excreted in urine and feces (animals and humans).

Nonclinical Toxicity Profile of BMS-663068

Single dose in vivo or in vitro safety pharmacology studies did not show remarkable effects of BMS-663068 or BMS-626529, except at doses and concentrations much higher than the no observed adverse effect level (NOAEL) as derived from chronic toxicity studies (see

Table 62, below). For example, (1) safety pharmacology-related functional effects included ataxia, decreased and/or labored breathing in mice (1,000 mg/kg single-dose), circling, tremors, abnormal gait, cage biting, lameness, head pressing against cage nausea/vomiting (from 1-month study at ≥100 mg/kg/day; safety factor [SF] >25); (2) BMS-626529 inhibited potassium channels in hERG assay (15, 30, 53% at 3, 10, 30µM, respectively), prolonged action potential duration in rabbit Purkinje fibers (12% at 30µM), and lengthened electrocardiogram (ECG) QT in conscious dogs (QT80, for ~8 to 18 msec, ~2.2 µg/ml). Additionally, there were treatment-related increases in heart rate in the dog at 75 mg/kg (2-week study) or 60 mg/kg (9-month study) reported. In humans, there have not been similar central nervous system (CNS)/behavioral effects, as mentioned above, that were reported (except gastrointestinal [GI] indigestion) as adverse events (AEs) in BMS-663068 clinical trials. In regard to cardiac potassium channel, action potential, QT, and heart rate findings, they could be associated with the modest effects found in the human QT trial completed, and the related tachycardia events listed from the clinical trials.

Major toxicity findings and key target organs of toxicities, as explored from repeat-dose chronic studies, with treatment duration up to 9 months in dogs or 2 years in rats, are highlighted below.

13.1.1. Target Organs of Toxicity

Kidney

Tubular dilatation (multifocal, involving cortical tubules such as distal convoluted tubules) or increased kidney organ weight were reported in 2-week, 1-month, and 6-month rat studies. NOAEL for the 6-month study was 30 mg/kg with the area under the curve (AUC) estimated at 593/908 (male/female) ug.h/ml, which were approximately 31/47-fold of the recommended human dose (600 mg bid with $AUC_{0\text{-}24h}$ =19.4 µg.h/ml). Renal tubular hyperplasia was also reported in a 2-year rat carcinogenicity study, consistent with the view that the kidney is a target organ of toxicity for this drug. Renal effects have been reported as AEs in BMS-663068 human clinical trials.

Liver

Increased bilirubin and multifocal canalicular pigment deposits in 9-month dog study (not fully reversible, for females at ≥10 mg/kg and males at 30 mg/kg) with the NOAEL at 10 mg/kg/day (Day 1 AUC =51 µg.h/ml, SF =2.6). Biliary chemistry findings such as increase in bilirubin,

alkaline phosphatase (ALP), or aspartate aminotransferase (AST) were reported in the 1-month range-finding (NOAEL: ≤50 mg/kg, AUC ≤187 µg.h/ml), and the 2-week dog studies (NOAEL =100 mg/kg, AUC =550 µg.h/ml). Significant liver toxicity was not reported in other animal species except that increased liver weight and ALP were reported in the 1-month range-finding in rats (NOAEL =100 mg/kg, AUC =1510 µg.h/ml). Hepatic toxicity has been reported as AEs in BMS-663068 human clinical trials.

Testicular Tissues

In rats, time-dependent toxicity development in testicular-related tissues could be reflected from the reduction of NOAELs from 300 to 30 mg/kg/day when treatment duration was prolonged: a 2-week study showed enlarged/elongated sperm in testes and epididymides (NOAEL =300 mg/kg, AUC =1,823 µg.h/ml, SF =94), a 1-month study showed degenerative seminiferous tubule epithelium (NOAEL =100 mg/kg, AUC =1,510 µg.h/ml, SF =78), and a 6-month study showed decreased sperm count/dysmorphology (misshapen head or abnormal flagellum; not fully reversible) (NOAEL =30 mg/kg, AUC =593 µg.h/ml, SF =31).

Adrenal Gland

Increased organ weight and angiectasis were reported in both the 6-month rat study (300 mg/kg, SF =33) and single-dose 3-month rat study. Organ weight increases in early embryofetal and fertility study (600 mg/kg) and adrenal necrosis in 2-year carcinogenicity rat study (100 mg/kg) were also reported. Adrenal effects seemed to be related to an increased incidence of pheochromocytoma in HD females (100 mg/kg) in carcinogenicity study. These effects occurred mostly in females, with the males showing organ weight increases only (3-month study). In dogs, adrenal necrosis and inflammation occurred in both 1-month (≥100 mg/kg), and 2-week (moribund dose 300/200 mg/kg) studies. Adrenal toxicity has not been reported as AEs in BMS-663068 human clinical trials.

Reproduction

Reproductive toxicology of BMS-663068 was studied in rats and rabbits. The key findings follow.

Rat

In the early embryonic development study, BMS-663068 showed no effects in females but caused decreases in prostate gland/seminal vesicle weights, sperm density/motility, and increased abnormal sperm in males, as observed similarly in repeat dose toxicity studies. The NOAEL in males was 10 mg/kg/day (AUC =189 µg.h/mL; SF =9.7) and in females was 600 mg/kg/day (AUC3610 µg.h/mL; SF =186.1). In the pre- and postnatal development study in rats, there were decreases in neonatal survival at 300 mg/kg/day (AUC =2550 µg.h/mL; SF =131.4). There was no maternal toxicity. The NOAEL for this study was 50 mg/kg/day (AUC =679 µg.h/mL; SF =35).

In the embryonic development study, BMS-663068 did not produce significant fetal toxicity at dose ≥600 mg/kg, whereas maternal toxicity occurred at ≥300 mg/kg. At 1,000 mg/kg, the

maternal toxicity included: decreased food consumption (56%), abnormal clinical chemistry, decreased BUN [0.77×], K [0.85×], eosinophil counts [0.39× control], and low fetal body weight (8.4% less than controls). Teratogenic effects occurred at the maternally toxic dose of 1,000 mg/kg/day (AUC =4,750 µg.h/mL) with findings presented in the head and jaw (cleft palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw, and protruding tongue) in 21 (20.4%) fetuses from 5 (62.5%) litters of this dosage group. The NOAEL for both maternal and fetal toxicity was 600 mg/kg/day (AUC =3,840 µg.h/mL; AUC SF =197.9).

Rabbits

In embryofetal toxicity study, BMS-663068 increased postimplantation loss and decreased fetal body weights at 100 mg/kg. Maternal toxicity (i.e., decreased food consumption and body weight) occurred at ≥50 mg/kg that became intolerable at ≥250 mg/kg (abortion, death, and moribund). The NOAEL for maternal toxicity was 25 mg/kg/day (AUC328 µg.h/mL; SF =16.9), and fetal toxicity at 50 mg/kg/day (AUC626 µg.h/mL; SF =32.3).

Genotoxicity

BMS-663068 and BMS-626529 tested negative in AMES and chromosome aberration assay using Chinese hamster ovary cells. BMS-663068 tested negative in the in vivo rat bone marrow micronucleus assay.

Carcinogenicity

BMS-663068 did not significantly change survival rate or induce tumor development in CByB6F1/Tg rasH2 hemizygous mice over the 6-month treatment duration. The doses employed produced drug exposures that were sufficiently higher than those in the humans. The AUCs in male and female mice were around 450 and 948 µg.h/ml, respectively (200 mg/kg at Week 26) compared to human AUC of 19.4 µg.h/ml at the recommended clinical dose.

BMS-663068 did not statistically increase neoplasm in Sprague-Dawley rats over a treatment duration of 69 to 100 weeks. The study was finished earlier than the planned 104 weeks, as agreed to by FDA's Executive CAC committee, because of decreased survival rates at the doses tested. Increased mortality in males was statistically significant in the mid- and high-dose groups. There were neoplastic and non-neoplastic findings in the kidney and adrenal gland that were emergent as potential targets resulting from long-term treatment of BMS-663068. The drug exposures from the submortal group (i.e., LD) in males were around ~100 µg.h/ml, and those in LD females were around ~300 µg.h/ml, which were both higher than the human AUC(19.4 µg.h/ml).

Juvenile Toxicology

A 10-week rat study performed using 3-week-old infant rats did not show significant toxicity findings as induced by BMS-663068 at the doses tested (up to 100 mg/kg/day po during postnatal days 21 to 90). The AUCs achieved at the high-dose were around 1,360 µg.h/ml. The study was intended to provide nonclinical safety information in support of indications in children at ≥2 years of age.

Impurities

There is no safety concern from the nonclinical perspective, as the Applicant's control strategy will be based on the International Conference on Harmonisation (ICH) M7 approaches. Additionally, the beta-lactam photodegradant (BMT-218946), which was formed under short wavelength visible light, had been thoroughly studied and reviewed by both FDA and Sponsor's expert panels. It was concluded that systemic sensitizing potential of the photodegradant is orders-of-magnitude less than that of beta-lactam antibiotics (e.g., penicillins, cephalosporins) and trace quantities of BMT-218946 are judged very unlikely to produce acute allergic reaction in patients previously sensitized to a beta-lactam antibiotic.

A summary of systemic exposures, NOAELs, and safety factors (SF, safe nonclinical exposures versus clinical exposure ratios) for potential toxicities are presented in tabular form below.

Table 62. Systemic Exposures, NOAELs, and Safety Factors for Potential Toxicities of BMT-218946

Study	NOAEL (mg/kg)	AUC (µg*hr/ml)	SF
Rat			
2-week	300	1,823 M, 2,451 F	94 M, 126 F
1-month	100	1,510	78
6-month	30	593 M, 908 F	31 M, 47 F
Reproductive toxicity (EEFT)			
Male	10	189	10
Female	600	3,610	186
Reproductive toxicity (EFT)			
Maternal	600	3,840	198
Fetal	600	3,840	198
Reproductive toxicity (PPNT)			
Maternal	300	2,550	131
Developmental	100	679	35
2-yr carcinogenicity	10/5 M, 10 F[b]	100 M, 300 F	5 M, 16 F
10-week juvenile	100	1,360	70
Rabbit			
Reproductive toxicity (EFT)			
Maternal	25	328	17
Fetal	50	626	32
2-week	30	168 M, 130 F	9 M, 7 F
Dog			
1-month	<50	<187	9.6
9-month	10	68 M, 56 F	3 M, 4 F
CByB6Fa mice			
1-month	300	712 M, 1,040 F	37 M, 54 F
6-month carcinogenicity	200	450 M, 948 F	23 M, 49 F

Source: Primary Reviewer's assessment.
[a] Based on exposure comparisons between animal exposures at NOAEL and human exposures at recommended human dose (RHD, 600 mg bid with $AUC_{0\text{-}24h}$ =19.4 µg.h/ml).
[b] Submortal dose without neoplasm and the low dose of the carcinogenicity study, 10/5 initial dosing/later dosing.
Abbreviations: EEFT, early embryo-fetal toxicity study; EFT, embryo-fetal toxicity study; F, female; M, male; NOAEL, no observed adverse effect level; PPNT, peri- and postnatal toxicity study; SF, safety factor.

The major metabolites, BMS-646915 and BMS-930644, that were >10% in human circulation (~20 and 32%, respectively [by AUC]) had been measured in 6-month rat, 3-month mouse, and 9-month dog studies. Their levels in all above species (AUC) were shown to exceed those in

humans, and thus potential effects of these two metabolites are considered adequately addressed and included in the toxicity profile of these studies. No additional nonclinical testing on the two metabolites is necessary as per FDA's Guidance for Industry *Safety Testing of Drug Metabolites* (March 2020).

In conclusion, the Sponsor has adequately explored nonclinical safety profile of BMS-663068 and BMS-626529. The target organs of toxicity were adequately identified. Human risks should be manageable and margins sufficient, from the nonclinical perspective, for the target population at the proposed dosing regimen.

The nonclinical safety profile of BMS-663068 is primarily derived from in vivo and in vitro studies conducted using BMS-663068 (or BMS-663068), including:

- In vivo and in vitro animal PK studies
- Safety pharmacology studies
- Single-dose toxicity studies in rats and mice
- Repeat-dose toxicity studies in rats (up to 6-month) and dogs (up to 9-month)
- Reproductive toxicity studies in rats and rabbits
- In vitro and in vivo mutagenicity assays
- Carcinogenicity studies in transgenic mice (6-month) and rats (2-year bioassay)

13.1.2. Pharmacology (Primary and Secondary)

For primary pharmacology, please see Microbiologist's review for a complete evaluation of the antiviral activities of FTR (or BMS-663068) and related compounds in animals.

BMS-663068 and the converted active drug moiety, BMS-626529, were evaluated for possible interactions in in vitro enzymes, receptors, and transporter binding site assays, as well as in isolated tissue assays. BMS-663068 and BMS-626529 had no significant interactions with a broad spectrum of pharmacological receptors. BMS-663068 did not inhibit acetylcholinesterase, phosphodiesterase III, monoamine oxidase A, or monoamine oxidase B activity. Similarly, BMS-626529 did not inhibit phosphodiesterase III, guanylyl cyclase, acetylcholinesterase, or histamine N-methyltransferase. (i.e., all assay results were ≤20% [≤28% for BMS-626529] stimulation or inhibition at 10μM) on the binding of any of the receptor or enzyme activities evaluated).

13.1.3. Safety Pharmacology

BMS-663068, BMS-626529 (the converted active drug) and the major metabolite BMS-646915 were tested for effects on the cardiovascular, CNS, and respiratory systems.

Cardiac Ikr and Action Potential

BMS-663068 at concentrations up to 30μM had no significant effects on any of the action potential duration (APD) in the rabbit Purkinje fiber assay, or on any of the cardiac ion channels investigated (<2% inhibition of potassium channel [Ikr, via hERG assay], sodium and calcium

channels. BMS-626529 inhibited Ikr by 14.7, 30.1, and 52.6% at 3, 10, and 30µM, respectively, and prolonged APD_{50} and APD_{90} in the rabbit Purkinje fiber assay by 12 and 11%, respectively at 30µM. The major metabolite BMS-646915 has weaker inhibitory effects on Ikr (4.9%/11.3% at 10/30 µM, respectively) and APD prolongation (10% for APD_{50} and none for APD_{90}). The above results suggest that BMS-626529 might have a potential in producing in vivo cardiovascular effects (see below).

ECG in the Dog

Oral BMS-663068 (3, 20, and 75 mg/kg bid) increased QT prolongation in telemetered dogs (QT_{80}, for ~8 to 18 msec) that occurred within 1 hr of the first twice daily (BID) doses of 20 and 75 mg/kg (≤12 and 23 µg/mL at 4 hr, respectively), which lasted for ~4 hours after the second BID dose of 20 mg/kg (13 µg/mL at 8 hr), whereas the effects continued through the remainder of the collection period after the second BID dose of 75 mg/kg (≤42 µg/mL at 8 hr). No observed effect level (NOEL) for BMS-663068-induced QT prolongation was 6 mg/kg/day (BMS-626529≤1.9 µg/mL). Oral BMS-626529 (5, 25, and 125 mg/kg bid) also increased QT prolongation in telemetered dogs (QT_{80}, for ~8 to 12 msec) for up to 1.5 hrs after the first BID dose of 125 mg/kg (250 mg/kg total dose), and up to 3 hrs after the second BID doses of 25 mg/kg and 125 mg/kg (50 and 250 mg/kg total doses, respectively; 2.5 to 6 µg/ml for both dosages at 4 and 8 hrs postdose). NOEL for BMS-626529-induced QT prolongation was 10 mg/kg/day (≤2.2 µg/mL). BMS-663068 also produced an increase in heart rate (55 bpm) in female dogs at ~30 minutes after the first BID dose of 75 mg/kg, which continued for 10 hrs after the second BID dose. Heart rate was also increased in male dogs (<30 bpm) for ≤1 hour following either BID dose of 75 mg/kg. NOEL for elevated heart rates in this study was 40 mg/kg/day (plasma levels ≤13 µg/mL). BMS-626529 did not significantly change the heart rate (250 mg/kg/day, ≤6 µg/mL). Note that in the later 9-month dog study, treatment-related tachycardia was reported at the high dose (HD) group (see report below). Please refer to the review of human QT study and discussion on tachycardia in human AE analysis.

CNS and Respiratory Effects

BMS-663068-related CNS and respiratory effects were noted in the mouse at overtly toxic doses of 1,000 and 2,000 mg/kg, which included ataxia (1 female at 1,000 mg/kg) and decreased and/or labored respiration (1 female at 1,000 mg/kg and 2 females at 2,000 mg/kg) on Days 1 to 2. No CNS or respiratory effects occurred at 500 mg/kg. Note that in repeat-dose dog studies, CNS effects (ataxia [n =3]; circling [2]; tremors [7]; abnormal gait [7], posture or pawing [6]; cage biting [2]; lameness [2]; nausea/vomiting [8], and head pressing against cage [1]) were reported in a 1-month pilot study (≥100 mg/kg/day; SF >25), and decreased musculoskeletal activity, pain response to pressing at the carpal joints in a 2-week study (1/3 low dose [LD], 3/3 intermediate dose and HD).

13.1.4. Absorption, Distribution, Metabolism, Excretion / Pharmacokinetics

The absorption, distribution, metabolism, and excretion (ADME) profile of BMS-663068 and related compounds has been studied in vitro and in vivo in animals. The information was

obtained to validate nonclinical safety studies that provide human risk assessment assistance prior to and during clinical trials.

Absorption

Following oral administration of BMS-663068, the prodrug was hydrolyzed by ALP to BMS-626529, at the brush border membranes of the intestinal lumen, which was then readily absorbed. The bioavailability of oral BMS-663068 was >80% in rats and dogs, as reflected by measurements of BMS-626529. In rats, increases in BMS-626529 AUC following BMS-663068 administration were approximately dose proportional at 5.5 to 200 mg/kg, suggesting significant exposures to the active drug BMS-626529.

Table 63. BMS-626529 Alone: Single-Dose PKs (IV & PO)

Parameters	Rat	Dog	Monkey	Chimpanzee
IV BMS-626529	N=3	N=3	N=3	N=2
Dose (mg/kg)	1	1	1	0.8
Cl (ml/min/kg)	1.3	2.6	7.5	6.6
Vss (l/kg)	0.36	0.93	0.4	0.76
$T_{1/2}$ (h)	4.3	4.6	0.92	1.9
PO BMS-626529	N=3	N=3	N=3	N=4
Dose (mg/kg)	5	5	5	5
Bioavailability (%)	82	89	64	16
C_{max} (ng/ml)	6353	4558	1974	176
T_{max} (h)	4	1.3	2.3	8.2
$T_{1/2}$ (h)	3	3.6	3.3	19
AUC_{0-t} (µg.h/ml)	52.4	29.3	6.88	2.1

Source: Applicant's table from NDA files
Abbreviations: $AUC_{0-t,}$ area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; IV, intravenous; PK, pharmacokinetic; PO, per os; T_{max}, time to maximum plasma concentration; $T_{1/2}$, half-life.

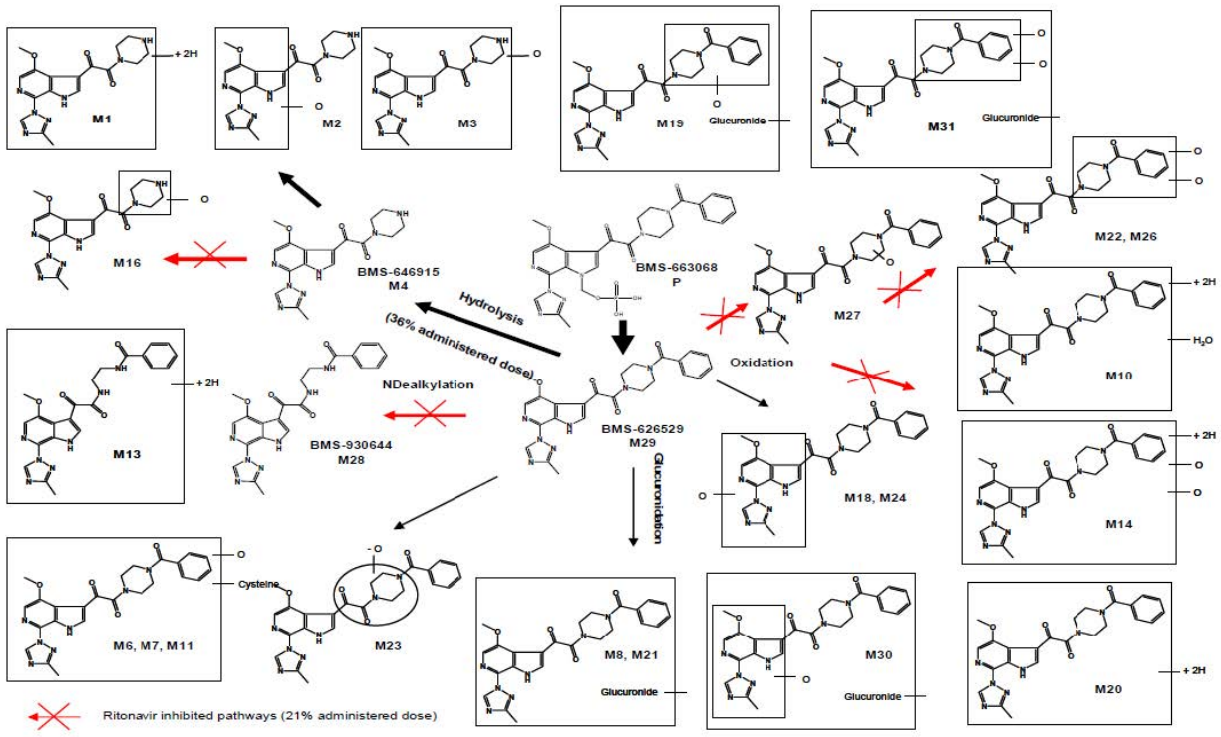
Distribution

The steady-state Vd of BMS-663068 ranged from 0.21 to 0.51 L/kg in rats, dogs, and monkeys, indicating limited extravascular (tissue) distribution. Penetration of BMS-626529 was low, as brain/plasma ratios were <0.01 in rats or <0.08 in mice. For BMS-626529, protein bindings in animals were 70.4% (dog), 98.6% (rabbit), 87.7% (mouse), 95.9% (rat), and 84.7% (cynomolgus monkey) (cf. 84% in humans). Radioactive BMS-663068 study conducted in rats showed radioactivity-related compounds widely distributed to tissues with the following ranking: GI > excretory (liver, bile, renal, bladder) > ocular (lens, uveal tract) > endocrine (adrenal, pituitary, thyroid) > vascular/lymphatic > dermal > testicular and related reproductive tissues. BMS-663068 and related compounds (primarily BMS-626529 and metabolites) also crossed the placenta and distributed to all fetal tissues including the brain in pregnant rats, and were present in the milk from lactating rats (milk/maternal radioactivity ratio =0.991).

Metabolism

Metabolic pathway FTR is shown in the following diagram, as provided by the Applicant:

Figure 8. Metabolic Pathway of Fostemsavir



Source: Applicant's table from NDA files

For in-depth analysis of metabolism-related information such as hepatic enzyme induction/inhibition etc., please refer to the clinical pharmacologist's review. In general, it appeared that the active drug BMS-626529 underwent through one major hydrolytic metabolic process in human, rabbit, and mouse. That pathway, however, played a minor role in rat, dog, and monkey. Thus, the major BMS-663068 metabolites existing in humans, namely BMS-646915 (debenzolylated TMR) and BMS-930644 (N-dealkylated TMR) that accounted for about half of the drug-related radioactivities, although present, were measured at a much smaller proportion in the rat and dog, the two main species used for toxicity studies. However, the plasma concentrations of BMS-646915 (AUC =5.68 µg.h/ml) and BMS-930644 (9.13 µg.h/ml) were 20 and 32% of the coexisting BMS-626529 in humans, the proportions of which were higher when compared to those from the 6-month rat (1% [28.7 µg.h/ml] and 0.8% [23 µg.h/ml], respectively) and 9-month dog study (2.7% [9.97 µg.h/ml] and 9% [33.7 µg.h/ml]; see Table 64, below for more details). Since the AUCs of these two metabolites achieved, as shown above, in the animal studies exceeded those in human, there is no safety concern on the metabolites, and no additional nonclinical studies are warranted as per FDA's Guidance for industry *Safety Testing of Drug Metabolites* (March 2020).

Table 64. Comparison of TMR, BMS-646915, BMS-930644 AUC and C_{max} Across Species

		C_{max} (ug/mL)			AUC (ug.h/mL)		
Species	FTR (mg/kg)	TMR	BMS-646915	BMS- 930644	TMR	BMS-646915	BMS-930644
Mouse	300	138	5.79	3.63	712	27.5	55.1
		(57)[a]	(19)	(7.9)	(25)	(4.8)	(6.0)

Species	FTR (mg/kg)	C_{max} (ug/mL) TMR	BMS-646915	BMS- 930644	AUC (ug.h/mL) TMR	BMS-646915	BMS-930644
Rat	300	194	2.55	1.16	2890	28.7	23.0
		(80)	(8.2)	(2.5)	(102)	(5.1)	(2.5)
Dog	60	51.1	0.81	2.18	373	9.97	33.7
		(21)	(2.6)	(4.8)	(13)	(1.8)	(3.7)
Human	1200	2.42	0.312	0.458	28.2	5.68	9.13

Source: Applicant's table from NDA files
[a] Values in parentheses indicate fold coverage compared to human.
Abbreviations: C_{max}, maximum plasma concentration; FTR, fostemsavir; TMR, temsavir.

Elimination

The total body clearance of BMS-663068 administered was high in rats (49 mL/min/kg), dogs (64 mL/min/kg), and monkeys (47 mL/min/kg). $T_{1/2}$ in rats, dogs, and monkeys were all <0.5 hour for BMS-663068 and 3.2, 4.2, and 3.2 hour for BMS-626529. In all the animal species studied, respective percentages of BMS-626529 eliminated unchanged were 1.6 to 2.6%, 2.6 to 5.8%, and 0.5 to 2.3% in urine, feces, and bile, respectively. BMS-646915 was the most prominent drug-related component in urine and feces. No BMS-663068 was detected in urine, feces, and bile, except that in the dog's urine (6.5%).

13.1.5. Toxicology

13.1.5.1. General Toxicology

Single-Dose Toxicity

Single-dose toxicity studies in dogs did not reveal any target organ/system of toxicity (up to 1,000 mg/kg, without histopathology performed), except postdose emesis occurred at ≥92 mg/kg/day in one study. In mice, lethality was observed at ≥1,000 mg/kg/day, and no significant findings were reported at the sublethal doses.

Repeat-Dose Toxicity

BMS-663068: 2-Week Oral Toxicity Study in Rats (Study # DN05006)

Key Study Findings

Primary target organ of toxicity was testes for this study. The NOAEL was designated at the mid-dose 300 mg/kg (AUC (BMS-626529) ≤2,451 µg.h/ml). At the high-dose (1,000 mg/kg), BMS-663068 produced transient decreases in body weight and/or food consumption as well as testicular toxicity characterized by the presence of enlarged spermatogenic cells in the testes and epididymides (AUC (BMS-626529) =3,045 to 4,116 µg.h/ml).

Conducting laboratory: Bristol-Myer-Squibb Research Laboratory, New Brunswick, NJ
GLP compliance: Yes

Table 65. 2-Week Rat Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing	Vehicle (water) or 50, 300, or 1,000 mg/kg/day (2 equally divided doses BID of 25, 150, or 500 mg/kg, approximately 4 hours apart)
Route of administration	Oral gavage
Formulation/vehicle	H_2O
Species/strain	Sprague-Dawley rats
Number/sex/group	10
Age	4 weeks
Satellite groups/unique design	10
Deviations affecting interpretation	None

Source: Applicant's table from NDA files
Abbreviation: BID, twice daily.

Table 66. 2-Week Rat Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. No drug-related findings.
Body weights	Measured at predose and at study termination. Transient body-weight loss in males (90 to 93% of control values over Days 5 to 12).
Food consumption	Measured at predose and at study termination. Transiently decreased food consumption in both sexes (53 to 90% of control values over Days 5 to 12).
Hematology	Measured at predose and at study termination. Mild increases in reticulocyte (both sexes, x1.5), neutrophil (males, 2.1x) and lymphocyte (females, 1.3) counts at the high dose, as well as increased reticulocyte counts in intermediate-dose (x1.4) females.
Clinical chemistry	Measured at predose and at study termination. Mild decreases in globulin levels at all doses in males (down to 88% of control) and albumin levels at the intermediate and high doses in females (down to 89% of control). Mild decreases in serum bicarbonate levels (down to 90% of controls) and urinary pH (down to 89% of control), and increased kidney weights (up to 17%) were reported and were considered by Applicant to be nonadverse and the changes to be consistent with the presumed liberation of formaldehyde/formic acid upon conversion of the prodrug, BMS-663068, to its active moiety. Potassium levels were decreased in intermediate- and high-dose males (down to 84% of controls) and high-dose females (91% of control), but this was also considered a mild, nonadverse effect of treatment with BMS-663068.
Gross pathology	Measured at study termination. Unremarkable.
Organ weights	Increased kidney weights (up to 17%) at doses above 300 mg/kg.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy. There were drug-related, adverse histological changes in the testes and epididymides at the 1,000-mg/kg high dose, with enlarged spermatogenic cells in the testis of 8 of the 10 high-dose males (versus none in the low- and intermediate-dose or control groups). These effects were minimal or slight in severity, and the enlarged spermatogenic cells, which were found amongst the elongate spermatids in the superficial parts of the seminiferous epithelium of stage VII and VIII testicular tubules, were characterized as having plentiful cytoplasm and nuclei that were sometimes enlarged and/or irregular in shape. In 6 of these animals, similarly enlarged cells were also present in the epididymal tubule lumens, probably due to passage of the abnormal cells from the testis.

Parameters	Major Findings
Toxicokinetics	Systemic exposure of rats to the prodrug, BMS-663068, was negligible with concentrations being less than the lower limit of quantification (LLOQ; 0.010 µg/mL) in all but a few plasma samples. Based upon C_{max} and AUC values, systemic exposure to the parent molecule, BMS-626529, increased in a less than dose-proportional manner on both Days 1 and 14. There was no accumulation during the 2-week study duration. Across all doses and study days, C_{max} and AUC values were 9 to 35% lower in male rats.

Toxicokinetics of 2-Week Oral Study of BMS-660368 in rats

Daily Dose [each of the 2 doses/day] (in mg/kg)	C_{max}(µg/mL) Day 1		C_{max}(µg/mL) Day 14		AUC_{0-24h} h(µg.hr/mL) Day 1		AUC_{0-24h} h(µg.hr/mL) Day 14	
	Male	Female	Male	Female	Male	Female	Male	Female
50 [25]	53	65	50	76	626	818	588	873
300 [150]	135	164	133	189	1,822	2,168	1,823	2,451
1,000 [500]	202	221	191	296	3,045	4,005	3,305	4,116

Levels were converted active drug BMS-626529.

Source: Applicant's table from NDA files
Abbreviations: $AUC_{0-24,}$ area under the curve from 0 to 24 hours; BID, twice daily; C_{max}, maximum plasma concentration; LLOQ, lower limit of quantitation.

BMS-663068: 2-Week Oral Toxicity Study in Dogs (Study #DN05003):

Key Study Findings

BMS-663068 at a daily dose of 300/200 mg/kg (BMS-626529 AUC =851 to 1,105 µg.h/mL) to dogs resulted in mortality and severe toxicity characterized by necrosis and inflammation in the adrenal gland; lymphoid depletion in the thymus, spleen, and lymph nodes; and inflammatory lesions of the joints, heart, and meninges. At 100 mg/kg/day (BMS-626529 AUC =307 to 593 µg.h/mL) transient decreases in activity, emesis, and pressure-induced joint pain were noted, but there were no microscopic correlates. The NOAEL was designated at 30 mg/kg (BMS-626529 AUC =130 (male) - 168 (female) µg.h/mL).

Conducting laboratory: Charles River Laboratories, Montreal, QC, Canada

GLP compliance: Yes

Table 67. 2-Week Dog Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing	Vehicle (Water) or 30, 100, 300 mg/kg/day for 2 weeks. However, due to marked toxicity and mortality at 300 mg/kg/day, the dose level was lowered to 200 mg/kg/day on Day 8. Dosing of this group was subsequently terminated, prior to the first BID dose, on Day 9 of the study. The remaining animals (including 2 survivors in the 300/200 mg/kg/day group) were euthanatized on Days 15 and 16.
Route of administration	Oral gavage
Formulation/vehicle	Water, 1 ml/kg.
Species/strain	Beagle dogs
Number/sex/group	3

Methods	Details
Age	5–6 months old
Satellite groups/unique design	Same animals
Deviations affecting interpretation	See above

Source:
Abbreviation: BID, twice daily.

Table 68. 2-Week Dog Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	Checked 1/day. At 300/200 mg/kg/day, 1 female was sacrificed in poor condition prior to dosing on Day 6, 1 male died prior to dosing on Day 7, and 1 male and 1 female died prior to dosing on Day 9. Clinical observation unique to sacrificed/dead dogs was increased respiration (1 male on day prior to death). There were no drug-related changes in excreta. Drug-related clinical observations included decreased activity of all dogs at all doses and emesis at 100 mg/kg/day (1 male and 2 females) and 300/200 mg/kg/day (all dogs) within 1 to 2 hours of dosing. Decreased activity was transient at 30 and 100 mg/kg/day but generally persistent at 300/200 mg/kg/day. At 300/200 mg/kg/day, ataxia and salivation were also noted.
Clinical signs	Checked 1/day. At 300/200 mg/kg/day, decreased activity/ataxia, emesis, and/or salivation were observed. The decreased activity/ataxia noted in the high dose was related to joint pain and the Applicant did not consider it a primary neurologic effect. At 100 and 300/200 mg/kg/day, a pain response was elicited by application of mild pressure to 1 or both carpal joints. At 30 mg/kg/day group, 1 female exhibited a pain response to palpation of both carpal joints on Day 14 but not Day 15. The Applicant stated that the finding was transient on Day 14 without a pathologic correlate at necropsy and considered it not drug-related. No additional drug-related changes were observed during physical examinations at 30 mg/kg/day.
Body weights	Measured at predose and at study termination. Body weight losses of 0.6 to 1.1 kg were seen at 300/200 mg/kg/day.
Food consumption	Measured at predose and at study termination. At 300/200 mg/kg/day, food consumption was decreased 70% (Week 1).
Ophthalmoscopy	Evaluated pretreatment and end of study. No drug-related findings.
ECG	Measured at predose and at study termination. At 100 and 300 mg/kg/day, increased heart rates (143 - 152 bpm, vs. ~100 bpm in controls) were noted in 3 males. Unremarkable at 30 mg/kg/day.
Hematology	Measured at predose and at study termination. Changes observed in the 2 surviving animals at 300/200 mg/kg/day included changes in red blood cell parameters [erythrocyte count (0.6 to 0.9x pretest), hemoglobin (0.6 to 0.9x pretest), hematocrit (0.6 to 0.9x pretest)], indicative of a decreased red cell mass (male) and a mild nonregenerative (female) anemia, and in the female, decreased reticulocyte (0.3x pretest), and MCV (0.9x pretest), and increased fibrinogen (3.5 to 5.1x pretest), indicative of inflammation. Other changes in the surviving female included decreased lymphocyte (0.6x pretest) counts. Unremarkable 30 or 100 mg/kg/day.

Parameters	Major Findings
Clinical chemistry	Measured at predose and at study termination. Changes observed in the 2 surviving animals at 300/200 mg/kg/day included increased globulins (1.5 to 1.6x pretest) and a decreased A/G ratio (0.5 to 0.6x pretest), which are consistent with an inflammatory process. Additionally, there were increases in serum total bilirubin (5.4 to 5.6x pretest), cholesterol (1.7 to 2.3x pretest), and triglycerides (2.3 to 2.5x pretest). Changes noted in the surviving female included decreased sodium, potassium and chloride (0.9x, 0.6x, and 0.9x pretest, respectively), and increased alkaline phosphatase (2.1x pretest); whereas findings noted in the male included decreased serum glucose (0.8x pretest) and bicarbonate (0.7x pretest). The majority of serum-chemistry changes are suspected to be associated with the inflammation and malaise of the 2 surviving animals. Unremarkable 30 or 100 mg/kg/day.
Gross pathology	Measured at study termination. Unscheduled Necropsies: No drug-related gross lesions were observed in unscheduled-necropsied females. Drug-related gross lesions in unscheduled-necropsied animals at 300/200 mg/kg were limited to joint spaces distended by cloudy, yellow, viscid fluid in both males, thickened stifle joint capsule and increased adrenal gland size in one male, and thickened pericardium in the other male. A focal area of red discoloration in the wall of the right atrium in one female was identified microscopically as a postmortem blood clot. Several additional gross lesions, including gross lesions in the tongue, stomach, and eyes, were considered to be incidental sporadic spontaneous lesions or secondary to oral dosing and/or stress in sick debilitated animals and not directly due to treatment with BMS-663068. Scheduled Necropsies: No drug-related gross lesions were observed in animals given 30 or 100 mg/kg of BMS- 663068. In end-of-dose-sacrificed animals at 300/200 mg/kg, drug-related gross lesions were limited to yellow, thickened synovium in the stifle joint of both animals and decreased thymus size in the female. Red discoloration in the hearts of 1 low-dose male and 1 intermediate-dose female was identified microscopically as postmortem blood clots and were not related to treatment with BMS-663068.
Histopathology Adequate battery: Yes Peer review: Yes	Unscheduled Necropsies: In unscheduled-necropsied animals, drug-related microscopic lesions consisted of inflammatory lesions in multiple organs and tissues. The adrenal glands from all 4 unscheduled-necropsied animals contained multifocal, mild to moderate variably-sized areas of necrosis, hemorrhage, and acute inflammation in the adrenal cortex, primarily involving the zona reticularis adjacent to the adrenal medulla. The thymus from all 4 animals exhibited diffuse, mild to moderate lymphoid depletion and/or hemorrhage. In addition, mild to moderate lymphoid depletion was also present in the mandibular and mesenteric lymph nodes in several animals and in the spleen from 1 male. Additionally, in the male that was found dead on Day 7 (4103), drug-related microscopic lesions consisted of multifocal areas of mild, acute inflammation in the atrial myocardium with extension into the overlying pericardial fat in the heart and moderate, diffuse, subacute inflammation in the synovium of the stifle joint that correlated with the thickened joint capsule observed at necropsy. In the male that was found dead on Day 9 (4102), multifocal, mild, acute/subacute inflammation was observed in the meninges of the brain, and pericardium of the heart that correlated with the thickened pericardium observed at necropsy. In 1 of the 2 unscheduled-necropsied females (4202), drug-related microscopic inflammatory changes were limited to minimal subacute inflammation in the synovium of the stifle joint, which correlated to a marked increase in the cellularity of the joint fluid; characterized by predominately neutrophils with fewer macrophages. Similar findings were evident in the joint fluid of 1 male (4102).

Parameters	Major Findings
	Scheduled Necropsies: No drug-related microscopic lesions were observed in animals given 30 or 100 mg/kg of BMS-663068. In scheduled-necropsied animals at 300/200 mg/kg, drug-related microscopic lesions included minimal to mild chronic inflammation with vacuolation, hemorrhage, and mineralization in the zona reticularis of the adrenal cortex, mild to moderate lymphoid depletion in the thymus, which correlated with decreased thymus size observed at necropsy in 1 female, and minimal to moderate, chronic-active to chronic inflammation in the synovium of the stifle joint synovium that correlated with a moderate increased cellularity consisting of predominately neutrophils and fewer macrophages in the joint fluid smear of 1 female (4203) and thickened yellow joint capsule observed in both animals at the scheduled necropsy. The lesions in the adrenal glands and lymphoid organs in high-dose unscheduled- and scheduled-sacrificed animals are most likely secondary to stress in sick, debilitated animals, but a possible role of overt toxicity to BMS-663068 cannot be ruled out. The definitive etiology of the drug-related, multi-organ inflammatory pathology is unknown. Clinical pathology changes supported the microscopic inflammatory changes. The Applicant claimed that the adreno-cortical changes observed in the high-dose animals are most likely secondary to stress in sick and/or debilitated animals; however, similar changes in the zona fasciculata and/or reticularis have been observed secondary to enterotoxemia and following the administration of some xenobiotic compounds. The joints appeared to be a target of BMS-663068, but the type of inflammation observed was not specific and the pathogenesis of the lesion was unclear.
Toxicokinetics	Systemic exposure to BMS-663068 was less than the lower limit of quantification (10 ng/mL) in all but a few plasma samples suggesting that there was little systemic exposure to this prodrug. Based on C_{max} and AUC values, systemic exposure to BMS-626529 following administration of 30 to 300 mg/kg/day (15 to 150 mg/kg, BID) of its prodrug BMS-663068, was similar for males and females on Days 1 and 13 (except for the high dose on Day 13, which was not evaluated). Increases in these values were dose related and were approximately dose proportional from 30 to 100 mg/kg/day but were less than dose proportional from 100 to 300 mg/kg/day (Day 1 only).

Toxicokinetics of BMS-663068 in 2-week oral study in dogs.

		Daily Dose (BID) (mg/kg/day)					
	Study	30 (15)		100 (50)		300 (150)	
Parameter	Day	Male	Female	Male	Female	Male	Female
C_{max} (µg/mL)	1	19±3	17±4	34±8	45±11	98±15	68±7
	13	16±2	16±2	46±2	55±4	N/A	N/A
AUC_{0-24h} (µg.h/mL)[a]	1	177±16	151±9	307±194	548±106	1,105±93	851±110
	13	168±9	130±11	508±44	593±61	N/A	N/A

[a] Levels are active drug BMS-626529

Source: Applicant's table from NDA files
Abbreviations: AUC, area under the curve; $AUC_{0-24h,}$ area under the curve from 0 to 24 hours; BID, twice daily; C_{max}, maximum plasma concentration; ECG, electrocardiogram; MCV, mean corpuscular volume.

BMS-663068: 28-Day Oral Toxicity Study in CByB6F1 Mice (Study # DM10049)

Key Study Findings

The purpose of this study was to provide background information on the future 6-month transgenic mouse carcinogenicity study. It also provided key information on systemic exposure of BMS-626529, and two metabolites: BMS-646915 and BMS-930644 in the mouse. NOAELs identified in the current study were 300 mg/kg/day in males ($AUC_{(0\text{-}24h)}$ =712 [male] – 1,040 [female] ug.h/ml) (cf. the Applicant claimed a NOAEL for female =600 mg/kg/day $AUC_{(0\text{-}24h)}$ =1,870 µg.h/ml). Lethality occurred at ≥600 mg/kg in males and ≥900 mg/kg in females. Treatment-related findings were minor decreases in RBC parameters and the associated extramedullary hematopoiesis in the spleen.

Conducting laboratory: Charles River Laboratories, Spencerville, OH 45887

GLP compliance: Yes

Table 69. 28-Day CByB6F1 Mouse Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing	Vehicle (water) or 300, 600, 900, 1,200 mg/kg/day (BID given 2 divided doses 4 hours apart)
Route of administration	Oral gavage
Formulation/vehicle	H_2O
Species/strain	CByB6F1 (Tg.rasH2 nontransgenic littermate) mice s
Number/sex/group	10
Age	8 weeks
Satellite groups/unique design	30/sex/group (control: 5/sex/group); levels measured included BMS-663068, BMS-626529, debenzoylated metabolite BMS-646915, N-dealkylated metabolite BMS-930644, after the first dose and after Week 4 dosing.
Deviations affecting interpretation	None

Source: Applicant's table from NDA files

Table 70. 28-Day CByB6F1 Mouse Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	Checked ≥1/day. The drug is lethal at ≥600 mg/kg for males and ≥900 mg/kg for females (occurred mostly during first 4 days of dosing): Toxicity Group: 1 male/1 female died at 900 mg/kg, 3 males/5 females at 1,200 mg/kg (Days 1-13). TK Group: 2 males at 600 mg/kg/day; 4 males and 7 females at 900 mg/kg; and 8 males and 11 females at 1,200 mg/kg (Days 1-29) died. No gross or microscopic findings were observed and causes of death were unknown (1 male at 300 mg/kg died of dosing error [perforation of esophagus] on Day 7).
Clinical signs	Checked 1/day. ≥900 mg/kg: dose-related incidences of decreased activity (both sexes) and cool to touch and shallow breathing (females). 1,200 mg/kg: prostration and partially closed eyelids (males), convulsions (1 female)
Body weights	Measured at predose and 1/week. Unremarkable.
Food consumption	Measured at predose and 1/week. Unremarkable.

Parameters	Major Findings
Hematology	Measured 1/week. ≥600 mg/kg males: increases in reticulocyte (1.39-1.45x 600, 900 mg/kg; 1.46-1.44x 1,200 mg/kg) and red cell distribution width (1.08 to 1.20x; 600 mg/kg) that correlated with extramedullary hematopoiesis in the spleen (see below). 900 mg/kg females: decreases in RBC, Hct (0.90 to 0.96x control), Hb (0.93- 0.94x); increases in MCV (1.05x), MCH (1.03-1.05x both sexes).

Dose (mg/kg/day):	300		600		900		1200	
Sex:	M	F	M	F	M	F	M	F
Red blood cell count	-	-	-	-	-	0.91*	0.93	0.90*
Hemoglobin	-	-	-	-	-	0.94*	-	0.93*
Hematocrit	-	-	-	-	-	0.96	0.94	0.94
Mean corpuscular volume	-	-	-	-	-	1.05*	-	1.05*
Mean corpuscular hemoglobin	-	-	-	-	1.03*	1.04*	1.05*	1.03
Mean corpuscular hemoglobin concentration	-	-	-	-	-	-	1.03*	-
Reticulocyte count	-	-	1.39*	-	1.45*	-	1.46*	1.44*
Red cell distribution width	-	-	1.08*	-	1.12*	1.09*	1.20*	1.17*

Clinical chemistry	Measured at predose and at study termination. ≥600 mg/kg: increases in serum total bilirubin (1.43 to 2.21x). 900 mg/kg females: increases in serum total protein and albumin (1.06-1.11x). 1,200 mg/kg females: increases in serum globulins (1.10x control)

Dose (mg/kg/day):	300		600		900		1200	
Sex:	M	F	M	F	M	F	M	F
Total bilirubin	-	-	1.50*	1.43	1.57*	1.71*	2.07*	2.21*
Total protein	-	-	-	-	-	1.06*	-	1.11*
Albumin	-	-	-	-	-	1.09*	-	1.11*
Globulin	-	-	-	-	-	-	-	1.10*

Gross pathology	Measured at study termination. Unremarkable.
Organ weights	1. Increased spleen weight (1,200 mg/kg, 13% in males, 9% in females). 2. Decreased thymic weight (≥900 mg/kg: 27-31% in males, 15-29% in females; 300-600 mg/kg 4-12%)(stress-related without microscopic correlate except lymphoid depletion (2 males/1 female at 1,200 mg/kg/day which died or euthanized moribund.) 3. Decreased adrenal weights (≥600 mg/kg: 11-18% in females)
Histopathology Adequate battery: Yes Peer review: Yes	Unremarkable, except for the spleen: Spleen: extramedullary hematopoiesis (erythroid series), increased incidence and/or severity (minimal to mild) in females at ≥300 mg/kg and males ≥900 mg/kg

Parameters	Major Findings				
Dose (mg/kg/day):	**0**	**300**	**600**	**900**	**1200**
No. of mice	**10/10**	**10/10**	**10/10**	**10/10**	**10/10**
Sex:	**M/F**	**M/F**	**M/F**	**M/F***	**M/F**
Spleen					
Hematopoiesis, extramedullary, increased	0/2	0/6	1/7	8/9	6/5
Minimal	0/2	0/4	1/6	8/7*	5/3
Mild	-	0/2	0/1	0/2	1/2

A dash (-) indicates absence of finding in the group.
* Number includes preterminal animal (No. 1186).

Toxicokinetics	AUC increases (BMS-626529) were less than dose proportional (300-1,200 mg/kg). No gender sex differences or accumulation was noted after repeat dosing. The prodrug BMS-663068 concentrations were less than detectable limits. AUC of the metabolites BMS-930644 and BMS-646915 were approximately 0.08x those of BMS-626529.

Parameters	Major Findings

Toxicokinetics of 28-Day Oral Study of BMS-660368 in CByB6F1 Mice

Parameter	Day	BMS-663068 Dose							
		300 mg/kg/day		600 mg/kg/day		900 mg/kg/day		1200 mg/kg/day	
		Male	Female	Male	Female	Male	Female	Male	Female
					BMS-663068				
Cmax (µg/mL)	1	ND	0.0769[a]	0.00960[a]	0.0656	0.0163	0.0673	0.0274	0.0277
	28	0.00922[a]	0.0564[a]	0.0141[a]	0.0843[a]	0.0115[a]	ND	0.0365[a]	0.0622
AUC(0-24h) (µg•h/mL)	1	ND	ND	ND	ND	ND	ND	ND	ND
	28	ND	ND	ND	ND	ND	ND	ND	ND
					BMS-626529				
Cmax [c] (µg/mL)	1	106	138	126	164	155	190	157	204
	28	138	120	145	149	166	179	210	188
AUC(0-24h) (µg•h/mL)	1	763	1120	1330	1,570	2,090	2,630	2,490	2,730
	28	712	1040	1,250	1,870	1,810	2,190	2,220	2,540
					BMS-646915				
Cmax (µg/mL)	1	4.35	4.39	6.24	6.66	7.66	8.46	9.36	8.63
	28	5.79	3.70	7.66	5.77	8.23	8.24	12.3	9.96
AUC(0-24h) (µg•h/mL)	1	30.8	12.3[b]	53.9	50.9	96.4	129	137	130
	28	27.5	29.8	57.5	55.8	77.3	76.0	112	98.9
					BMS-960644				
Cmax (µg/mL)	1	2.30	3.48	3.34	2.86	3.53	2.84	3.71	2.76
	28	3.63	1.56	2.24	3.23	3.26	3.79	2.99	4.14
AUC(0-24h) (µg•h/mL)	1	31.8	43.2	52.5	47.1	76.9	65.1	61.0	61.7
	28	55.1	29.9	38.6	61.3	59.1	58.6	64.6	73.9

ND - Not determined due to insufficient data.
[a] C_{max} for BMS-663068 was obtained from less than 3 plasma samples, with remaining samples that were < LLOQ (0.00500 µg/mL).
[b] The exposure is AUC(0-4h), as all plasma BMS-646915 concentrations at 24 hours post dose were < LLOQ.
[c] Combined (Male + Female) $AUC_{(0-24)}$ for BMS-626529 were as follows: Day 28 at 300 mg/kg/day (876 µg.h/mL), 600 mg/kg/day (1560 µg.h/mL), 900 mg/kg/day (2000 µg.h/mL), 1,200 mg/kg/day (2380 µg.h/ml).

Source: Applicant's table from NDA files
Abbreviations: AUC, area under the curve; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; RBC, red blood cell; TK, toxicokinetics.

BMS-663068: 1-Month Oral Gavage Dose-Range Finding Toxicity Study in Rats (Non-GLP Study #DS09003)

Key Study Findings

This study appeared to be a pilot study for a later 6-month rat study (i.e., bypassed definitive 1-month rat study). Findings are included here because the study provided bridging information on toxicity profile in rats explored from between 2-week and 6-month treatment durations. Rats were orally dosed with BMS-663068 at 0, 100, 300, 1,000 mg/kg/day (n=10). All animals survived to the end of treatment (no death). At doses ≥300 mg/kg/day, findings such as: increases in reticulocyte count, triglyceride, kidney and liver weight, ALP; decreases in

RBC/Hct/Hb and uterus weight (plus estrous cycling changes); and degenerative seminiferous tubule epithelium were reported. The NOAEL was designated at 100 mg/kg (AUC =1510 μg.hr/ml).

BMS-663068: 1-Month Oral Gavage Dose-Range Finding Toxicity Study in Dogs (Non-GLP Study #DS09008)

Key Study Findings

This appeared to be a pilot study for a later nine-month dog study (i.e., bypassed definitive one-month dog study). The study provided bridging information on toxicity profile in dogs explored from between 2-week and 9-month treatment durations for 1 month. The dogs were dosed at 0, 50, 100, 150, 200 mg/kg/day (n=3) and BMS-663068 was barely tolerated at 50 mg/kg ('NOAEL' as the Applicant designated, AUC =187 μg.h/ml at Day 29), which was associated with fecal changes (liquid, unformed, mucous, yellow or green color) and vomitus, so no NOAEL can be identified for this study. Neurologic toxicity (cage biting, abnormal gait, abnormal and hunched posture, abnormal pawing, tremors and red mucous membranes), body weight loss, increases in bilirubin, adrenal cortical hemorrhage/coagulative necrosis were reported at ≥100 mg/kg/day (AUC ≥477 μg.hr/ml at Day 29). Morbidity and moribundity occurred at 200 mg/kg/day (AUC ≥853 μg.hr/ml Day 19/18) resulting in euthanasia of 1 female on Day 15 and early termination of the remaining animals in this dose group on Days 19 or 20. Other treatment-related findings reported at doses higher than NOAEL included increased incidence and severity of thymic lymphoid depletion, and/or minimal decrease in splenic germinal centers. Additionally, there were increased ALP (associated with increased total bilirubin), and histologically inactive prostate (correlated with decreased prostate weight) that occurred at ≥150 mg/kg/day; and mild increases in M:E ratio in bone marrow at moribund dose of 200 mg/kg/day.

BMS-663068: A 6-Month Oral Toxicity Study in Rats Followed by a 2-Month Recovery (Study # DS09100)

Key Study Findings

This 6-month rat study revealed 3 major target organs of toxicity: kidney, adrenal gland and testes. NOAEL was considered to be 30 mg/kg/day by the Applicant.

Conducting laboratory: Charles River Laboratories Preclinical Services Montreal CA

GLP compliance: Yes

Table 71. 6-Month Rat Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing	Vehicle (water) or 30, 100, or 300 mg/kg/day), qd
Route of administration	Oral gavage
Formulation/vehicle	H_2O
Species/strain	Sprague Dawley Crl:CD (SD), (Rattus norvegicus)
Number/sex/group	25 (males), 20 (females)
Age	6 weeks

Methods	Details
Satellite groups/unique design	5/sex/recovery (recovery for 8 weeks), with the following additional unique design:

Group Number Identification	Dose Level (mg/kg/day)[b]	Number of Animals[a]					
		Main Study[c,d] (Animals for End-of-Dose Necropsy)		Recovery Study[e] (Animals for Post Dose Necropsy)		Hormone Study[f]	
		Males	Females	Males	Females	Males	Females
1/ Vehicle control	0	25	20	5	5	10	10
2/ BMS-663068	30	25	20	5	5	10	10
3/ BMS-663068	100	25	20	5	5	10	10
4/ BMS-663068	300	25	20	5	5	10	10
5/ Sentinel Monitoring[g]	-	6	6	-		-	

[a] Any animal replaced during the study was documented in the study file. For animals replaced after initiation of dosing, all data were included in the study records and the final report.
[b] 5 mL/kg dosing volume, concentrations of the dose formulations for these were 6, 20 & 60 mg/ml.
[c] In the Main Study groups, the last 5 males/group were necropsied after 1 month of dosing (on Day 29) whereas the remaining 20/sex/group were necropsied at the end of 6-month dosing period.
[d] The first 10 rats/sex/group were used for T-cell dependent antibody response (TDAR) evaluations.
[e] Recovery animals were necropsied after 6-months dosing plus 2-month recovery period.
[f] Hormone Study animals were used only for hormone level determinations relating to clinical examination, body weight and food consumption collected from these animals were retained, but not reported.
[g] Tests were conducted on sentinel animals as indicated in protocol section 11.7. Data from these animals were retained, but not reported.

Deviations affecting interpretation:	None

Source: Applicant's table from NDA files

Table 72. 6-Month Rat Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	Checked 2/day. 8 nontreatment related mortalities (dosing errors) as following: 4 Main Study animals were euthanized early during the dosing period (Vehicle Control Animal No. 1516 died on Day 11, Animal Nos. 3502 and 3510 at 100 mg/kg/day died on Day 169 and Day 78, respectively, and Animal No. 4518 at 300 mg/kg/day died on Day 114). 4 Main Study and 1 Recovery Study animals were found dead during the dosing.
Clinical signs	Checked 1-2/day. Salivation, wet (lower jaw), oily (entire dorsal area), yellow/red/brown-stained (urogenital area, tail, lower jaw, and cranium) fur were reported.
Body weights	Measured 1/week. Unremarkable.
Food consumption	Measured 1/week. Unremarkable.
Hematology	Measured Clinical Pathology was evaluated Weeks 4, 13, 26 of treatment, and end of recovery Week 34/35. Increases in lymphocyte count (1.27x - 1.68x controls, majority of males and females at 300 mg/kg/day on Weeks 13 and 26/27; also reported in 1-month study). Minimal and transient variations in red blood cell mass and absolute reticulocytes count (vs. controls) were noted in males and in females throughout the dosing period. These changes were considered by the Applicant to be nondrug-related due to their inconsistency and lack of a dose-level relationship. Post-Dose Recovery: lymphocyte counts were unremarkable.

Parameters	Major Findings
Clinical chemistry	Measured at predose and at study termination. Decreases in serum K, Cl, & increases in total bicarbonates at ≥30 mg/kg/day, plus decreases in total proteins and albumin at ≥100 mg/kg/day. These changes may be associated renal histopathology reported (see below). The decreases in K were reported in 1-month rat toxicity study.

Text Table 3.7.2.1A BMS-663068-Related Serum Chemistry Changes during Collection period corresponding to Week 4 (Days 22/23 and Days 24/25)

Females						
Day 24[a]	**Sampled vessel**	**↓Potassium**	**↓Chloride**	**↑Bicarbonate**	**↓Total proteins**	**↓Albumin**
1501-1525	Jugular Vein	—	—	—	—	—
2501-2520	Jugular Vein	—	—	—	—	—
Day 25						
2521-2525	Jugular Vein	—	—	—	—	—
3501-3525	Jugular Vein	—	—	—	0.95×(8/25)	0.94×(4/25)
4501-4525	Jugular Vein	0.86×(13/25)	0.98×(10/25)	—	0.92×(13/25)	0.91×(6/25)

[a] Range of individual animal numbers sampled at noted interval; A dash (-) indicates absence of change in group; Note: The numerical values in brackets represent the incidence of the change within the group, i.e., the number of rats whose value is below the lowest individual value in the control group for potassium, chloride, total proteins and albumin concentrations.

Gross pathology	Measured at study termination. Adrenal gland at ≥100 mg/kg/day in females. Adrenal enlargement was noted in 5 females at 300 mg/kg/day (correlated microscopically with angiectasis). Other findings noted in various organs or tissues, including enlargement of mandibular lymph nodes and pale areas in the liver in all dose groups, were considered by Applicant to be incidental or agonal. Post-Dose Recovery Necropsy: 2 females (1 at 300 mg/kg/day and 1 at 100 mg/kg/day) had pale discoloration of the kidney (correlated with histopathology of tubular dilatation). Other findings noted in various organs or tissues were considered incidental or agonal.
Organ weights	End-of-Dose Necropsy: Kidney at ≥100 mg/kg/day in both sexes: statistically significant dose-related increase in absolute and relative (to body and brain) (correlated with histopathology of tubular dilatation). Adrenal gland at 300 mg/kg/day in females: There was a statistically significant increase in adrenal gland weight (absolute and relative to body and brain) (correlated microscopically with angiectasis). in females at 300 mg/kg). Heart, liver and spleen weights (absolute and relative to body and/or brain) were generally statistically significant and dose-related increased in both sexes at ≥100 mg/kg/day. The Applicant stated that the toxicological significances of these changes are uncertain. Post-Dose Recovery Necropsy: Unremarkable.

Parameters	Major Findings

Text Table 3.9.1.1 BMS-663068-Related Organ Weight Changes in End-of-Dose Animals

Dose (mg/kg/day):	30		100		300	
Sex:	M	F	M	F	M	F
Kidney						
Absolute/ %body/ %brain	-	-	↑24**/ 23**/ 24**	↑28**/21**/ 27**	↑34**/37**/ 36**	↑37**/29**/ 35**
Adrenal gland						
Absolute/ %body/ %brain	-	-	-	-	-	↑34**/27**/ 32**
Heart						
Absolute/ %body/ %brain	-	-	↑10*/9*/10*	↑10**/4/9*	↑18**/20**/ 19**	↑14**/ 8/14**
Liver						
Absolute/ %body/ %brain	-	-	↑14/13**/14	↑19**/12**/ 17**	↑16*/19**/ 18*	↑33**/25**/ 31**
Spleen						
Absolute/ %body/ %brain	-	-	↑13/12*/ 14*	↑21*/14/ 19*	↑18*/20**/ 20**	↑44**/36**/ 43**

A dash (-) indicates absence of change in group;
* P<0.05;
** P<0.01 for absolute values
Note: The numerical values in the table represent the respective percent increase [↑] or percent decrease [↓] from control mean value [(treated group mean - control group mean) / control group mean]x100.

Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy. Target Organs: Kidney (females at all doses and males at ≥100 mg/kg/day), Adrenal Gland (≥100 mg/kg/day in both sexes) and Testis (males at ≥100 mg/kg/day). End-of-Dose Necropsy: 1. Kidney of females from all dose groups and males ≥100 mg/kg/day: Dose-related increase in incidence and/or severity of minimal to moderate tubular dilatation; multifocal and usually consisted of small groups of cortical tubules (likely distal convoluted tubules) that were dilated (correlated with increased kidney weight in both sexes at ≥100 mg/kg/day). 2. Adrenal gland of both sexes ≥100 mg/kg/day: Minimal to slight angiectasis, dose-related increase in incidence and severity, characterized by small to medium-sized areas, likely dilated sinusoids, filled with erythrocytes (correlated with increased adrenal weight in females at 300 mg/kg/day and, in five females, with enlargement seen macroscopically at 300 mg/kg/day). 3. Testis at 300 and 100 mg/kg/day: Increased incidence of degeneration/atrophy of the seminiferous epithelium (multifocal, randomly distributed and usually affecting segment of a tubule; minimal to moderate) at 300 mg/kg, which correlated with a decrease in sperm count and motility at this dose (see below). Marked locally extensive degeneration/atrophy was seen in the testis of 1 male at 100 mg/kg/day, which correlated with a decreased sperm motility and count in this rat; for this finding the Applicant admitted that the effects may be treatment-related. But the Applicant claimed that the minimal testicular degeneration noted in

Parameters	Major Findings
	another male at 100 mg/kg/day was not considered drug-related because there were no morphology findings, for which this reviewer disagrees.

Text Table 3.9.3.1A BMS-663068-Related Microscopic Findings in End-of-Dose Animals

Dose (mg/kg/day):	0	30	100	300
No. of rats (M/F):	20/21	20/20	21/20	20/20
Sex:	M/F	M/F	M/F	M/F
Kidney: Dilatation: tubular	5/4	6/7	13/15	19/17
Minimal	5/4	6/4	13/10	14/13
Slight	-/-	0/3	0/5	5/3
Moderate	-/-	-/-	-/-	0/1
Adrenal gland: Angiectasis	0/6	0/8	1/11	13/17
Minimal	0/5	0/5	1/7	8/5
Slight	0/1	0/3	0/4	5/12
Testis: Degeneration/atrophy: seminiferous epithelium	1/0	-/-	2/0	7/0
Minimal	1/0	-/-	1/0	5/0
Slight	-/-	-/-	-/-	1/0
Moderate	-/-	-/-	-/-	1/0
Marked	-/-	-/-	1/0	-/-

A dash (-) indicates absence of finding in group

Recovery Necropsy:

Renal tubular dilatation - minimal to slight in females at ≥100 mg/kg/day (correlated with pale discoloration in 2 rats).

Angiectasis in adrenal - minimal to slight in females at 300 mg/kg/day degeneration/atrophy of seminiferous epithelium in the testis - slight of 1 male at 300 mg/kg/day.

The Applicant thus claimed: ‘partial recovery of testicular changes’, ‘full recovery of kidney and adrenal in males’ and ‘partial recovery of kidney and adrenal in females’.

Parameters	Major Findings

Text Table 3.9.3.1B BMS-663068-Related Microscopic Findings in Post-Dose Recovery Animals

Dose (mg/kg/day):	0	30	100	300
No. of rats (M /F):	5/4	5/5	4/5	5/5
Sex:	M/F	M/F	M/F	M/F
Kidney: Dilatation: tubular	0/1	1/0	0/3	0/3
Minimal	0/1	1/0	0/2	0/2
Slight	—/—	—/—	0/1	0/1
Adrenal gland: Angiectasis	0/2	—/—	0/1	0/5
Minimal	0/1	—/—	—/—	0/3
Slight	0/1	—/—	0/1	0/2
Testis: Degeneration/atrophy: seminiferous epithelium	—/—	—/—	—/—	1/0
Slight	—/—	—/—	—/—	1/0

A dash (-) indicates absence of finding in group

1. Immunotoxicity and Pituitary-Gonadal Axis Neuroendocrine Toxicity:

T-cell-dependent IgM or IgG antibody responses to KLH immunization or changes in serum reproductive hormones (luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol or progesterone) were unremarkable.

2. Testicular Evaluations:

Day 29 Necropsy:
Decreases in sperm count with morphologic abnormalities in males at 300 mg/kg/day (mean sperm count 593.866 mil/g vs. 756.634 mil/g in controls).

Morphologic abnormalities (11.6% vs. 7.7% in controls): sperm heads separated from flagellum and, less frequently, misshapen heads with normal flagellum and normal heads with abnormal flagellum.

End-of-Dose Necropsy:
Decreases in sperm count with morphologic abnormalities in males at 300 mg/kg/day (658.915 mil/g vs. 718.117 mil/g in controls), whereas at 100 mg/kg group, there was sperm morphologic abnormalities without changes in mean sperm counts (please not one mid-dose male showed reduced in counts).

Sperm motility: 52.3% and 37.9% (of control) at 100 and 300 mg/kg/day, respectively (statistically significant). There was a higher percentage of morphologic abnormalities (5.6 and 9.6% at 100 and 300 mg/kg/day, respectively, vs. 2.4% in controls)(see below).

Morphologic abnormalities: normally shaped heads separated from flagellum and, less frequently, misshapen heads separated from flagellum or with normal flagellum and normal heads with abnormal flagellum.

Parameters	Major Findings
	These necropsy results correlated with minimal to moderate degeneration/atrophy of the seminiferous epithelium at 300 mg/kg/day and marked degeneration/atrophy seen in 1 male at 100 mg/kg/day. Post-Dose Recovery Necropsy: Unremarkable.
Toxicokinetics	BMS-626529 $AUC_{0\text{-}24h}$ increased with dose but less than dose proportional. No sex differences in $AUC_{0\text{-}24h}$ were observed and there was no accumulation. The metabolites BMS-930644 and BMS-646915 $AUC_{0\text{-}24h}$ were low and were <0.02x those of BMS-626529.

Toxicokinetics of 6-Month Oral Study of BMS-660368 in rats

		BMS-660368 (mg/kg/day)					
		30		100		300	
		Male	Female	Male	Female	Male	Female
Parameter	Period	BMS-626529 (Active Drug)					
C_{max} (µg/mL)	Day 1	31.0	51.3	65.8	90.2	102	110
	Day 30	41.8	60.6	87.3	135	190	209
	Day 180	60.8	104	133	175	194	276
$AUC_{0\text{-}24h}$ (µg.h/mL)	Day 1	315	468	956	1,280	1,790	2,360
	Day 30	409	488	1,110	1,400	2,850	2,720
	Day 180	593	908	1,740	1,990	2,890	3,570
T_{max} (h)	Day 1	2.0	1.0	6.0	1.0	6.0	4.0
	Day 30	2.0	1.0	4.0	1.0	4.0	4.0
	Day 180	2.0	1.0	2.0	1.0	4.0	4.0
		BMS-930644 (Major Metabolite)					
C_{max} (µg/mL)	Day 1	NA	NA	NA	NA	0.856	0.604
	Day 30	NA	NA	NA	NA	2.51	1.26
	Day 180	NA	NA	NA	NA	1.16	1.10
$AUC_{0\text{-}24h}$ (µg.h/mL)	Day 1	NA	NA	NA	NA	16.9	10.4
	Day 30	NA	NA	NA	NA	44.1	27.7
	Day 180	NA	NA	NA	NA	23.0	22.5
T_{max} (h)	Day 1	NA	NA	NA	NA	8.0	24
	Day 30	NA	NA	NA	NA	8.0	6.0
	Day 180	NA	NA	NA	NA	8.0	4.0
		BMS-646915 (Major Metabolite)					
C_{max} (µg/mL)	Day 1	NA	NA	0.489	0.464	1.01	0.712
	Day 180	NA	NA	1.13	1.11	2.55	2.51
$AUC_{0\text{-}24h}$ (µg.h/mL)	Day 1	NA	NA	6.42	6.20	16.2	12.7
	Day 180	NA	NA	11.0	10.1	28.7	27.5
T_{max} (h)	Day 1	NA	NA	1.0	1.0	8.0	4.0
	Day 180	NA	NA	2.0	1.0	4.0	4.0

Source: Applicant's table from NDA files
Abbreviations: $AUC_{0\text{-}24h}$, area under the curve from 0 to 24 hours; C_{max}, maximum plasma concentration; KLH, keyhole limpet haemocyanin; T_{max}, time to maximum plasma concentration.

BMS-663068: A 9-Month Oral Toxicity Study in Dogs Followed by a 2-Month Recovery (Study # DS09099):

Key Study Findings

BMS-663068 was administered daily as oral doses of 0, (vehicle), 10, 30, or 60 mg/kg/day to groups of 6 dogs per sex (2/sex/group included for recovery) for 9 months. The study revealed major target organs of toxicity being liver and testes. The uncertain testicular toxicity in the previous 1-month study was dismissed by the Applicant, appeared to be evident in this study.

The NOAEL was considered to be 30 mg/kg/day by the Applicant (Week 39 combined-sex mean $AUC_{0\text{-}24h}$ to be 177 µg.h/mL for BMS-626529). However, because histopathology findings were present in female liver and male testes at 10 mg/kg, there should be no NOAEL for this study.

Conducting laboratory: Charles River Laboratories, Montreal, QC, Canada

GLP compliance: Yes

Table 73. 9-Month Dog Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	BMS-663068 was administered daily as oral doses of 0, (vehicle), 10, 30, or 60 mg/kg/day to groups of 6 dogs per sex (2/sex/group included for recovery).
Route of administration:	Oral by capsule gavage 1 cap/dose/day
Formulation/vehicle:	Empty gelatine capsule
Species/strain:	Beagle dogs
Number/sex/group:	6
Age:	10 - 12 months
Satellite groups/unique design:	Same animals
Deviations affecting interpretation:	None

Source: Applicant's table from NDA files

Table 74. 9-Month Dog Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	Checked 2/day. No mortality.
Clinical signs	Checked 1-2/day. 60 mg/kg/day: salivation and wet fur. There were additional neurological and respiratory evaluations performed in treated groups and the results were unremarkable.
Body weights	Evaluated 2/week. Slight body weight decreases and reduced body weight gains in treated groups (these were nondose-related and not statistically significant)
Food consumption	Evaluated 1/day. Unremarkable.
Ophthalmoscopy	Evaluated 1/pretreatment, Weeks 12, 26, and 39 of treatment. Unremarkable.
ECG	Evaluated 1/pretreatment, Weeks 12, 26, and 39 of treatment. 60 mg/kg/day: tachycardia (consistent, both sexes, up to 135 bpm in males, for Week 26 females HR reached 175 bpm which was statistically significant). The Applicant indicated that this effect was inconclusive and might require further investigations.
Hematology	Clinical Pathology was evaluated 1/pretreatment, Weeks 4, 13, 26 and 39. Unremarkable.
Clinical chemistry	60 mg/kg/day: increases in total bilirubin (vs. pretreatment values in 3/6 females in Week 39; 2x - 3.4x). These increases were associated with liver histopathology and occurred only at this dose (unremarkable in recovery groups). Urinalysis was unremarkable
Gross pathology	Measured at study termination. Unremarkable.

Histopathology
Adequate battery: Yes
Peer review: Yes

Target organ 1:

Liver: females (all doses) & males at ≥30 mg/kg/day); increases in total bilirubin in females at 60 mg/kg/day correlated with bile deposits. Minimal to slight multifocal canalicular pigment deposits identified as bile (Hall's positive staining) occurred in 1 female at 10 mg/kg/day, 1 female and 2 males at 30 mg/kg/day and 3 females and 1 male at 60 mg/kg/day. In 2 additional males at 60 mg/kg/day and 1 additional female at 30 mg/kg/day, minimal canalicular bile lipofuscin pigment deposits in the Kupffer cells were also noted.

Dose (mg/kg/day):	0	10	30	60
No. of dogs (M/F):	4/4	4/4	4/4	4/4
Sex:	M/F	M/F	M/F	M/F
Liver: Pigment deposits: Kupffer cell				
Minimal	-/-	-/1	2/3	2/1
Slight	-/-	-/-	1/-	-/-
Pigment deposits: canalicular				
Minimal	-/-	-/1	2/1	1/1
Slight	-/-	-/-	-/-	-/2
Liver, Hall's: Positive staining: canalicular				
Minimal	-/-	-/1	2/2	3/1
Slight	-/-	-/-	-/-	-/2
Liver, Kinyoun's: Positive staining: Kupffer cell				
Minimal	1/1	3/1	2/1	2/3
Slight	-/1	-/1	1/2	2/1
Moderate	-/-	-/-	1/-	-/-

A dash (-) indicates absence of finding in group.

Target organ 2:

Testes: Minimal to slight unilateral or bilateral intratubular cellular debris in epididymides of a 1 male at 10 mg/kg/day, 1 male at 30 mg/kg/day and 3 males at 60 mg/kg/day BMS-663068 (not seen in controls). The Applicant stated that intratubular epididymal cellular debris is a common background change in dogs and considered it not clearly BMS-663068-related. Please note that testicular examination below showed degeneration/depletion or atrophy of seminiferous epithelium, which the Applicant did not remark probably because the control group showed similar incidences/frequency, which persisted through the recovery phase in the 10 and 30 mg/kg group while controls no longer showed similar incidences (NAD: nothing abnormal discovered).

Testicular histopathology findings in the treatment phase of 9-month dog study

Treatment Phase Dose (mg/kg):		0	10	30	60
Epididymis	Examin:	4	4	4	4
	N.A.D.	4	2	3	1
- Cellular debris: intratubular		-	1	1	3
	Grade 1	-	1	1	2
	Grade 2	-	-	-	1
- Infiltration: mononuclear cell		-	2	-	2

	Grade 1	-	2	-	2
- Vasculitis/perivasculitis		-	-	-	1
	Grade 2	-	-	-	1

Testis Examin: in treatment phase	4	4	4	4
N.A.D. (nothing abnormal discover).	2	1	1	1
- Degeneration/depletion:	1	3	1	2
seminiferous epithelium Grade 1	1	3	1	2
- Atrophy: seminiferous epithelium	2	1	3	2
Grade 1	1	1	1	2
Grade 2	1	-	1	-
Grade 3	-	-	1	-

Recovery Phase:

Liver: Not Reversible. Lipofuscin pigment deposits in the Kupffer cells persisted in both recovery males at 60 mg/kg/day. Microscopic findings persisted in the liver of females at ≥30 mg/kg/day and males at 60 mg/kg/day. Canalicular bile pigment deposits persisted in females at ≥30 mg/kg/day and 1 male at 60 mg/kg/day. The Applicant claimed liver toxicity profile partially reversed based on the generally decreased incidence and severity at 10 and 30 mg/kg/day. Serum bilirubin changes were not seen in the 2 recovery animals.

Text Table 3.8.3.2 Incidence of Noteworthy Hepatic Microscopic Findings (End of Recovery)

Dose (mg/kg/day):	0	10	30
No. of dogs (M/F):	2/2	2/2	2/2
Sex:	M/F	M/F	M/F
Pigment deposits: canalicular			
Minimal	-/-	-/-	-/1
Liver, Hall's: Positive staining: canalicular			
Minimal	-/-	-/-	-/1
Liver, Kinyoun's: Positive staining: Kupffer cell			
Minimal	1/1	1/-	1/1
Slight	-/-	-/-	1/-

A dash (-) indicates absence of finding in group.

Testis: One in low- and mid- dose group of the recovery animals (2/group) still showed degeneration/depletion or atrophy of seminiferous epithelium.

Testicular histopathology findings in the recovery phase of 9-month dog study

Testis in recovery phase:	2	2	2	2
N.A.D. (nothing abnormal discover).	2	1	1	1
Degeneration/depletion:	-	-	1	-
seminiferous epithelium Grade 1	-	-	1	-
Atrophy: seminiferous	-	1	1	1
epithelium Grade 1	-	1	-	-
Grade 2	-	-	1	1
Epididymis:	2	2	2	2
N.A.D.	2	2	2	2

Parameters	Major Findings
	Reviewer's Comment: *According to a publication (Toxicologic Pathology, 36: 465-471, 2008) that dogs assigned to the control group of an histopathology study with an age of <12 months old often showed spontaneous epididymal changes similar to those mentioned above in the current 9-month study. The age of dogs used here was 10-12 months old. It is not known whether the age-factor played a role in the current marginal findings.*
Toxicokinetics	BMS-626529 AUCs(0-24h) were approximately dose proportional, and there were no gender differences, and no accumulation (Day 1, Week 39). AUC_{0-24h} of the N-dealkylated metabolite BMS-930644 and debenzoylated metabolite BMS-646915 were ≤0.13x those of BMS-626529.

Mean Toxicokinetic Parameters for BMS-626529, BMS-930644, BMS-646915

Parameter	Period	10 mg/kg/day		30 mg/kg/day		60 mg/kg/day	
		Male	Female	Male	Female	Male	Female
BMS-626529							
Cmax	Day 1	10.7	10.2	33.1	25.7	42.9	34.9
(µg/mL)	Week 39	12.1	13.3	31.3	29.4	51.1	55.2
AUC (0-24h)	Day 1	58.4	42.9	184	121	297	238
(µg·h/mL)	Week 39	68.1	56.4	195	158	373	372
BMS-930644							
Cmax	Day 1	NA	NA	NA	NA	1.46	1.10
(µg/mL)	Week 39	NA	NA	NA	NA	2.18	2.62
AUC (0-24h)	Day 1	NA	NA	NA	NA	24.4	19.8
(µg·h/mL)	Week 39	NA	NA	NA	NA	33.7	48.0
BMS-646915							
Cmax	Day 1	NA	NA	0.293	0.263	0.604	0.445
(µg/mL)	Week 39	NA	NA	0.346	0.325	0.806	0.838
AUC (0-24h)	Day 1	NA	NA	3.26	2.39	7.03	5.52
(µg·h/mL)	Week 39	NA	NA	3.79	3.27	9.97	9.13

NA - Not applicable; plasma BMS-930644 not evaluated following 10 and 30 mg/kg/day doses of BMS-663068; plasma BMS-646915 not evaluated following 10-mg/kg/day doses of BMS-663068.

Source: Applicant's table from NDA files
Abbreviations: AUC_{0-24h}, area under the curve from 0 to 24 hours; bpm, beats per minute; ECG, electrocardiogram.

13.1.5.2. Genetic Toxicology

Mutagenicity Testing of BMS-663068 With *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 and *Escherichia coli* WP2 uvrA (Exploratory Study: #DS4147; Definitive Study: #DS5017)

Key Study Findings

BMS-663068 was not genotoxic in the bacterial mutation assay when tested (up to the maximum concentrations up to 5,000 µg/ml) either in the presence or absence of S9-mix. There were no drug-related increases in cytotoxicity or mean revertant counts in any of the BMS-663068 - treated cultures in this assay.

Mutagenicity Testing of BMS-626529 With *S. typhimurium* TA1535, TA1537, TA98 and TA100 and *E. coli* WP2 uvrA (Study: #DS4075)

Key Study Findings

BMS-626529 was not genotoxic in the bacterial mutation assay when tested (up to the maximum concentrations up to 5,000 µg/ml) either in the presence or absence of S9-mix. There were no drug-related increases in cytotoxicity or mean revertant counts in any of the BMS-626529-treated cultures in this assay.

Cytogenetics Study on BMS-663068 and BMS-626529 in Chinese Hamster Ovary Cells (Study: #DS4128 (BMS-663068) #DS5016 (BMS-626529))

Key Study Findings

BMS-663068 and BMS-626529 was not clastogenic in CHO cells when tested to the maximum concentrations up to 5,000 µg/ml. There were no statistically significant increases in the frequency of chromosome aberrations in any of the assays.

In Vitro Micronucleus Screening Assay in Study in Rats Following Oral Dosing with BMS-663068 (Study: #DS4289)

Key Study Findings

Administration of BMS-663068, which was rapidly converted to BMS-626529 in rat's systemic circulation, did not show genotoxic activities in the oral rat bone-marrow micronucleus test when evaluated up to the maximum dose (2,000 mg/kg po).

13.1.5.3. Carcinogenicity

BMS-663068: 6-Month Oral Carcinogenicity Study in CByB6F1 Mice

Key Study Findings

- BMS-663068 administered by oral gavage to transgenic mice at doses of 0, 30, 100, and 300 mg/kg/day in females; and 0, 25, 75, and 200 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 in both males (200 mg/kg dose at Week 26 $AUC_{0\text{-}24h}$ =450 µg.h/ml) and females (200 mg/kg dose Week 26 $AUC_{0\text{-}24h}$ =948 µg.h/ml) were sufficiently higher than the human AUC of 19.4 µg.h/ml observed.

BMS-663068: Two-Year Oral Gavage Carcinogenicity Study in Rats

Key Study Findings:

- Administration of BMS-663068 by oral gavage to Sprague-Dawley rats for 69 to 100 weeks at doses 10/5, 30/10 and at 100/20 mg/kg/day (in males) or 10, 30 and 100 mg/kg/day (in females) increased mortality in males given ≥30/10 mg/kg/day. No tumor findings, including pheochromocytoma, had met the statistical evaluation criteria for being indicated as statistically significant.
- There were neoplastic and non-neoplastic findings in the kidney and adrenal gland that were emergent as potential targets as results of long-term treatment of BMS-663068.
- Systemic drug exposures from the submortal group (i.e., LD as NOAEL) in males who survived to terminal sacrifice were around ~100 µg.h/ml, and those in LD females (NOAEL) survived to terminal sacrifice were around ~300 µg.h/ml, which were both higher than the human AUC of 19.4 µg.h/ml at the recommended clinical doses.

13.1.5.4. Reproductive Toxicology

BMS-663068 - Oral Study of Fertility and Early Embryo-Fetal Development in Rats (Study #DN11192)

Key Study Findings

This early embryonic development and fertility study in rats showed that male reproductive toxicities (i.e., reductions in prostate gland/seminal vesicle weights, and decreased sperm density) occurred at 100 and 300 mg/kg/day, additionally, decreased motility and increased abnormal sperm were reported at 300 mg/kg/day (NOEL =10 mg/kg, AUC =189 µg.h/ml). Reproductive effects observed in females were not significant at all doses tested (NOAEL =600 mg/kg; mean BMS-626529 AUC =3,610 µg.h/ml).

Conducting laboratory: Charles River Laboratories, Horsham, PA

GLP compliance: Yes

Table 75. Rat Oral Fertility and Early Embryo-Fetal Development Study Design

Methods	Details
Dose and frequency of dosing	Study Group 1: Males: 0, 10, 100, or 300 mg/kg/day; 70 days precohabitation, +14 days with untreated females, prior to scheduled euthanasia; Study Group 2: Females: 10, 100, or 600 mg/kg/day, 15 days precohabitation (with untreated males) through GD 7.
Route of administration	Oral gavage
Formulation/vehicle	H_2O
Species/strain	Sprague-Dawley rats (Crl:CD(SD))
Number/sex/group	25 /group
Satellite groups	10 females/group Day 14-15 for TK
Study design	

Methods	Details

2.6.2 Male Rats

Group Number	Daily Dose BMS-663068 (mg/kg/day)	Daily Dose Volume (mL/kg)	Concentration BMS-663068 (mg/mL)	Number of Males
1	0	5	0	25
2	10	5	2	25
3	100	5	20	25
4	300	5	60	25

2.6.1 Female Rats

Group Number	Daily Dose BMS-663068 (mg/kg/day)	Daily Dose Volume (mL/kg)	Concentration BMS-663068 (mg/mL)	Number of Females
1	0	5	0	25, 10[a]
2	10	5	2	25, 10[a]
3	100	5	20	25, 10[a]
4	600	5	120	25, 10[a]

Expressed as active ingredient – corrected for salt content and potency.
[a] Satellite female rats assigned to study for blood sample collected on Day 14 of study (DS 14).

Deviations affecting interpretation	None

Source: Applicant's table from NDA files

Table 76. Rat Oral Fertility and Early Embryo-Fetal Development Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Assessed at least once daily. Males MD & HD: excess salivation (slight, moderate, and/or extreme) and perioral substance (red, dried red, and/or yellow). HD: red perinasal substance in 2 males. Females MD & HD: excess salivation (slight and/or moderate), red or brown perioral substance, and urine-stained abdominal fur.
Body weights	Measured once daily. Unremarkable at LD.
Food consumption	Measured once weekly. Unremarkable except HD females and males showed reductions (16-18% v. control on Day1-8, without BW changes).
Estrous cycle	Unremarkable.
Fertility parameters	Unremarkable. The fertility index was not significantly changed.
Early Embryonic Development	Unremarkable except HD females showed preimplantation loss decreased vs. controls.

Parameters	Major Findings
Cesarean sections	The number of pregnant females was decreased from 25 in controls to 21 at the high dose (84% vs. 100% in controls) after the first cohabitation, but no changes were observed after the second cohabitation. and is within historical control ranges (78.3-100.0%). Because these percentages were within Applicant's historical ranges and was not repeated in the second cohabitation after a longer dosing period, these changes were likely incidental.
External fetal exams	No drug-related changes.
Necropsy findings	Unremarkable except HD males showed small epididymides (related to hypospermia or aspermia), and small, purple, and/or flaccid testes, (related to seminiferous tubule atrophy).
Organ weights	Males: decreased absolute and relative prostate with seminal vesicles (with or without fluid) weights (9 - 14% < controls) at HD and MD, decreased absolute and relative epididymal weights (left, right, and left cauda; 7- 10% < controls) at HD. Females: increased absolute adrenal gland weights at HD.
Sperm evaluation	Sperm density: reduced at HD and MD (17% and 28% <controls, respectively). Sperm motility: decreased at HD (80.2% motile vs. 92.3% in controls). Sperm morphology: 12.0% abnormal (detached heads or no heads) at HD vs. 0.9% in controls.
Histopathology	Testes: dose-dependent bilateral atrophy of seminiferous tubule epithelium (minimal to marked). Epididymis: dose-dependent increases in cell debris in epididymal ducts. There was minimal bilateral seminiferous tubule atrophy in 1 LD male and 1 MD male plus unilateral seminiferous tubule atrophy in some males at all dose groups (including controls) were remarked by the Applicant as background findings and were claimed to be occasionally observed in normal rats and in controls from other studies.

Table 2: Incidence of BMS-663068-Related Microscopic Findings

Dose (mg/kg/day):	0	10	100	300
No. of male rats:	25	25	25	25
Testes:				
Atrophy: seminiferous tubule: bilateral				
Minimal	-	-	-	8
Slight	-	-	1	2
Moderate	-	-	-	1
Marked	-	-	-	1
Epididymis, right:				
Cell debris: increased				
Minimal	-	-	1	5
Hypospermia				
Moderate	-	-	-	1
Aspermia	-	-	-	1

Toxicokinetics	TK profiles of this study are shown in Applicant's table below. AUC increased less than dose proportional at MD and HD. No gender differences were observed at LD and MD. After repeated dosing, mean AUC for both metabolites BMS-930644 and BMS-646915 were <0.009x those of BMS-626529.

Parameters	Major Findings						
		BMS-663068 Dose (mg/kg/day)					
Parameter	Day	10		100		300	600
		M	F	M	F	M	F
		BMS-626529					
Cmax (µg/mL)	14	NA	22.3	NA	133	NA	220
	94	20.6	NA	108	NA	150	NA
AUC(0-24h) (µg•h/mL)	14	NA	166	NA	1640	NA	3610
	94	189	NA	1560	NA	2420	NA
NA: Not applicable							

Source: Applicant's table from NDA files
Abbreviations: AUC, area under the curve; HD, high dose; LD, low dose; MD, intermediate dose; TK, toxicokinetics.

BMS-663068 – 10-Day Oral Range-Finding Study in Pregnant Rats (Study #DN09011)

Key Study Findings

This is a non-GLP embryo-fetal pilot study performed in the rat (0, 100, 300, 600, or 1,000 mg/kg/day, from gestation Day 6 to 15). No developmental toxicity occurred at doses ≤600 mg/kg/day (AUC: 3,980 µg.h/mL), which was selected as the top dose of the later definitive EFT study (see below). Maternal toxicity occurred at 1,000 mg/kg with the following findings: decreased food consumption (56%), abnormal clinical chemistry (decreased BUN [0.77×], K [0.85×], eosinophil counts [0.39× control] and low fetal body weight (8.4% less than controls). Teratogenic effects occurred at the maternal toxic dose of 1,000 mg/kg/day (AUC: 4,750 µg.h/mL) with findings presented in the head and jaw (cleft palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw, and protruding tongue) in 21 (20.4%) fetuses from 5 (62.5%) litters of this dosage group.

BMS-663068 - Oral Study of Embryo-Fetal Development in Rats (Study #DN10017)

Key Study Findings

This embryo-fetal study in the rat did not show any teratogenicity findings at all doses of BMS-663068 tested. At the HD of 600 mg/kg/day, Incidences of fetal variations (supernumerary ribs) were increased (14% vs. 6% of control offspring) that were not considered teratogenic. NOAEL for both maternal and fetal toxicity were 600 mg/kg/day (maternal BMS-626529 AUC =3,840 µg.h/ml).

Conducting laboratory: BMS Research Laboratory

GLP compliance: Yes

Table 77. Rat Oral Female Fertility and Embryofetal Developmental Study Design

Methods	Details
Dose and frequency of dosing	0 (water), 50, 200, and 600 mg/kg/day, GD 6 to 15 inclusive
Route of administration	Oral gavage

Methods	Details
Formulation/vehicle	H_2O
Species/strain	Sprague-Dawley rats: Crl: OFA (SD) Charles River Laboratories Raleigh, NC. Age: ~9 - 10 weeks at mating.
Number/sex/group	22 females/group
Satellite groups	8 TK, Day 15
Study design	

Group Number/ Treatment	Dose Level (mg/kg/day)[a]	Dose Volume (mL/kg/day)	Dose Concentration (mg/mL)[a]	Number of Female Rats	
				Main Study	Satellite
1.Control/vehicle	0	4	0	22	8
2. Low dose (LD)	50	4	12.5	22	8
3. Intermediate dose (MD)	200	4	50	22	8
4. High dose (HD)	600	4	150	22	8

[a] Expressed as active ingredient – corrected for salt content and potency.

Deviations affecting interpretation	None

Source: Applicant's table from NDA files
Abbreviation: GD, gestation day; TK, toxicokinetics.

Table 78. Rat Oral Female Fertility and Embryofetal Developmental Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. No drug-related findings.
Body weights	Measured once daily. Unremarkable at LD. BW losses at ≥ MD (2.2 for MD and 5.3 g HD from GDs 6 to 7, respectively, vs. gain of 3.2 g in controls; 2 to 3% < controls on GD 7. After GD7: unremarkable.
Food consumption	Measured 1-3× weekly. Unremarkable except ≥ MD showed reduced food consumption (14 to 43% < control from GDs 6 to 8).
Fertility parameters	No drug-related findings.
Necropsy findings	No drug-related findings.
Cesarean sections	No drug-related findings. Litter data were unremarkable including corpora lutea, implantations, live and dead fetuses, resorption indices, fetal sex ratios, and fetal body weights at GD21.
Fetal examinations	No significant treatment-related teratogenicity finding. No BMS-663068-related changes in fetal gross external or visceral evaluations at the doses tested. External observations: Unremarkable. Visceral findings: Convoluted or distended ureters were seen in all groups and controls (common findings in rats of this strain). Innominate artery was absent in 1 MD and 3 HD fetuses (variations within historical controls). Skeletal observations: Incidences of lumbar and cervical ribs were increased in HD (which resulted in overall increases in variations 14% of fetuses with variations relative to 6% in controls; the Applicant stated that supernumerary ribs were a common background finding in rodent fetuses)
Toxicokinetics	TK profiles of this study are shown in the table below. C_{max} and AUC_{last} increased less than dose proportional. T_{max} were 2-4hrs.

Parameters	Major Findings		
	BMS-663068 Dose (mg/kg/day)		
	50	200	600
Parameter	BMS-626529		
C_{max} (µg/mL)	67.2	167	225
AUC_{0-24h} (µg.h/mL)	837	2,410	3,840
T_{max}(h)	2.0	2.0	4.0

Source: Applicant's table from NDA files
Abbreviations: AUC_{0-24h}, area under the curve from 0 to 24 hours; BW, body weight; $C_{max,}$ maximum plasma concentration; GD, gestation day; HD, high dose; LD, low does; MD, intermediate dose; TK, toxicokinetics; T_{max}, time to maximum plasma concentration.

BMS-663068 – 13-Day Oral Range-Finding Study in Pregnant Rabbits (Study #DN09038):

Key Study Findings

This is a non-GLP range-finding EFT study on BMS-663068 in pregnant rabbits (0, 50, 100, 250, or 500 mg/kg/day from gestation Day 7 to 19). Maternal toxicity (≥250 mg/kg/day; AUC ≥2,760 µg.h/mL) occurred in the 2 high dosage groups, as a result of inappetence. Severe inappetence caused decreased fold change (FC) (<30 g/day 2 to 11 days) and weight loss (loss of 380 g and 150 g at 250 and 500 mg/kg/day, respectively, versus gain of 180 g in controls GD 7 to 20). There were 1 (GD 17), 2 deaths (GD 12), and 1 abortion (GD 18, 500 mg/kg/day), due primarily to inappetence, with the rest of females euthanized for humane reasons (GD 17 to 20). At euthanasia or abortion, BW lost by 11 to 24% from GD 7's own levels, FC reduced by ≤85% versus controls. Other maternal toxicity included dose-related elevations in serum bilirubin (3.25 to 16x control), triglyceride (2.9 to 3.9x control) and cholesterol (1.8 to 3.2x control) in the 2 high dosage groups. Developmental toxicity occurred at ≥100 mg/kg/day (AUC ≥1,230 µg.h/mL). For the 100 mg/kg/day group, postimplantation loss was slightly increased (8.7% versus controls 2.4%). For the 2 high dosage groups, postimplantation losses were high in 2/6 does at 250 and 4/5 does at 500 mg/kg/day, with 100% early resorptions. Fetuses from remaining does appeared to be normally-developed.

No teratogenic finding was revealed in this rabbit dose-range-finding EFT study. NOAEL for maternal toxicity was 100 mg/kg/day (maternal BMS-626529 AUC =1230 µg.h/mL). NOAEL for developmental toxicity was 50 mg/kg/day (AUC =485 µg.h/mL).

BMS-663068 - Oral Study of Embryo-Fetal Development in Rabbits (Study #DN10019):

Key Study Findings

BMS-663068 was administered once a day (QD) by oral gavage at doses of 0 (vehicle), 25, 50, 100 mg/kg/day to pregnant rabbits on Gestation Day (GD) 7 to 19. No teratogenic finding was revealed in this definitive rabbit EFT study. The NOAEL for maternal (reduced BW/FC) and developmental toxicity (increased postimplantation loss) was 25 and 50 mg/kg/day, respectively (maternal BMS-626529 AUC =328 and 626 µg.h/ml). In the previous rabbit range-finding study (report submitted under SN115/SDN132), NOAEL for maternal toxicity was 100 mg/kg/day (AUC =1,230 µg.h/mL) and NOAEL for developmental toxicity was 50 mg/kg/day (AUC =485 µg.h/mL).

Conducting laboratory: BMS Research Laboratory

GLP compliance: Yes

Table 79. Rabbit Oral Embryofetal Developmental Study Design

Methods	Details
Dose and frequency of dosing	0 (water), 25, 50, 100 mg/kg/day, GD 7 to 19 inclusive
Route of administration	Oral gavage
Formulation/vehicle	H_2O
Species/strain	Female rabbits Hra:(NZW)SPF rabbits (Covance Research Products, Denver, PA).
Number/sex/group	22 pregnant rabbits/group
Satellite groups	5 does/group 2-5 for TK, Day 20
Study design	

Group Number	Daily Dose BMS-663068 (mg/kg/day)	Daily Dose Volume (mL/kg)	Concentration BMS-663068 (mg/mL)	Number of Females Assigned to Study[a]
1 (Control)	0 (Vehicle)	5	0	27
2	25	5	5	27
3	50	5	10	27
4	100	5	20	27

[a] The first 22 rabbits/group were used for maternal and developmental toxicity evaluations and the remaining 5 rabbits/group were used for maternal TK evaluations

Deviations affecting interpretation	None

Source: Applicant's table from NDA files
Abbreviations: GD, gestation day; TK, toxicokinetics.

Table 80. Rabbit Oral Embryofetal Developmental Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. Absent/scant feces (50 and 100 mg/kg/day).
Body weights & food consumption	Reduced FC at 50 and 100 mg/kg/day (15% and 22%, respectively, vs. control during the dosing interval) with concurrent reduced maternal weight gain (does gained 0.11 and 0.08 kg, respectively, vs. control of 0.22 kg).
Necropsy findings	No drug-related findings.

Parameters	Major Findings
Litter data	100 mg/kg/day: increased postimplantation loss (8.6% vs. 0.9% in controls) without concomitant reduction in mean litter size; 6 of 22 does had postimplantation loss that were >20%. The Applicant indicated that this reflected more extensive postimplantation loss at higher doses that were seen in the dose range-finding study (report submitted under SN115/SDN132). In that dose range-finding study, severe inappetence caused a high postimplantation loss, accompanied by dose-related decreases in BW/FC and increases in serum bilirubin (3.25-16x control), triglyceride (2.9-3.9x control) and cholesterol (1.8-3.2x control)(250-500 mg/kg), without any teratogenic effects.
Fetal examinations	No drug-related fetal gross alterations in fetal external, visceral, or skeletal evaluations.
Toxicokinetics	On GD19, the converted active drug BMS-626529 AUCs increased with doses studied (T_{max} =1-1.2hrs).

Parameter	BMS-663068		
	25 mg/kg/day	50 mg/kg/day	100 mg/kg/day
	BMS-626529		
Cmax (µg/mL)	55.8	102	189
AUC[0-24h] (µg•h/mL)	328	626	1320

Source: Applicant's table from NDA files
Abbreviations: AUC, area under the curve; BW, body weight; FC, fold change.

BMS-663068 - Oral Study of Pre- and Postnatal Development in Rats (Study #DN15030)

Key Study Findings

This pre- and postnatal development study in rats showed no significant maternal toxicity at 300 mg/kg (maternal NOAEL AUC =2,550 µg.h/mL) and a decreased pup survival during the peak lactation period (LD/PNDs 7 to 14) without commensurate maternal toxicity. The Applicant concluded that BMS-663068 is a selective developmental toxicant in postnatal life (developmental NOAEL =100 mg/kg/day AUC679 µg.h/ml).

Conducting laboratory: Charles River Laboratories, Senneville, Canada

GLP compliance: Yes

Table 81. Rat Oral Pre- and Postnatal Development (PPND) Study Design

Methods	Details
Dose and frequency of dosing	0, 10, 50, or 300 mg/kg/day;(GD 6 through postnatal Day 20).
Route of administration	Oral gavage
Formulation/vehicle	H_2O
Species/strain	Sprague-Dawley rats (Crl:CD(SD))
Number/sex/group	25 females/group
Satellite groups	5/group as sentinel
Study design	

Methods	Details

Group No. Identification	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg/day)	F0 Female Identification
1/ Vehicle control	0	0	5	151-175
2/ BMS-663068	10	2	5	251-275
3/ BMS-663068	50	10	5	351-375
4/ BMS-663068	300	60	5	451-475
5/ Sentinel	-	-	-	551-552

Deviations affecting interpretation: None

Source: Applicant's table from NDA files
Abbreviations: GD, gestation day; PND, postnatal day.

Table 82. Rat Oral Pre-and Postnatal Development (PPND) Study Findings (F_0 Generation)

Parameters	Major Findings
Mortality	None was determined to be treatment related (11 F0 terminated including 5 controls).
Clinical signs	Examined at least once daily. Unremarkable except that during lactation, there were salivation and increased incidences of red fur staining in F0 females at ≥10 mg/kg/day, with sporadic episodes of wet fur (on the lower jaw) also noted at 300 mg/kg/day.
Body weights	Measured once daily. Unremarkable at ≤50 mg/kg/day. 300 mg/kg/day: decreased maternal weight gains on GDs 6 - 8 (1.7 g vs. 9.0 g in controls, including weight loss after the initial dose), with 2% - 3% decreases in maternal body weights on GDs 7 - 20. Unremarkable during lactation.
Food consumption	Unremarkable at ≤50 mg/kg/day. 300 mg/kg/day: decreased maternal food consumption (26% - 33% < controls; GDs 6 – 8) and lower overall food intake on GD 6 - 21 (-7% vs. controls). Unremarkable during lactation.
Pregnancy status	Unremarkable (F0).
Necropsy findings	No drug-related findings.
Toxicokinetics	Converted active drug BMS-626529's systemic exposures ($AUC_{0\text{-}24h}$) in dams on PND 4 increased approximately dose proportionally between 10 and 50 mg/kg/day, and less than dose proportionally between 50 and 300 mg/kg/day. On PND 11, mean milk BMS-626529 concentrations at 2 hours postdose were similar to or lower than (0.5 to 1.2×) the corresponding plasma concentrations. On PND 4, mean BMS-626529 plasma concentrations in pups at 4 hours after maternal dosing were lower (0.1×) than maternal concentrations.

Parameters	Major Findings

BMS-626529 Toxicokinetic Summary

Parameter	BMS-663068 Doses (mg/kg/day)		
	10	50	300
Maternal AUC0-24h on LD 4 (µg•h/mL)	114	679	2550
Maternal Milk/Plasma Conc. on LD 11 (µg/mL)	10.8/9.29	29.8/41.8	58.2/123
Pup/Maternal Plasma Conc. on LD 4 (µg/mL)	1.50/10.2	5.60/46.4	13.2/130

Note: LD (Lactation Day) in dams is also known as PND (Postnatal Day) in pups.
Conc. = Concentrations

Source: Applicant's table from NDA files
Abbreviations: $AUC_{0\text{-}24h}$, area under the curve from 0 to 24 hours; GD, gestational day; PND, postnatal day.

Table 83. Rat Oral Pre- and Postnatal Development (PPND) Study Findings (F_1 Generation)

Parameters	Major Findings
Mortality	Unremarkable for the number of pups delivered or pup viability at birth. However, at PND 7-14 decreased pup survival was noted at 300 mg/kg/day, with 16 pups from 7 litters affected. Thus, overall survival index (PND 14, 91.7%) at 300 mg/kg/day was decreased (controls =98.7%). The affected pups (300 mg/kg/day) showed decreased activity, suspected dehydration/empty stomach, thinness, weakness, deep/labored breathing, cold to touch, and/or lying on side (no gross lesion necropsy findings).

Table 3.9-1: Incidences of Pup Mortality During PNDs 7 to 14

Day of Occurrence (PND)	Maternal BMS-663068 Dose (mg/kg/day)			
	0	10	50	300
7	-	-	-	2 (1M, 1F)
8	-	2 (M)	-	-
9	-		-	7 (6M, 1F)
10	-	1 (M)	1 (M)	1 (F)
11	-	-	-	2 (1M, 1F)
12	1 (M)	-	-	3 (2M, 1F)
13	-	1 (M)	-	-
14	1 (M)	-	-	1 (F)

A dash (-) indicates absence of findings in the group.
M = Male
F = Female

Clinical signs	Examined at least once daily. Unremarkable.
Body weights	Measured 1-2× weekly. Unremarkable.
Food consumption	No drug-related findings.
Sexual maturation	Unremarkable.
Behavior and activity	Unremarkable.
Fertility parameters	No drug-related findings.
Pregnancy parameters	Unremarkable.
Necropsy observations	No drug-related findings.

Source: Applicant's table from NDA files
Abbreviation: PND, postnatal day.

13.1.5.5. Other Toxicology / Specialized Studies

BMS-663068: Three-Month Oral Qualifying Toxicity Study in Rats (Study #DN12011)

Key Study Findings

This 3-month 1-dosage (300 mg/kg/day) rat study confirmed previous 6-month repeat-dose study that uncovered 3 major target histological organs of toxicity: kidney, adrenal gland, and testes, in addition to the hematological changes. Toxicity profile and severity of toxicity appeared to be not significantly different between two formulation (BMS-663068-SP and BMS-663068-NS [nonspiked]) treatment groups. BMS-663068-SP group was spiked with 7 impurities (BMS-912805, BMS-912806, BMS-736822, BMS-926465, BMS-932208, BMT-069583, and BMT-067434), each at ≤0.8% for a total impurity level of approximately 3%, thus of the study could be used to qualify BMS-663068 batches containing these specified impurities, as they did not alter the toxicity profile (target organs) of FTR. Nevertheless, the study provided and bridged information on toxicity profile at the treatment duration of 3-month. (Another qualifying rat study with identical study design was performed with 2 other impurities, BMT-128716, BMT-226853 [study 339280], that showed similar findings without altering overall toxicity profile of FTR).

Conducting laboratory: Testing: WuXi AppTec (Suzhou) Co., Ltd. 1318 Wuzhong Avenue, Wuzhong District, Suzhou 215104, China

Bioanalytical: Intertek Pharmaceutical Services (formerly Alta Analytical Laboratory), 1100 Windfield Way, El Dorado Hills, CA

GLP compliance: Yes

Table 84. 3-Month Rat Oral Qualifying Toxicity Study Design

Methods	Details
Dose and frequency of dosing	Vehicle (water) or 300 mg/kg/day for 3 months
Route of administration	Oral gavage
Formulation/vehicle	H_2O
Species/strain	Sprague-Dawley Crl:CD (SD), (*Rattus norvegicus*)
Number/sex/group	10
Age	6 weeks
Satellite groups/unique design	NA
Deviations affecting interpretation	None

Description	(mg/kg)	(mL/kg)	(mg/mL)	Male	Female
1/vehicle control	0	5	0	1,001-1,010	1,501-1,510
2/BMS-663068-NS	300	5	60	2,001-2,010	2,501-2,510
3/BMS-663068-SP	300	5	60	3,001-3,010	3,501-3,510

Source: Applicant's table from NDA files

Table 85. 3-Month Rat Oral Qualifying Toxicity Study Findings

Parameters	Major Findings
Mortality	Checked 2/day. None reported.

Parameters	Major Findings
Clinical signs	Checked 1-2/day. Salivation (5/10 - 8/10 males, 7/10 females in both treated groups). Red/brown material around the mouth/nose (7/10 - 9/10 in males, 7/10 - 10/10 females in both treated groups).
Body weights	Measured 1/week. BW gain reduced in Week 1 (16% - 30% in males, 32% - 43% in females vs. controls) in both treated groups. No differences between the spiked and nonspiked groups.
Food consumption	Measured 1/week. Reduced in Week 1 (12% - 14% in males, 14% - 17% in females vs. control). No differences between the spiked and nonspiked groups.
Ophthalmoscopy	Measured 1/pretreatment, 1/13th week of treatment. Unremarkable.
Hematology	Evaluated pretest and at termination. BMS-663068-NS: increased lymphocytes (1.46× control) with corresponding increases in WBC (1.41× control) in males (see below). BMS-663068-SP: decreased RBC (0.94× control), Hb (0.94× control), Hct (0.93× control) in males; and decreased eosinophil % (0.44× control) and count (0.56× control) in males (see below). These hematology changes had been reported in prior rat studies. The changes were considered nonadverse due to its magnitude.

Hematology findings (ratios, compared to controls) in the three-month rat oral qualifying toxicity study

	300 NS		300 SP	
Dose (mg/kg/day)	**Male**	**Female**	**Male**	**Female**
White blood cells	1.41	-	-	-
Lymphocyte count	1.46	-	-	-
Eosinophil count	-	-	0.56	-
Eosinophil percentage	-	-	0.44	-
Red blood cells	-	-	0.94	-
Hemoglobin	-	-	0.94	-
Hematocrit	-	-	0.93	-
Red cell distribution width	1.05	1.09	1.11	1.05
Reticulocyte count	1.15	1.35	1.31	1.17

Clinical chemistry	Decreases in serum K (0.80 to 0.85× control) and Cl (0.96 to 0.98×control); increases in bicarbonate (total CO_2) (1.13 to 1.15× control); and increases in serum total cholesterol (1.22 to 1.23× control) in females. Similar changes had been reported in previous rat studies. The differences between the spiked and nonspiked groups were considered by Applicant to be not toxicologically significant.
Urinalysis	Increased urine volume (1.67 - 2.33xcontrol) and decreased urine pH (0.90 - 0.91xcontrol), plus: BMS-663068-NS: decreased urine creatinine in males (0.60xcontrol) BMS-663068-SP: increased urine total protein output in males (2.63xcontrol). Similar changes had been reported in the previous rat studies, and the differences between the spiked and nonspiked formulation were considered by Applicant to be not toxicologically significant.
Gross pathology	Measured at study termination. 1. Dark focal discoloration of the adrenal gland (1 female NS BMS-663068; correlated microscopically with angiectasis). 2. Small thymus (males NS BMS-663068; 2 males and 2 females SP BMS-663068; plus1 control female; no microscopic correlates). 3. Enlarged spleen (1 male treated NS BMS-663068; no microscopic correlates).

Parameters	Major Findings
Histopathology Adequate battery: Yes Peer review: Yes	Target organs of toxicity were: adrenal gland, kidney, spleen and testes (see also table below): 1. Angiectasis in the adrenal glands: females of both groups, correlated to organ weights increases in females. Increased severity of cortical vacuolation of the adrenal noted in 2 males (nonspiked BMS-663068, but considered to be incidental by Applicant [but this was also reported in males of 6-month study). BMS-663068-related adrenal angiectasis of female rats has been observed previously in prior 6-month study (including angiectasis and high organ weight in males). The differences in incidence or severity between nonspiked and spiked groups were not considered significant. 2. Tubular dilatation of the kidneys: Increased incidence and severity of multifocal dilatation of renal tubules (males and females for both groups); characterized by a widening of the tubule lumen in the corticomedullary and outer medullary region (correlated to increased kidney weights). Dilatation of cortical tubules was previously observed in the 6-month rat study (males and females). 3. Increased extramedullary hematopoiesis of the spleen: occurred in 1male/3 females of the nonspiked and 2 males/3 females for spiked groups. 4. Testicular degeneration: 2 males treated with spiked BMS-663068.

Parameters	Major Findings

Text Table 3: Incidence of BMS-663068-related Microscopic Findings

	Dose (mg/kg/day):	0	300 NS	300 SP
	No. of Rats (M/F):	10/10	10/10	10/10
	Sex:	M/F	M/F	M/F
Adrenal Gland:				
Angiectasis				
Minimal		1/2	0/6	0/5
Slight		-	-	0/2
Kidneys:				
Dilatation, tubular lumen				
Minimal		0/1	4/5	6/5
Slight		-	2/1	2/1
Mild		-	-	0/1
Spleen:				
Hematopoiesis, extramedullary, increased				
Minimal		-	1/3	3/2
Testes:				
Degeneration, seminiferous tubule				
Slight		-	-	1/0
Mild		-	-	1/0

Toxicokinetics	Blood sampled on Day 1 and Day 86 (0.5-ml from 3-4 males or 3-4 females/group/timepoint at 1, 2, 4, 8, and 24 hours after dosing). Results: AUC: BMS-663068-SP ≈BMS-663068-NS (males ≤ females: 0.6 to 0.7×). After repeated dosing, AUCs were 1.1 - 1.2 × first dose (steady state).

Toxicokinetics of Three-Month Oral Qualifying Toxicity Study in Rats

		BMS-663068-NS 300 mg/kg/day		BMS-663068-SP 300 mg/kg/day	
Parameter	**Timepoint**	**Male**	**Female**	**Male**	**Female**
C_{max}	Day 1	135	156	139	179
(µg/mL)	Week 13	192	232	156	233
AUC_{0-24h}	Day 1	1,960	3,200	2,230	3,040
(µg.h/mL)	Week 13	2,440	3,820	2,370	3,400
T_{max}	Day 1	2.0	8.0	8.0	1.0
(h)	Week 13	2.0	4.0	2.0	1.0

Source: Applicant's table from NDA files
Abbreviations: BW, body weight; RBC, red blood cell; WBC, white blood cell.

BMS-663068: Ten-Week Oral Toxicity Study in Juvenile Rats With an Eight-Week Recovery Period (Study # DN15031)

Key Study Findings

This juvenile rat (3-week old) study on BMS-663068 did not uncover remarkable organ-weight changes or macro- and microscopic findings at the doses tested (up to 100 mg/kg/day po during postnatal days 21 to 90). This study was intended to provide nonclinical safety information in support of indications in children at ≥2 years of age.

Conducting laboratory: Charles River Laboratories Montreal, Canada

GLP compliance: Yes

Table 86. Ten-Week Juvenile Rat Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing	Vehicle (water), 10, 30, or 100 mg/kg from postnatal days (PNDs) 21-90 (see experimental design below)
Route of administration	Oral gavage, 1/day
Formulation/vehicle	H_2O
Species/strain	Sprague-Dawley Crl:CD (SD) rats
Number/sex/group	Subset 1: 10/sex/group; Subset 2: 15/sex/group; TK: 4/sex/control group & 20/sex/group 2-4
Age	3 weeks
Satellite groups/unique design	TK: 4/sex/control group & 20/sex/group 2-4
Deviations affecting interpretation	None

Group No.	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Conc. (mg/mL)	No. of F_1 Rats Assigned					
				Subset 1[a]		Subset 2[a]		TK Satellite[b]	
				M	F	M	F	M	F
1/ Vehicle Control	0	5	0	10	10	15	15	4	4
2/ BMS-663068	10	5	2	10	10	15	15	20	20
3/ BMS-663068	30	5	6	10	10	15	15	20	20
4/ BMS-663068	100	5	20	10	10	15	15	20	20
5/ Sentinels	-	-	-	2[c]	2[c]	2[c]	2[c]	-	-

Each group had 2 subsets. Subset 1 (10/sex/group) was euthanatized at the end of the dosing period on PND (postnatal day) 91, whereas Subset 2 (15/sex/group) continued on study and was evaluated for reversibility (of any observed changes) and reproductive performance. Scheduled necropsies for Subset 2 were conducted on PND 147. Observations included viability, clinical signs, body weights, food consumption, sexual maturation, estrous cyclicity, ophthalmoscopy, BMS-626529 toxicokinetics (PND 84), clinical pathology, mating, fertility, organ weights, and gross/microscopic pathology. Conceptuses/pups of the Subset-2 rats were evaluated (at scheduled cesarean-sections on Gestation Day 13 or during the first 7 days after birth) for viability, body weights, and/or alterations in gross external morphology. Additionally, plasma concentrations of BMS-663068 and/or BMS-626529 were determined in satellite rats on PND 21.

[a] Groups 1-4 were dosed from PNDs 21 to 90 (Main Study). Scheduled necropsies were conducted on Subset-1 rats at the end of the dosing period (PND 91) and on Subset-2 rats at the end of the recovery period (PND 147).

[b] TK groups were dosed on PND 21 and euthanatized after TK sampling on PND 21 or 22.

[c] Sentinel rats were not dosed; they were evaluated for parameters described in the study plan/protocol.

Source: Applicant's table from NDA files

Abbreviations: Conc., Concentration; F, females; M, males; NA, not applicable, PND, postnatal day; TK, toxicokinetics.

Table 87. 10-Week Juvenile Rat Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	All males survived to scheduled termination. Nine females (3 controls, 3 10 mg/kg/day, 2 30 mg/kg/day, and one 100 mg/kg/day) were found dead or euthanatized due to non BMS-663068-related events.
Clinical signs	Not reported.
Body weights	Unremarkable.
Food consumption	Unremarkable.
Ophthalmoscopy	Unremarkable.
Hematology	End of the Dosing Period (PND 91): There were decreases (0.93x controls) in RBC counts, Hb and Hct in females at 100 mg/kg/day. Similar changes had been reported in previous adult rat studies. Decreases in mean platelet volume were observed in females at both 10 and 30 mg/kg/day, which were not considered treatment related by the Applicant as it was not dose-related. End of the Recovery Period (PND 147): Unremarkable.
Clinical chemistry	End of the Dosing Period (PND 91): There were decreases (0.89× to 0.94×) in potassium in both sexes and decreases (0.91× to 0.92×) in total protein, albumin, and globulin in females at 100 mg/kg/day. Similar changes had been reported in previous adult rat studies. Urinalysis was unremarkable. End of the Recovery Period (PND 147): Unremarkable. Urinalysis was unremarkable.
Gross pathology	1. Main Group (subset 1, PND 91): Changes in mean organ weights were neither dose-related nor statistically significant and were not considered to be BMS-663068-related. The gross pathology findings (including unscheduled subsets 1 and 2 necropsies) were low in incidence, common background changes seen in rats, and/or independent of dose and were not considered BMS-663068-related. 2. Recovery Group (subset 2, PND 147): Changes in mean organ weights were related to the absolute or relative weights only (i.e., adrenal weight in males), not dose-related and were not considered to be BMS-663068-related. The gross pathology findings were low in incidence, common background changes seen in rats, and/or independent of dose and were not considered BMS-663068-related.

Parameters	Major Findings
Histopathology Adequate battery: Yes Peer review: Yes	1. Main Group (subset 1) and Unscheduled (Subsets 1 and 2) Necropsies: No BMS-663068-related histopathologic findings at PND-91necropsies were reported. Minimal mixed cell infiltrate in the heart (compatible with early cardiomyopathy), was reported in 6/10 males at 10 mg/kg/day and 4/10 males at each dose of 30 and 100 mg/kg/day. The incidences were higher than the concurrent controls (2/10 males affected), the Applicant considered it nontreatment related as they were not dose dependent and the values at ≥30 mg/kg/day were within the test facility's historical control range. The Applicant indicated that the incidence of murine progressive cardiomyopathy in individual studies ranged from 0 to 40% based on 11 studies conducted at this test facility [2007-2012], in which 110 males Crl:CD(SD) rats (approximately 2 - 4 months old) were evaluated. 2. Recovery Group (subset 2): No BMS-663068-related histopathologic findings at PND-147 were reported. No further finding in the heart was remarked.
Toxicokinetics	AUC_{0-t} (BMS-626529) increased with dose. AUC on PND 21 were 0.3× - 0.5× those on PND 84. BMS-663068 was detected in approximately 5% of the plasma samples (at 100 mg/kg/day on PND 21, and the levels were <0.1% of those for BMS-626529.

Toxicokinetics of 10-Week Oral Study of BMS-660368 in Juvenile Rats

BMS-626529 Toxicokinetic Summary - Mean-Sex Combined Values

Parameter	Age	BMS-663068 Dose		
		10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Cmax (µg/mL)	PND 21	10.2	28.8	59.3
	PND 84	18.0	46.5	126
AUC0-24h (µg•h/mL)	PND 21	49.2[a]	216	729
	PND 84	153	454	1,360

[a] Calculated from AUC0-8h values; as plasma concentrations at 24 hours postdose were below the assay LLOQ (0.2 µg/mL).

Source: Applicant's table from NDA files
Abbreviations: AUC, area under the curve; AUC_{0-t}, area under the curve to the last quantifiable time point; PND, postnatal day.

13.1.6. Impurities/Degradants

Two 13-week oral rat impurity qualification toxicity studies, one rat oral micronucleus study, and Ames bacterial mutagenicity studies were performed and showed that they did not alter the toxicity of FTR. FDA has accepted Applicant's CMC control strategy for seven mutagenic impurities (including intermediates BMS 983533, 371000 and 931691; and 4 contained in the starting material or reagents) that would be based on ICH M7 approach, which included that each impurity would be purged and kept below the specification <30% of the ICH M7 TTL-based acceptable limit of 1.2 µg/day for the daily dose of FTR, 1,200 mg/day).

BMT-218946, a beta-lactam photodegradant impurity (formed under short wavelength visible light) had been thoroughly studied and reviewed by both FDA and Applicant's expert panels. It was concluded that systemic sensitizing potential of the photodegradant is orders-of-magnitude less than that of beta-lactam antibiotics (e.g., penicillins, cephalosporins) and trace quantities of

BMT-218946 are judged very unlikely to produce acute allergic reaction in patients previously sensitized to a beta-lactam antibiotic.

13.1.7. Referenced NDAs, BLAs, DMFs

Not applicable.

13.1.8. Individual Reviews of Studies Submitted to the NDA

Two reports on the active drug, BMS-626529, were included in the NDA submission that were not submitted to the IND previously. They are reviewed below.

BMS-626529: 2-Week Oral Toxicity Study in Dogs (Study #DS04097):

Key Study Findings

BMS-626529 was administered BID (4 hours apart, oral gavage) to beagle dogs (3/sex/group) at 0 (vehicle control), 15, 75, or 250 mg/kg/day for 14 consecutive days. Liver appeared to be the target organ that increases in Kupffer cell pigmentation were observed in livers of 2/3 treated males and females in all treatment groups. The NOAEL was not designated as this report was submitted as a draft and unaudited format to the NDA (not previously submitted to the IND). As the current drug product is not presented in a formulation of BMS-626529 (instead, in the prodrug BMS-663068 format), the toxicodynamics of the results may not be critical to the nonclinical evaluation, except that the liver was identified as a target organ of toxicity in this study.

Conducting laboratory: MPI Research Inc, Michigan

GLP compliance: Yes (conducted in May, 2004)

Table 88. 2-Week Dog Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing	Vehicle or 15, 75, or 250 mg/kg/day (bid with divided dose and given 4 hr apart) for 2 weeks.
Route of administration	Oral gavage
Formulation/vehicle	90% polyethylene glycol 400, 5% polyvinylpyrrolidone K30, and 5% d-alpha tocopherol polyethylene glycol-1000 succinate
Species/strain	Beagle dogs
Number/sex/group	3
Age	Not provided.
Satellite groups/unique design	Same animals for TK
Deviations affecting interpretation	N/A

Source: Applicant's table from NDA files
Abbreviation: TK, toxicokinetics.

Table 89. 2-Week Dog Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	Checked 1/day. None.
Clinical signs	Checked 1/day. Unremarkable.

Parameters	Major Findings
Body weights	Measured at predose and at study termination. Unremarkable.
Food consumption	Measured at predose and at study termination. Unremarkable.
Ophthalmoscopy	Evaluated pretreatment and end of study. No drug-related findings.
ECG	Measured at predose and at study termination. Unremarkable.
Hematology	Measured at predose and at study termination. Unremarkable.
Clinical chemistry	Measured at predose and at study termination. Unremarkable.
Gross pathology	Measured at study termination. Unremarkable.
Histopathology Adequate battery: Yes Peer review: Yes	Minimal to mild increases in Kupffer cell pigmentation were observed in livers of 2/3 treated males and females in all groups, and in 1 control female. Affected females often had a minimal to mild concomitant increase in hepatocellular pigmentation.
Toxicokinetics	Systemic exposure to BMS-626529 was less than dose-proportional and comparable between males and females, and between Day 1 and 14 with C_{max} achievable within 4 hr of the second daily dose.

Dose (mg/kg/day)	Study Day	BMS-626529			
		C_{max} (ng/mL)		AUC_{0-24hr} (ng·hr /mL)	
		Male	Female	Male	Female
0	1	NC	NC	NC	NC
	14	8.03	7.58	91.6	125
15	1	7280	7200	64400	75700
	14	4740	6920	57900	95600
75	1	10000	9810	98300	97400
	14	4680	7370	61700	91000
250	1	10100	10600	128000	144000
	14	14900	7400	127000	59800

Source: Applicant's table from NDA files
Abbreviations: C_{max}, maximum plasma concentration; ECG, electrocardiogram.

BMS-626529: 2-Week Oral Toxicity Study in Rats (Study #DS04096):

Key Study Findings

BMS-626529 was administered BID (4 hours apart, oral gavage) to rat at 0 (vehicle control), 15, 75, or 250 mg/kg/day for 14 consecutive days. No remarkable findings were reported from this study, including clinical chemistry and histopathology. The NOAEL was designated at 250 mg/kg/day (AUC =866 µg.h/ml). This report was submitted as a draft and unaudited format to the NDA (not previously submitted to the IND). As the current drug product is not presented in a formulation of BMS-626529 (instead, in the prodrug BMS-663068 format), the toxicodynamics of the results may not be critical to the nonclinical evaluation.

Conducting laboratory: MPI Research Inc, Michigan

GLP compliance: Yes (conducted in August 2004)

Table 90. 2-Week Rat Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing	Vehicle or 15, 75, or 250 mg/kg/day (bid with divided dose and given 4 hr apart) for 2 weeks.
Route of administration	Oral gavage
Formulation/vehicle	90% polyethylene glycol 400, 5% polyvinylpyrrolidone K30, and 5% d-alpha tocopherol polyethylene glycol-1000 succinate
Species/strain	Hsd: Sprague-Dawley rats
Number/sex/group	10
Age	Not provided.
Satellite groups/unique design	9/sex/group for TK
Deviations affecting interpretation	N/A

Source: Applicant's table from NDA files
Abbreviation: TK, toxicokinetics.

Table 91. 2-Week Rat Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	Checked 1/day. None.
Clinical signs	Checked 1/day. Unremarkable.
Body weights	Measured at predose and at study termination. Unremarkable.
Food consumption	Measured at predose and at study termination. Unremarkable.
Ophthalmoscopy	Evaluated pretreatment and end of study. No drug-related findings.
ECG	Measured at predose and at study termination. Unremarkable.
Hematology	Measured at predose and at study termination. Unremarkable.
Clinical chemistry	Measured at predose and at study termination. Unremarkable.
Gross pathology	Measured at study termination. Unremarkable.
Histopathology Adequate battery: Yes Peer review: Yes	Unremarkable.
Toxicokinetics	Systemic exposure to BMS-626529 was less than dose-proportional (no increase between 75 and 250 mg/kg/day), and comparable between males and females, and between Day 1 and 14.

Parameters	Major Findings

Dose (mg/kg/day)	Study Day	BMS-626529			
		C_{max} (ng/mL)		AUC_{0-24hr} (ng·hr/mL)	
		Male	Female	Male	Female
0	1	49.4	85.1	691	1190
	14	95.4	218	1460	2100
15	1	32200	40000	249000	445000
	14	21600	18100	246000	264000
75	1	28900	47800	439000	802000
	14	32300	42700	442000	866000
250	1	44100	48200	568000	865000
	14	37400	37100	611000	643000

Source: Applicant's table from NDA files
Abbreviation: ECG, electrocardiogram.

14. Clinical Pharmacology Assessment: Additional Information

14.1. In Vitro Studies

FTR (GSK3684934, formerly known as BMS-663086) is a prodrug of TMR, GSK2616713, formerly known as BMS-626529. FTR is hydrolyzed to TMR (active moiety) by (ALP) in the GI lumen. TMR is predominantly present in systemic circulation, therefore TMR was evaluated in several invitro studies.

14.1.1. Plasma Protein Binding (2018N386318)

The binding of TMR to plasma proteins was determined by equilibrium dialysis for 5 hours. TMR (300, 1,000, and 10,000 ng/mL), was added to human plasma and isolated human plasma proteins including HSA (human serum albumin), AAG (α1-acid glycoprotein), and GG (gamma-globulin). Plasma protein binding was independent of concentration. The mean unbound fraction was ranged from 10.5 to 21%, with a mean value of 16.4%. TMR primarily binds to HSA (69.8 to 72.8%), with low binding to AAG and GG (8.34 to 21.4%).

14.1.2. Blood-to-Plasma Partitioning (2018N386318)

The distribution of TMR between red blood cells and human plasma was determined in blood at concentrations of 300, 1,000, and 10,000 ng/mL with incubation for 60 minutes. The observed blood to plasma concentration ratios ranged from 0.79 to 0.96 (0.87±0.06) and was independent of concertation within the concentration range tested.

14.1.3. Metabolism of TMR (2017N338649, 2017N338907)

The metabolism of TMR was investigated in human liver microsomes (HLM) and hepatocytes, and cDNA-expressed recombinant enzymes.

HLM and Human Hepatocytes

The rates of metabolism of TMR in human HLM and hepatocytes were low.

In both HLMs and human hepatocytes, two metabolic pathways were identified; a hydrolysis pathway leading to formation of BMS-646915 (M4) and benzoic acid and an oxidative pathway leading to the formation of monooxygenated TMR (M27). The oxidative pathway was completely inhibited by 1 μM RTV and 1 μM ketoconazole, indicating the main enzyme responsible for oxidation was CYP3A4. The formation of M4 was inhibited by phenylmethylsulfonylfluoride, indicating that the hydrolysis was mediated by esterases.

Recombinant Human CYP Enzymes

Incubation of TMR (1, 10, or 100μM) with recombinant human enzymes (Supersomes™; CYP1A1, 1A2, 2A6, 1B1, 2B6, 2C8, 2C9, 2C19, FMO3, 4A11, 2D6, 2E1, 3A4, and 3A5) was conducted for 30 min. No quantifiable turnover was observed with any of the enzymes except for with CYP3A4 and a 1μM concentration of TMR, which had a turnover of 7.8%. The formation of M27 was also observed when TMR was incubated with CYP3A4.

14.1.4. Inhibition and Induction of CYP Isozymes by TMR and Metabolites (BMS-930644 and BMS-646915)

Table 92. In Vitro Assessments of FTR, TMR and Its Metabolites as an Inhibitor of CYPs and UGTs

Isozyme Test Article	IC_{50} µM (No Preicubation)	IC_{50} µM (Time-Dependent)[a]	Conclusion	CYP Assay	Positive Controls	Study Report	System[b]
CYP1A2							
Fostemsavir	NT	NT	Not an inhibitor	Phenacetin O-dealkylation, Tacrine 1'-hydroxylation/ CEC O-deethylation	Furafylline, fluvoxamine,	2017n338908, 2017N339953	Human liver microsome, recombinant CYP1A2
Temsavir (2nM-40µM)	>40	>40					
BMS-646915(2nM-40µM)	>40	>40					
BMS-930644(2nM-40µM)	>40	>40					
CYP2B6							
Fostemsavir	NT	NT	Not an inhibitor	Bupropion hydroxylation/ EFC O-deethylation	Ticlopidine, clotrimazole, paroxetine	2017n338908, 2017N339953	Human liver microsome, recombinant CYP2B6
Temsavir (2nM-40µM)	>40	>40					
BMS-646915 (2nM-40µM)	>40	>40					
BMS-930644 (2nM-40µM)	>40	>40					
CYP2C8							
Fostemsavir	NT	NT	Not an inhibitor	Amodiaquine N-deethylation/ DBF O-debenzylation	Montelukast, ketoconazole, clotrimazole	2017n338908, 2017N339953	Human liver microsome, recombinant CYP2C8
Temsavir (2nM-40µM)	>40	>40					
BMS-646915 (2nM-40µM)	32.9	36.2					
BMS-930644 (2nM-40µM)	>40	>40					
CYP2C9							
Fostemsavir	NT	NT	Not an inhibitor	Diclofenac 4'-hydroxylation/ MFC O-demethylation	Sulfaphenazole, tienilic acid	2017n338908, 2017N339953	Human liver microsome, recombinant CYP2C9
Temsavir (2nM-40µM)	>40	>40					
BMS-646915 (2nM-40µM)	>40	>40					
BMS-930644 (2nM-40µM)	>40	>40					

Isozyme Test Article	IC_{50} µM (No Preicubation)	IC_{50} µM (Time-Dependent)[a]	Conclusion	CYP Assay	Positive Controls	Study Report	System[b]
CYP2C19							
Fostemsavir	NT	NT		S-mephenytoin 4'-hydroxylation/ CEC O-deethylation	Fluvoxamine, ticlopidine	2017n338908, 2017N339953	Human liver microsome, recombinant CYP2C19
Temsavir (2nM-40µM)	>40	>40	Not an inhibitor				
BMS-646915 (2nM-40µM)	>40	>40					
BMS-930644 (2nM-40µM)	>40	>40					
CYP2D6							
Fostemsavir	NT	NT		Dextromethorphan O-demethylation/ AMMC O-demethylation	Quinidine, paroxetine, Mibefradil	2017n338908, 2017N339953	Human liver microsome, recombinant CYP2D6
Temsavir (2nM-40µM)	>40	>40	Not an inhibitor				
BMS-646915 (2nM-40µM)	>40	>40					
BMS-930644 (2nM-40µM)	>40	>40					
CYP3A4							
Fostemsavir	NT	NT				2017n338908, 2017N339953	Human liver microsome, recombinant CYP3A4
Temsavir (2nM-40µM)	>40	>40	Not an inhibitor	Midazolam 1'-hydroxylation/ BFC O-debenzylation	Mibefradil, clotrimazole, Mibefradil, verapamil		
BMS-646915 (2nM-40µM)	9.9	15.2	Inhibitor				
BMS-930644 (2nM-40µM)	>40	>40	Not an inhibitor				
CYP2A6							
Fostemsavir	NT	NT		Coumarin 7-hydroxylation	Methoxsalen, tranylcypromine, pilocarpine/--	2017n338908	Human liver microsome, recombinant CYP1A6
Temsavir (2nM-40µM)	>40	>40	Not an inhibitor				
BMS-646915 (2nM-40µM)	NT	NT					
BMS-930644 (2nM-40µM)	NT	NT					

Isozyme Test Article	IC_{50} µM (No Preicubation)	IC_{50} µM (Time-Dependent)[a]	Conclusion	CYP Assay	Positive Controls	Study Report	System[b]
UGT1A1							
Fostemsavir (0.14µM-100µM)	>100	NT	Not an inhibitor	Estradiol	Atazanavir	2017N339587 2017N339588	Human liver microsome, recombinant UGT1A1
Temsavir (0.14µM-100µM)	>100	>40	Not an inhibitor				
BMS-646915 (1.5nM to 10µM)	>100	NT					
BMS-930644 (1.5nM to 10µM)	>100	NT					
UGT1A4							
Fostemsavir (0.14µM-100µM)	>100	NT	Not an inhibitor	Trifluoperazine glucuronidation	Hecogenin	2017N339587 2017N339588	Human liver microsome, recombinant UGT1A4
Temsavir (0.14 to 100µM)	>100	NT					
BMS-646915 (1.5nM to 10µM)	>200	NT					
BMS-930644 (1.5nM to 10µM)	>200	NT					
UGT1A9							
Fostemsavir (0.14µM-100µM)	>100	NT	Not an inhibitor	Propofol glucuronidation	Niflumic acid	2017N339587 2017N339588	Human liver microsome, recombinant UGT1A9
Temsavir (0.14 to 100µM)	>100	NT					
BMS-646915 (1.5nM to 10µM)	>200	NT					
BMS-930644 (1.5nM to 10µM)	131/53.7	NT					
UGT1A6							
Fostemsavir (1.5nM-10µM)	>10	NT	TMR and FTR Concentration range beyond 10µM was not tested. Not a potential inhibitor	5-OH tryptophol - β-D-glucuronidation	Celastrol	2017N339488 2017N339588	Human liver microsome, recombinant UGT1A6
Temsavir (1.5nM to 10µM)	>10	NT					
BMS-646915 (1.5nM to 10µM)	>200	NT					
BMS-930644(1.5nM to 10µM)	>200	NT					

Isozyme Test Article	IC_{50} µM (No Preicubation)	IC_{50} µM (Time-Dependent)[a]	Conclusion	CYP Assay	Positive Controls	Study Report	System[b]
UGT2B7							
Fostemsavir (1.5nM to 10µM)	>10	NT	Not a potential inhibitor BMS-930644 may have low inhibition potential based on r UGT IC_{50}	Zidovudine O-glucuronidation	Mefenamic acid	2017N339488 2017N339588	Human liver microsome, recombinant UGT2B6
Temsavir (1.5nM to 10µM)	>10	NT					
BMS-646915(1.5nM to 10µM)	113.5/87.9(rUGT)	NT					
BMS-930644(1.5nM to 10µM)	42/28(rUGT)	NT					

Source: Clinical Pharmacology Reviewer's table
Positive controls: known inhibitors of respective CYP isoforms
[a] Tested with a 15 min preincubation period.
[b] Human liver microsomes (pooled)
Abbreviations: CYP, cytochrome P450; FTR, fostemsavir; NT, not tested; TMR, temsavir.

Table 93. In Vitro Assessments of FTR, TMR and its Metabolites as an Inducer of CYP Enzymes

Isozyme Test Article	Enzyme Activity (% Adjusted Positive Control)[a] (3 Donors) Hu1217/Hu1218/Hu1219	mRNA Content (% Adjusted Positive Control) (3 Donors) Hu1217/Hu1218/Hu1219	Conclusion	Positive Control	Study Report	System
CYP1A2						
Temsavir (2µM)	7.8/1.2/6.3	3.4/3.4/4.6	Not an inducer	3-MC	2017n338882	Primary human hepatocytes; mRNA and phenacetin O-dealkylation
Temsavir (5µM)	7.1/2.4/6.1	4.4/3.5/4.9	Showed <20% of mRNA content as compared to positive control up to TMR concentration 20µM			
Temsavir (20µM)	12.5/5.1/8.9	8.0/5.7/9.7				
Temsavir (100µM)	34.8/29.9/23.2	23.2/15.2/26.0				

Isozyme Test Article	Enzyme Activity (% Adjusted Positive Control)[a] (3 Donors) Hu1217/Hu1218/Hu1219	mRNA Content (% Adjusted Positive Control) (3 Donors) Hu1217/Hu1218/Hu1219	Conclusion	Positive Control	Study Report	System
CYP2B6						
Temsavir (2µM)	9.2/-2.1/0.31	1.5/3.1/2.4	Not an inducer	Phenobarbital	2017n338882	Primary human hepatocytes; mRNA and bupropion hydroxylation
Temsavir (5µM)	5.7/0.5/-0.03	1.9/1.9/2.1				
Temsavir (20µM)	9.3/0.5/-0.03	3.5/2.3/3.2				
Temsavir (100µM)	13.7/7.7/4.5	11.7/17.8/10.0				
CYP3A4						
Temsavir (2µM)	16.2/-5.3/-2.5	-0.24/2.5/0.37	Not an inducer	Rifampicin	2017n338882	Primary human hepatocytes; mRNA and testosterone 6ß-hydroxylation
Temsavir (5µM)	-10.5/-3.9/-3.0	0.09/1.2/0.60				
Temsavir (20µM)	30.7/-0.8/-1.9	0.7/5.3/2.2				
Temsavir (100µM)	21.3/10.5/11.8	8.3/24.1/7.0				

Source: Clinical Pharmacology Reviewer's table
Positive controls: known inducers of respective CYP isoforms
[a] Enzyme activities for CYP1A2, CYP2B6, and CYP3A4 were determined (at concentrations of 2, 5, 20µM) by microsomes were isolated from TMR-treated hepatocytes.
Abbreviations: CYP, cytochrome P450; FTR, fostemsavir; TMR, temsavir.

14.1.5. Evaluation of Drug Transporters Involved in the Disposition of TMR and metabolites (BMS-930644 and BMS-646915)

Table 94. In Vitro Assessments of FTR, TMR and its Metabolites as a Substrate of Human Uptake and Efflux Transporters

Transporter Drug	Results	Positive Controls	Conclusion	Study Report	System
P-gp					
Fostemsavir	ND				
Temsavir 0.1, 1µM	ER 11.1 (at 0.1µM) and 8.9 (at 1µM)	Digoxin, mannitol	Temsavir is a substrate of P-gp	2017n339477	MDCK-MDR1
BMS-646915 0.1, 1µM	ER 3.1 (at 0.1µM) and 6.2 (at 1µM)	Digoxin, mannitol	BMS-646915 is a substrate of P-gp	2017N353538	
BMS-930644 0.1, 1µM	ER 3.0 (at 0.1µM) and 3.0 (at 1µM)	Digoxin, mannitol	BMS-646915 is a substrate of P-gp	2017N339481	
BCRP					
Fostemsavir	ND				
Temsavir 0.1 and 1µM	ER 11.1 (at 0.1µM) and 8.9 (at 1µM)	Cladribine, mannitol	Temsavir is a substrate of BCRP	2017n339478	MDCK-hBCRP
BMS-646915 0.1, 1, 4µM	ER 1.1 (at 0.1µM), 1.6 (at 1µM) and 1.5 (at 4µM)	Digoxin, cladribine	Not a substrate	2017N353539, 2017N338660	
BMS-930644 0.1, 1, 3µM	ER 1.5 (at 0.1µM), 1.5 (at 1µM) and 6.8 (at 3µM)	Cladribine, mannitol	BMS-930644 is a substrate of BCRP	2017N339482, 2017N338659	MDCK-BCRP

Transporter Drug	Results	Positive Controls	Conclusion	Study Report	System
OATP					
Fostemsavir	ND				
Temsavir 0.5µM	44%[a]	Rosuvastatin	OATs and/or OCTs might be involved in the hepatic uptake	2017n339485	Human hepatocytes[b]
BMS-646915 0.5µM	27.0%[c]	Rosuvastatin	OATPs are involved in hepatic uptake		
BMS-930644 0.5µM	35.8%[c]	Rosuvastatin			

Source: Clinical Pharmacology Reviewer's table
Positive controls: known substrates of the respective transporters; Mannitol, a paracellular marker, was studied to determine the integrity of the monolayer
Efflux ratio of MDR1 (or BCRP) expressing cells to efflux ratio of wild type (ratio of ratios)
[a] Percent inhibition in CLu of BMS-626529 by 100 µM Quinidine and 1mM PROB, inhibitors OATs and/or OCTs, respectively.
[b] Human hepatocytes uptake assays: incubation TMR Concentration (0.5µM); Incubation Time (min) 0.25, 1.0, 1.5, 5µM.
[c] Percent inhibition in uptake of BMS-646915 in Cryopreserved Human Hepatocytes in the presence of rifamycin SV (an inhibitor of OATP), CLu (uptake clearance) reduced for both metabolites at 37°C by rifamycin SV (200 µM) by 27.0% and 35.8%.
Abbreviations: BCRP, breast cancer resistance protein; ER, efflux ratio; ND; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter.

14.1.6. Evaluation of Inhibition of Drug Transporters by FTR, TMR and Metabolites (BMS-930644 and BMS-646915)

Table 95. In Vitro Assessments of FTR, TMR and its Metabolites as an Inhibitor of Human Uptake and Efflux Transporters

Transporter Drug	Results IC_{50} (µM)	Conclusion	Study Report	Positive Controls	Substrate	System
OATP1B1						
Fostemsavir	ND			Sulfobromophthalein, cyclosporin A, rifampicin	Pitavastatin 0.3µM	OATP1B1 - HEK293
Temsavir (0.0025 to 50µM)	32	Potentially an inhibitor (R =1.44) R >1.1	2017n338910			
BMS-646915 (0.0025 to 50µM)	>50	Not an inhibitor	2017n338660			
BMS-930644 (0.0025 to 50µM)	50	Not an inhibitor	2017n338659			

Transporter Drug	Results IC_{50} (µM)	Conclusion	Study Report	Positive Controls	Substrate	System
OATP1B3						
Fostemsavir	ND			Sulfobromophthalein, cyclosporin A, rifampicin	[3H]CCK-8, 1.3 µM	OATP1B3 - HEK293
Temsavir (0.0025 to 50µM)	16±6	Potentially an inhibitor (R =1.88)	2017n338910			
BMS-646915 (0.0025 to 50µM)	>50	Not an inhibitor	2017n338660			
BMS-930644 (0.0025 to 50µM)	23.2±11.4	Not an inhibitor	2017n338659			
BCRP						
Fostemsavir (1 to 250µM)	>250	Not an inhibitor	2017n339472	Ko143 FTC	$[^3H]$cladribine 1 µM $[^{14}C]$Mannitol 1µM	MDCK-BCRP
Temsavir (1 to 50µM)	12.4±3.4	Inhibitor; I_{gut}/IC_{50}=332 R1,gut >11	2017n339484			
BMS-646915 (0.1 to 100µM)	35.2±9.4	Inhibitor	2017n353537			
BMS-930644 (0.1 to 100µM)	3.5±0.9	Inhibitor	2017n339475			
P-gp						
Fostemsavir (1 to 250µM)	>250	Not an inhibitor	2017n339471	GF120918 Ketoconazole	$[^3H]$Digoxin 1 µM	MDCK-MDR1
Temsavir (0.1 to 25µM)	>25	10% maximum inhibition was seen at 25µM; Not an inhibitor	2017n339476	GF120918 Ketoconazole		
BMS-646915 (0.1 to 100µM)	>100	Not an inhibitor	2017n353536	Quinidine Ketoconazole		
BMS-930644 (0.1 to 100µM)	>100	Not an inhibitor	2017n339473	Quinidine Ketoconazole		

Transporter Drug	Results IC_{50} (µM)	Conclusion	Study Report	Positive Controls	Substrate	System
OAT1						
Fostemsavir	ND			Probenecid	Tenofovir 5µM	HEK- OAT1
Temsavir (0.01 to 200µM)	110	Not an inhibitor	2019n400799			
BMS-646915 (0.0025 to 50µM)	>50	Not an inhibitor	2017n338910	Sulfobromophthalein Diflunisal	[3H]para-aminohippurate1µM	
BMS-930644 (0.0025 to 50µM)	>50	Not an inhibitor	2017n338910			
OAT3						
Temsavir (0.0025 to 50µM)	>50	Not an inhibitor	2017n338910	Sulfobromophthalein Diflunisal Fluvastatin Indomethacin	[3H]estrone-3-sulfate 1µM	HEK- OAT3
BMS-646915 (0.0025 to 50µM)	>50					
BMS-930644 (0.0025 to 50µM)	>50					
MATE1						
Temsavir (0.14 to 100µM)	18.5±2	R value <0.1	2017n338662	Pyrimethamine	[^{14}C]metformin 2µM	HEK-MATE1
BMS-646915 (0.14 to 100µM)	15.2±2.5					
BMS-930644 (0.14 to 50µM)	40.6±2.2					

Transporter Drug	Results IC_{50} (µM)	Conclusion	Study Report	Positive Controls	Substrate	System
MATE-2K						
Temsavir (0.14 to 100µM)	12.2±1.6	R >0.1, inhibitor for MATE-2K. At clinically relevant concentrations, significant interactions are unlikely	2017n338662	Pyrimethamine	[^{14}C]metformin 2µM	HEK-MATE2K
BMS-646915 (0.14 to 100µM)	11.2±1.5					
BMS-930644 (0. 14 to 50µM)	9.4±1.9					
MRP2						
Temsavir (0.0025 to 50µM)	>50	Not an inhibitor	2017n338910	Sulfobromophthalein Cyclosporin A	[3H]estradiol-17β-glucuronide 50µM	SF9-MRP2
BMS-646915 (0.0025 to 50µM)	>50					
BMS-930644 (0.0025 to 50µM)	>50					
NTCP						
Temsavir (0.0025 to 50µM)	>50	Not an inhibitor	2017n338910	Sulfobromophthalein Cyclosporin A Pioglitazone	Taurocholate 1µM	HEK-NTCP
BMS-646915 (0.0025 to 50µM)	>50					
BMS-930644 (0.0025 to 50µM)	>50					

Transporter Drug	Results IC_{50} (µM)	Conclusion	Study Report	Positive Controls	Substrate	System
OCT2						
Temsavir (0.14 to 100µM)	>100	Not an inhibitor	2017n338662	Pyrimethamine	[^{14}C]metformin 2µM	HEK-OCT2
BMS-646915 (0.14 to 100µM)	>100					
BMS-930644 (0. 14 to 50µM)	33.2±2	Not likely an inhibitor at therapeutic concentration				
BSEP						
Temsavir (0.0025 to 50µM)	>50	Not an inhibitor	2017n338910	Cyclosporin A Pioglitazone Saquinavir Ketoconazole	[^{3}H]taurocholic acid, [^{3}H]TCA; 1µM	SF9-BSEP
BMS-646915 (0.0025 to 50µM)	>50	Not an inhibitor				
BMS-930644 (0.0025 to 50µM)	16.2±2.2	Not likely an inhibitor at therapeutic concentration				
OCT1						
Temsavir (0.14 to 100µM)	32.8±7.4	Not likely an inhibitor at therapeutic concentration	2017n338662	Pyrimethamine	[^{14}C]metformin 2µM	HEK- OCT1
BMS-646915 (0.14 to 100µM)	>100	Not an inhibitor				
BMS-930644 (0. 14 to 50µM)	4.3±0.66	Not likely an inhibitor at therapeutic concentration				

Source: Clinical Pharmacology Reviewer's table
Positive controls: known inhibitors of the respective transporters
R-value: ratio of victim AUC in the presence and absence of perpetrators (inhibitors), predicted with basic models
Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; ER, efflux ratio; FTR, fostemsavir; MATE, multidrug and toxin extrusion protein extrusion protein; ND, not determined; NTCP, sodium taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; RIF, rifampicin; TMR, temsavir.

14.2. In Vivo Studies

Mass Balance of Temsavir Following Administration of [^{14}C]-FTR (Fostemsavir) and [^{14}C]-FTR + RTV (Ritonavir) (206265)

Study Design

Study 206265 was a nonrandomized, open-label, single-dose design in 18 healthy male participants assigned to four groups: A, B, C, and D.

Groups A and C

Six subjects in each group received a single oral dose of 300 mg [^{14}C]FTR containing 100 µCi (3.7 MBq) of total radioactivity administered without and with ritonavir (RTV), respectively.

Groups B and D

Three subjects in each group received a single oral dose of 300 mg [^{14}C]FTR containing 100 µCi (3.7 MBq) of total radioactivity administered without and with RTV, respectively, and bile samples were collected from these groups.

Subjects in Groups A and B were dosed with [^{14}C]FTR on Day 1. Subjects in Groups C and D received BID dosing of 100 mg RTV with food on Days 1 to 9, and on Day 10, these subjects received 100 mg of RTV with a single oral dose of 300 mg [^{14}C]FTR.

Blood samples were collected to measure total radioactivity, TMR concentrations, and metabolite profiling for at least 120 hours post-dose. Urine and fecal samples were collected to measure the levels of TMR metabolites, and total radioactivity, predose through 240 hours after FTR dosing. Bile collection for TMR, TMR metabolites, and total radioactivity, was done continuously from 3 to 8 hours after FTR dosing.

Results and Conclusion

The blood:plasma C_{max} and AUC ratios of TMR were 0.74 and 0.19, respectively, which suggests low association of TMR with red blood cells.

FTR Alone (Groups A and B)

For Group A (FTR alone), 78% of the administered dose was recovered in the excreta; 44% of the dose was recovered in urine and 33% was recovered in feces. For Group B (FTR alone, bile collection group), 89% of the administered dose was recovered in the excreta; 51% of the dose was recovered in urine, 33% was recovered in feces, and 5% was recovered in bile. TMR was extensively metabolized, only 1.9% and 1.1% of the dose was recovered in urine and feces, respectively, as unchanged TMR.

The major circulating form of TMR in plasma were the metabolites BMS-646915 (M4; a product of hydrolysis of TMR) and BMS-930644 (M28; a product of N-dealkylation of TMR).

BMS-646915 (M4) and its metabolites (M1, M2, M3) account for 46.5% of the recovered dose (36.1% of the administered dose). CYP3A4-mediated oxidative metabolites, which includes BMS-930644 (M28), accounted for 27.3% of the recovered dose (21.2% of the administered dose). The AUC_{0-24} BMS-930644/AUC_{0-24} TMR is approximately 0.33, while the AUC_{0-24} BMS-646915/AUC_{0-24} TMR is approximately 0.12. (Data Source: CSR 206265 Biotransformation, Table 12). Therefore, BMS-930644 is the major metabolite.

Coadministration of RTV (Groups C and D)

Coadministration of RTV + FTR did not change the excretion pattern of total radioactivity. Over the 240-hour collection time for Group C (FTR + RTV), 87% of the administered dose was recovered in the excreta; 51% of the dose was recovered in urine and 36% was recovered in feces. Excretion of total radioactivity in bile was similar between coadministration of RTV + FTR (5%) and FTR alone (5%).

TMR plasma C_{max} and AUC were increased with RTV coadministration by approximately 45% and 66%, respectively, compared to administration of TMR alone. BMS-930644 (M28; CYP3A4 metabolite) accounted for 80.3% of radioactivity in plasma at the 24-hour time point when FTR was administered alone and 13.7% when FTR was co-administered with RTV. No BMS-646915 (M4) was detected at the 24-hour time point when FTR was administered alone and 21% M4 was found when FTR was co-administered with RTV (Data Source: Study 206265 Biotransformation Report Table 3, Table 4).

Absolute Bioavailability of TMR (206218)

Study Design

Study 206218 was an open-label, sequential, single-period study to assess the absolute bioavailability of TMR following oral dosing of FTR and IV infusion of [^{13}C]-TMR in healthy male subjects.

Treatment A

A single oral dose of FTR 600 mg extended-release (ER) tablet following overnight fasting

Treatment B

A single IV infusion of 100 µg [^{13}C]-TMR over 15 min beginning at 2.75 hours post oral dose of BMS-663068

Blood was collected for up to 72 hours after study drug administration for PK analysis.

Results

Table 96. Statistical Analysis of Dose-Normalized AUC_{0-t} and AUC_{inf} of TMR

Parameter (Unit)	TMR (Oral)	[^{13}C]-TMR (IV)	TMR (Oral) vs. [^{13}C]-TMR (IV)
AUC(0-t)/Dose ((ng*h/mL)/mg; (pg*h/mL)/µg)			
Adjusted Geo. Mean	14.832	55.834	0.266
(90% CI)	(12.304, 17.880)	(46.317, 67.306)	(0.232, 0.305)
[N]	[8]	[8]	[8]
AUC inf/Dose ((ng*h/mL)/mg; (pg*h/mL)/µg)			
Adjusted Geo. Mean	15.073	55.976	0.269
(90% CI)	(12.503, 18.171)	(46.432-67.481)	(0.234, 0.310)
[N]	[8]	[8]	[8]
Vss (L)			
Geo. Mean		29.5	
(%CV)		26	
[N]		[8]	
CL or CL/F (L/h)			
Geo. Mean	81.8	17.9	
(%CV)	36	21	
[N]	[8]	[8]	

Source: Study 206218 CSR Table 9.2-1 and Table 9.2-2.
If UNIT column has 2 values it will be in the format, 'Unit of TRT A; Unit of TRT B'. The oral dose equivalent (486.89 mg) of TMR was used for dose normalization; the molecular weights of TMR and FTR were 473.5 and 583.5 g/mol, respectively. The actual dose was used for the dose normalization of the IV infusion. CL for IV dosing and CL/F for oral dosing.
Abbreviations: AUC_{0-t}, area under the curve to the last quantifiable time point; AUC_{inf}, area under the curve to infinity; CL, plasma clearance; CV, coefficient of variation; IV, intravenous; TMR, temsavir.

Conclusion

The absolute bioavailability of TMR following administration of a single oral dose of FTR was 26.9%.

Fostemsavir ER Tablet Single Ascending Dose and Impact of Ritonavir (206261)

Study Design

Study 206261 was a two-part study. Part 1 compared the bioavailability of 3 prototype FTR ER Tablet 600 mg formulations to the Immediate Release capsule formulation. Two FTR ER Tablet formulations selected from Part 1 for evaluation in Part 2

Part 2 was a Phase 1, nonrandomized, open-label, 3-period, single-sequence, crossover trial to evaluate PK following oral administration of FTR ER tablets as single doses of 1,200 mg, 1,800 mg, and 600 mg with RTV 100 mg. The impact of RTV on plasma TMR PK following co-administration with FTR ER tablets was evaluated using a parallel design; comparison was made between subjects who received the combination (FTR 600 mg + RTV 100 mg) in Part 2 and subjects who received FTR alone (FTR 600 mg) in Part 1 of the study. FTR doses were administered with a standard meal. Serial plasma PK samples for TMR analysis were collected over 48 hours after FTR dosing in each period.

Table 97. TMR PK Parameters Following Administration of FTR ER Tablets as Single Doses in the Fed State

	Geometric Mean (CV%)				Median (min-max)	Mean (SD)
FTR Dose	**C_{max} (ng/mL)**	**AUC_{inf} (ng.h/mL)**	**AUC_{last} (ng.h/mL)**	**C_{12} (ng/mL)**	**T_{max} (h)**	**$T_{1/2}$ (h)**
FTR ER tablet slow release[a]						
FTR 600 mg	1,693 (28)	11,038 (33)	10,729 (33)	234 (91)	3.99 (2.98-9.97)	9.98 (8.10)
FTR 1,200 mg	5,553 (43)	31,075 (41)	30,765 (41)	654 (68)	4.03 (3.95-6.12)	10.76 (10.30)
FTR 1,800 mg	7,968 (34)	45,696 (37)	45,419 (37)	622 (46)	3.98 (3.95-5.97)	9.02 (6.88)
FTR 600 mg+RTV 100 mg	2,890 (41)	18,751 (36)	18,448 (37)	427 (91)	4.00 (3.98-9.98)	8.14 (6.70)
FTR ER tablet intermediate release[b]						
FTR 600 mg	2,890 (37)	14,107 (23)	13,959 (22)	194 (35)	4.00 (3.97-5.98)	7.43 (4.92)
FTR 1,200 mg	6714 (50)	31,989 (49)	33,243 (48)	354 (119)	4.00 (2.98-5.97)	9.68 (5.82)
FTR 1,800 mg	12,123 (47)	57,484 (57)	57,045 (57)	679 (105)	4.98 (2.98-7.97)	11.86 (5.78)
FTR 600 mg+RTV 100 mg	4,236 (44)	22,719 (48)	23,424 (46)	402 (103)	4.00 (3.95-10.0)	7.5 (4.66)

Source: Study 206261 CSR Table 9.2.1, Table 9.2.2
FTR 600 mg data from Part 1 and FTR 1,200 mg and 1,800 mg data from Part 2 of Study 206261 are included for assessment of dose proportionality.
[a] FTR ER Tablet (no film coat) dry granulation by slugging slow release, 600 mg;
[b] FTR ER Tablet (no film coat) dry granulation by slugging intermediate release, 600 mg
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last concentration time point; C_{max}, maximum plasma concentration; CV, coefficient of variation; $C_{12,}$, concentration at 12 hours after dosing ; ER, extended release; FTR, fostemsavir; RTV, ritonavir; T_{max}, time to maximum plasma concentration; $T_{1/2}$, half life.

Conclusion

Administration of a single dose of FTR 600 mg as the slow release ER tablet formulation with RTV 100 mg Q12h increased TMR C_{max} by 68%, AUC_{inf} by 71%, and Ctau by 74%.

TMR C_{max} and AUC_{inf} increased in a slightly > dose proportional manner between 600 and 1800 mg for both FTR ER tablet formulations.

Multiple Ascending Dose (206262)

Study Design

Study 206262 is double-blind, placebo-controlled multiple ascending dose study to evaluate the PK following oral administration of FTR for 10 days. Within each dose group, eight subjects were randomized to FTR or placebo in a ratio of 3:1. The study also evaluated the impact of RTV on plasma TMR PK following co-administration with FTR using a parallel design. Panel 1 and 2 had IR capsule formulation therefore, not reviewed here.

FTR doses were administered with a standard meal. Serial plasma PK samples were collected on Day 1 up to 12 hours (Panels 3 to 5) after the morning dose. Serial plasma PK samples were collected on Day 10 up to 72 hours (Panels 3 to 5) after the last morning dose. In addition, serial plasma PK samples were collected up to 12 hours after the evening dose on Day 9 to assess diurnal variation in the 1,200 mg Q12h group (Panel 4). All PK samples were analyzed for TMR; PK samples collected for Treatment D and Treatment E were also analyzed for FTR. PK samples for were obtained on Days 2, 3, 4, 5, 7, and 9 prior to the morning dose for C_{trough} and steady-state assessment.

Table 98. FTR ER Tablet Multiple Ascending Dose Study Design

FTR Formulation	Panel	FTR Dosage Regimen (Days 1-10) (n=6/panel)
ER tablet	3	C: FTR 600 mg + RTV 100 mg Q12h
	4	D: FTR 1,200 mg Q12h
	5	E: FTR 1,200 mg + RTV 100 mg Q12h

Source: Study 206262 CSR Section 3.1
Abbreviations: ER, extended release; FTR, fostemsavir; RTV, ritonavir.

Results

Table 99. Plasma TMR PK Parameters Following Repeat Dose Administration of FTR ER Tablets in the Fed State

Regimen	Day	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	AUC_{24} (ng·h/mL)	C_{tau} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)
C	1	6	3,508 (38)	14,658 (32)	29,317 (32)	353 (72)	4.00 (4.0-6.0)	-
	10	5	3,612 (45)	20,308 (47)	40,616 (47)	333 (76)	4.00 (4.0-5.0)	7.42 (6.63)
D	1	6	3,851 (25)	17,218 (32)	34.436 (32)	194 (73)	4.00 (3.0-5.0)	-
	10	6	4,548 (25)	23,785 (26)	47,570 (26)	338 (29)	4.00 (4.0-5.0)	7.45 (1.15)
E	1	6	6,705 (42)	38,251 (49)	76,502 (49)	1,171 (91)	5.01 (4.0-8.0)	-
	10	5	7,461 (34)	50,229 (40)	100,457 (40)	1,399 (73)	4.00 (4.0-6.0)	14.2 (7.85)

Data Source: Study 206262 CSR Table 9.2.1.1
All values are expressed as geometric mean (CV), except for t_{max}, which is presented as median (min-max) and $t_{1/2}$, which is presented as mean (SD).
FTR ER Tablet (no film coat) dry granulation by slugging slow release, 600 mg
Dosage regimen C: FTR ER 600 mg + RTV 100 mg Q12h
Dosage regimen D: FTR ER 1,200 mg Q12h
Dosage regimen E: FTR ER 1,200 mg + RTV 100 mg Q12h
Abbreviations: AUC_{24}, area under plasma concentration-time curve over 24 hours; AUC_{tau}, area under plasma concentration-time curve over dosing interval; C_{max}, maximum observed plasma concentration; C_{tau}, concentration at the end of the dosing interval; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; t_{max}, time of maximum observed plasma concentration; TMR, temsavir.

Table 100. Accumulation Index (Day 10 vs. Day 1) for Plasma TMR PK Parameters Following Repeat Dose Administration of FTR ER Tablets in the Fed State

Dosage Regimen	C_{max} (ng/mL)	C_{tau} (ng/mL)	AUC_{tau} (ng·h/mL)
C	1.01 (0.561, 1.805)	1.23 (0.908, 1.66)	1.64 (1.15, 2.33)
D	1.18 (0.855, 1.63)	1.74 (1.05, 2.89)	1.38 (1.12, 1.70)
E	1.03 (0.893, 1.19)	1.11 (0.769, 1.59)	1.27 (1.13, 1.42)

Data Source: Study 206262 CSR Table 9.2.1.4
All values are expressed as geometric mean ratio (90% confidence interval).
C: FTR ER tablet 600 mg + RTV 100mg Q12h
D: FTR ER tablet 1200 mg Q12h
E: FTR ER tablet 1200 mg + RTV 100 mg Q12h
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; C_{max}, maximum observed plasma concentration; C_{tau}, concentration at the end of the dosing interval; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; TMR, temsavir.

Table 101. Diurnal Variation (Evening Day 9 vs. Morning Day 10 Dose) in Plasma TMR PKs Following Administration of FTR ER Tablets 1,200 mg Q12h in the Fed State

Plasma TMR PK Parameter	Diurnal Variation
C_{max}	1.43 (1.27,1.60)
C_{tau}	1.99 (1.18, 3.35)
AUC_{tau}	1.45 (1.38,1.52)

Data Source: Study 206262 CSR Table 9.2.1.5
All values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{tau}, concentration at the end of the dosing interval; ER, extended-release; FTR, fostemsavir; GMR, geometric mean ratio; PK, pharmacokinetic; TMR, temsavir.

Table 102. Effect of RTV on Plasma TMR PKs Following Coadministration of FTR ER Tablets 1,200 mg Q12h + RTV 100 mg Q12h

Plasma TMR PK Parameter	FTR+RTV vs. FTR
C_{max}	1.64 (1.14, 2.37)
AUC_{tau}	2.11 (1.34, 3.34)
C_{tau}	4.14 (1.93, 8.87)

Data Source: Study 206262 CSR Table 9.2.1.3
Comparison of panel D and panel E
All values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{tau}, concentration at the end of the dosing interval; ER, extended-release; FTR, fostemsavir; GMR, geometric mean ratio; PK, pharmacokinetic; RTV, ritonavir; TMR, temsavir.

The mean C_{trough} (predose concentration) versus study day plot showed that steady-state plasma TMR concentrations are achieved by Day 2 to 3 following administration of FTR 600 mg BID (Data Source: Study 206262 CSR Supplemental Table S.8.2.1F and Supplemental Figure S.8.2.3.)

Conclusion

- Steady-state plasma TMR concentrations are achieved by Day 2 to 3 following administration of FTR 600 mg BID. Accumulation observed was <2-fold consistent with FTR BID dosing and a $t_{1/2}$ of approximately 11 hours.
- There was diurnal variation in plasma TMR PK, with higher exposure observed following the evening dose compared with the morning dose.
- No PK analysis was completed for the prodrug because most of the plasma FTR concentrations were below the LLQ (1.00 ng/mL). In those subjects with quantifiable FTR concentrations ranged from 3.3 to 15.5 ng/mL.

Food Effect (Standard Meal) (206283)

Study Design

Study 206283 was an open-label, randomized, two-period, two-treatment, crossover study with a 3-day washout in between each period. Subjects received FTR (ER tablet) BID on Days 1 through 3 of each period and a single dose on Day 4 of each period. Serial PK sampling was performed for up to 12 hours following administration of FTR for the determination of TMR concentrations on Day 4 of each period. Ctrough for TMR was also obtained on Days 1, 2, and 3 of each period, prior to the morning and evening doses.

A standard breakfast (423 kcal, 36% fat, 47% carbohydrates, and 17% protein) was served to subjects prior to each morning dose of Treatment B. The meal was consumed within 25 minutes and FTR was administered within 5 minutes following meal completion.

Study design of food effect of high fat meal is described as part of Study 206295.

Results

Table 103. Effect of a Standard Meal and a High-Fat Meal on Plasma TMR PKs

Study	Treatment	C_{max} (ng/mL)	T_{max} (h)	AUC (ng·h/mL)	C_{tau} (ng/mL)
Study 206283	Treatment A	1,717 (1,412, 2,086)	2.00 (1.00-6.00)	8,854 (7,398, 10,597)	185 (149, 229)
	Treatment B	1,643 (1,359, 1,986)	4.00 (2.00-8.00)	9,695 (8,073, 11,641)	311 (229, 421)
	B vs. A	0.96 (0.83, 1.10)	-	1.10 (0.95, 1.26)	1.68 (1.36, 2.07)
Study 206295	Treatment C	1,356 (1,113, 1,651)	2.00 (1.00-4.02)	7,276 (5,958, 8,886)	100 (75.3, 133)
	Treatment D	1,321 (1,158, 1,507)	6.53 (1.00-12.10)	13,141 (11,463, 15,065)	567 (434, 741)
	D vs. C	0.97 (0.81, 1.17)	-	1.81 (1.54, 2.12)	5.66 (4.43, 7.24)

Data Source: Study 206283 CSR Table 9.2.1-1, Table 9.2.1-2; Study 206295 CSR Table 9.2.1-1
All values are expressed as adjusted geometric mean (90% CI) except for those in the Trt B vs. Trt A and Trt D vs. Trt C rows. The data in these columns are expressed as geometric mean ratio (90% CI). Values in the T_{max} column are presented as median (min, max).
Study 206283: Effect of a standard meal (composed of approximately 423 kcal, 36% fat, 47% carbohydrates, and 17% protein) on steady-state TMR PK.
Study 206295: Effect of a high-fat meal on single-dose TMR PK
Treatment A: FTR ER tablet 600 mg BID fasted
Treatment B: FTR ER tablet 600 mg BID with standard meal
Treatment C: FTR ER tablet 600 mg single dose fasted
Treatment D: FTR ER tablet 600 mg single dose with a high-fat meal
AUC = AUCtau for repeat dose Study 206283
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_{tau}, concentration at the end of the dosing interval; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; TMR, temsavir.

Conclusion

TMR AUC was increased by 81% with a high-fat meal but was not impacted by a standard meal. Regardless of calorie and fat content, food had no significant effect on plasma TMR C_{max}.

The absorption rate of TMR was prolonged with food; median plasma TMR t_{max} was 2 hours when subjects were fasted, 4 hours with a standard meal, and 6.5 hours with a high-fat meal. As a result of prolonged absorption with food, plasma TMR C_{tau} was 68% higher with a standard meal.

FTR can be administered without regard to food.

Effect of Famotidine and High Fat Meal (206295)

Study Design

Study 206295 was a randomized, single-dose, open-label, 3-period, 6-sequence, complete crossover study to evaluate the effect of a high-fat meal on the TMR exposure following administration of FTR ER tablets and the interaction between FTR and famotidine. High-calorie/high-fat meal comprised of ~985 kcal, 60% fat, 28% carbohydrates, and 12% protein. Serial plasma PK samples for TMR analysis were collected up to 72 hours after dosing in each period.

Treatment A: FTR ER Tablet 600 mg single dose fasted

Treatment B: FTR ER Tablet 600 mg single dose with a high-fat meal

Treatment C: FTR ER Tablet 600 mg single dose administered 2 hours after famotidine 40 mg fasted

Results

Table 104. Effect of Famotidine on Plasma TMR PKs When a Single Dose of FTR ER Tablets 600 mg was Administered 2 Hours After a Single Dose of Famotidine 40 mg

Treatment	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	C_{12} (ng/mL)	T_{max} (h)
A	1,356 (1,113, 1,651)	7,047 (5,777, 8,596)	7,276 (5,958, 8,886)	100 (75.3, 133)	2.00 (1.00, 4.02)
B	1,321 (1,158, 1,507)	12,834 [24] (11,198, 14,708)	13,141 (11,463, 15,065)	567 (434, 741)	6.53 (1.00, 12.10)
C	1,370 (1,237, 1,517)	7,077 (6,155, 8,137)	7,559 (6,556, 8,716)	90.4 (67.2, 122)	2.00 (1.00, 4.00)
B vs A	0.97 (0.81, 1.17)	1.82 (1.56, 2.13)	1.81 (1.54, 2.12)	5.66 (4.43, 7.24)	
C vs A	1.01 (0.85, 1.21)	1.004 (0.838, 1.203)	1.04 (0.87, 1.25)	0.90 (0.64, 1.28)	

Data Source: Study 206295 CSR Table 9.2.1-1
All values are expressed as adjusted geometric mean (90% CI) except for those in the B vs. A and C vs. A rows. The data in these columns are expressed as geometric mean ratio (90% CI). Values in the T_{max} column are presented as median (min, max).
AUC_{0-inf} for single dose; $C_{tau} = C_{12}$ for single dose
There was a 4 days washout between periods
Treatment A: FTR ER tablet 600 mg
Treatment B: FTR ER tablet 600 mg + high-fat meal
Treatment C: FTR ER tablet 600 mg + Famotidine
Abbreviations: AUC_{0-inf}, area under plasma concentration-time curve from time zero to infinity; AUC_{0-t}, area under plasma concentration-time curve from time zero to time t; C_{12}, concentration at the end of the 12-hour interval; CI, confidence interval; C_{max}, maximum observed plasma concentration; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; TMR, temsavir.

Conclusion

$AUC_{0\text{-}inf}$ of TMR was 80% higher when FTR was administered with a high-fat meal as compared to fasting conditions. However, there was no impact on C_{max}. Famotidine, when administered 2 hours prior to the administration of FTR, did not affect TMR exposure.

Fostemsavir PK in Subjects with Renal Impairment (206217)

Study Design

Study 206217 was an open-label study to evaluate the PKs and safety of FTR in subjects with normal renal function and subjects with mild, moderate, severe, and end-stage renal disease (ESRD). The study enrolled six subjects in each RI group based on estimated glomerular filtration rate (determined by the Modification of Diet in Renal Disease formula). Subjects received a single dose of 600 mg ER tablets under fed conditions. In addition, effects of hemodialysis on the PK of TMR was also determined in subjects with ESRD. Subjects with ESRD received a single dose of FTR ER tablets 600 mg under fed condition in Period 1 after HD (off HD) and in Period 2 four hours before HD (on HD).

Plasma, urine, and dialysate samples were collected up to 96 hours for TMR PK, one 4-hour PK sample was collected to evaluate TMR plasma protein binding.

Results

Table 105. TMR PK Parameters After Single Dose Administration in Subjects With Renal Impairment (RI)

Degree of RI	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)
Normal	1,337.7 (956.9, 1,870.1)	7,867.6 (5,523.6, 11,206.5)	8,311.0 (5,900.7, 11,705.9)
Mild	1,849.4 (1,322.9, 2,585.3)	11,644.6 (8,175.2, 16,586.3)	11,757.7 (8,347.8, 16,560.4)
Moderate	1,631.9 (1,167.4, 2,281.4)	10,702.3 (7,513.7, 15,244.1)	9,785.0 (6,723.8, 14,239.9)
Severe	1,432.9 (1,025.0, 2,003.1)	11,249.9 (7,898.1, 16,024.1)	10,316.3 (6,781.8, 15,692.9)
ESRD (off HD)	888.4 (635.5, 1,242.0)	7,695 (5,402.4, 10,960.6)	8,028.1 (5,699.8, 11,307.4)

Data source: CSR 206217 Table 15
All values are expressed as geometric mean (90% CI).
Mild RI= eGFR 60 to 89 mL/min/1.73m^2; Moderate RI =eGFR 30 to <60 mL/min/1.73m^2; Severe RI = eGFR <30 and not requiring HD; ESRD= eGFR <30 and requiring HD
Abbreviations: AUC_{0-inf}, area under the concentration-time curve from time 0 to infinity after drug administration; AUC_{0-t}, area under plasma concentration-time curve from time zero to time t; CI, confidence interval; C_{max}, maximum plasma concentration of drug; ESRD, end-stage renal disease; HD, hemodialysis; PK, pharmacokinetic; TMR, temsavir.

Table 106. Unbound TMR PK Parameters After Single Dose Administration in Subjects With Renal Impairment (RI)

Degree of RI	$C_{max,fu}$ (ng/mL)	$AUC_{0-t,fu}$ (ng·h/mL)	$AUC_{0-inf,fu}$ (ng·h/mL)
Normal	157.4 (114.8, 215.7)	925.5 (669.4, 1,279.8)	977.7 (726.8, 1,315.2)
Mild	226.6 (165.4, 310.6)	1,427.0 (1,032.1, 1,973.2)	1,440.9 (1,071.2, 1,938.3)
Moderate	216.0 (157.6, 296.0)	1,416.3 (1,024.3, 1,958.4)	1,299.6 (939.1, 1,798.4)
Severe	266.8 (194.7, 365.6)	2,094.5 (1,514.8, 2,896.1)	1,811.4 (1,259.8, 2,604.6)
ESRD (off HD)	141.4 (103.2, 193.8)	1,224.8 (885.8, 1,693.6)	1,277.8 (949.9, 1,718.9)

Data source: CSR 206217 Table 15
All values are expressed as geometric mean (90% CI).
Unbound plasma PK parameter values were derived by multiplying the plasma total PK parameter value by the unbound fraction measured from the 4-hour post-dose PK sample.
Abbreviations: $AUC_{0-inf,fu}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity for free drug; $AUC_{0-t,fu}$ area under plasma concentration-time curve from time zero to time t for free drug; CI, confidence interval; $C_{max,fu}$, maximum plasma concentration of free drug; ESRD, end-stage renal disease; fu, fraction of unbound drug; HD, hemodialysis; PK, pharmacokinetic; TMR, temsavir.

Table 107. Effect of Renal Impairment on Plasma Total and Unbound TMR PK Parameters

RI Comparison	C_{max}	AUC_{0-t}	AUC_{0-inf}	$C_{max,fu}$	$AUC_{0-t,fu}$	$AUC_{0-inf,fu}$
Mild vs. normal	1.38 (0.861, 2.22)	1.48 (0.897, 2.44)	1.42 (0.872, 2.30)	1.44 (0.922, 2.25)	1.54 (0.975, 2.44)	1.47 (0.969, 2.24)
Moderate vs. normal	1.22 (0.760, 1.96)	1.36 (0.825, 2.24)	1.18 (0.708, 1.96)	1.37 (0.879, 2.14)	1.53 (0.968, 2.42)	1.33 (0.856, 2.06)
Severe vs. normal	1.07 (0.667, 1.72)	1.43 (0.867, 2.36)	1.24 (0.722, 2.13)	1.70 (1.09, 2.65)	2.26 (1.43, 3.58)	1.85 (1.16, 2.96)
ESRD* vs. normal	0.664 (0.414, 1.07)	0.978 (0.593, 1.61)	0.966 (0.595, 1.57)	0.899 (0.575, 1.40)	1.32 (0.837, 2.09)	1.31 (0.859, 1.99)

Data source: CSR 206217 Table 14
All values are expressed as adjusted geometric mean ratio (90% CI).
N=6 for each group, except AUC_{0-inf} and $AUC_{0-inf,fu}$ for moderate RI (N=5) and severe RI (N=4). Unbound plasma PK parameter values derived by multiplying total by the unbound fraction measured from a 4-hour post-dose PK sample.
* Subjects with ESRD received a single dose of FTR ER tablets 600 mg under fed condition after HD.
Abbreviations: $AUC_{0-inf,fu}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity for free drug; $AUC_{0-t,fu}$ area under plasma concentration-time curve from time zero to time t for free drug; CI, confidence interval; $C_{max,fu}$, maximum plasma concentration of free drug; ESRD, end-stage renal disease; fu, fraction of unbound drug; PK, pharmacokinetic; RI, renal impairment; TMR, temsavir.

HD in subjects with ESRD was associated with an 11% reduction in TMR $AUC_{0\text{-}inf}$ and a 46% increase in C_{max} compared to the same subjects with ESRD off HD. Approximately 12.3% of the administered dose was removed during the 4-hour HD session.

Conclusions

Plasma total TMR C_{max} and $AUC_{0\text{-}inf}$ were <2-fold higher in subjects with varying degrees of renal impairment as compared to subjects with normal renal function. The unbound fraction of TMR was slightly higher in subjects with severe renal impairment compared to those with normal renal function. No significant difference in TMR PK was observed between patients on-dialysis and off-dialysis.

Fostemsavir PK in Subjects with Hepatic Impairment

Study Design

Study 206280 was an open-label, parallel group study to evaluate FTR safety and PK in subjects with hepatic impairment (HI) compared to subjects with normal hepatic function. The study enrolled six subjects in each HI group based on Child-Pugh classification, and 12 subjects with normal hepatic function.

Subjects received a single dose of 600 mg FTR ER tablets under the fasted state. Serial plasma PK samples for analysis of TMR were collected up to 72 hours (normal hepatic function) or 96 hours (HI groups) after dosing. PK samples were collected at 1 hour and 3 hours after dosing were collected to evaluate TMR plasma protein binding.

Results

Table 108. TMR PK Parameters After Single Dose Administration in Subjects With Hepatic Impairment (HI)

Degree of HI	C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng·h/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)
Normal	1,473 (1,246, 1,741)	7,676 (6,181, 9,534)	7,884 (6,370, 9,758)
Mild	1,967 (1,553, 2,492)	9,054 (6,664, 12,301)	9,420 (6,967, 12,735)
Moderate	2,174 (1,716, 2,755)	12,088 (8,897, 16,423)	12,780 (9,453, 17,279)
Severe	2,529 (1,996, 3,205)	13,371 (9,842, 18,167)	13,606 (10,064, 18,396)

Data Source Table 9.2.2-1: CSR 206280
All values are expressed as adjusted geometric mean (90% CI).
Mild HI = Child-Pugh A; Moderate HI = Child-Pugh B; Severe HI = Child-Pugh C
Abbreviations: $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time 0 to time infinity; $AUC_{0\text{-}t}$, area under plasma concentration-time curve from time zero to time t; CI, confidence interval; C_{max}, maximum plasma concentration; HI, hepatic impairment; PK, pharmacokinetic; TMR, temsavir.

Table 109. Unbound TMR PK Parameters After Single Dose Administration in Subjects With Hepatic Impairment (HI)

Degree of HI	$C_{max,fu}$ (ng/mL)	$AUC_{0-t,fu}$ (ng·h/ mL)	$AUC_{0-inf,fu}$ (ng·h/ mL)
Normal	268 (222, 325)	1,399 (1,086, 1,803)	1,437 (1,121, 1,843)
Mild	392 (299, 514)	1,806 (1,262, 2,583)	1,878 (1,321, 2,670)
Moderate	380 (290, 499)	2,115 (1,478, 3,026)	2,236 (1,573, 3,179)
Severe	578 (441, 757)	3,054 (2,135, 4,370)	3,108 (2,186, 4,418)

Data Source Table 9.2.2-1: CSR 206280
All values are expressed as adjusted geometric mean (90% CI).
Unbound plasma PK parameter values were derived by multiplying the plasma total PK parameter value by the unbound fraction measured.
Abbreviations: AUC0-inf,fu, area under the plasma concentration-time curve from time 0 extrapolated to infinity for free drug; AUC_{0-t}, area under plasma concentration-time curve from time zero to time t for free drug; CI, confidence interval; $C_{max,fu}$, maximum plasma concentration of free drug; fu, fraction of unbound drug; HI, hepatic impairment; PK, pharmacokinetic; TMR, temsavir.

Table 110. Effect of Hepatic Impairment (HI) on Plasma TMR PK Parameters

HI Comparison	C_{max}	AUC_{0-inf}	$C_{max,fu}$	$AUC_{0-inf,fu}$
Mild HI vs. normal	1.34 (1.00, 1.79)	1.20 (0.826, 1.73)	1.46 (1.05, 2.04)	1.31 (0.850, 2.01)
Moderate HI vs. normal	1.48 (1.11, 1.97)	1.62 (1.12, 2.35)	1.42 (1.02, 1.97)	1.56 (1.01, 2.39)
Severe HI vs. normal	1.72 (1.29, 2.30)	1.73 (1.19, 2.50)	2.15 (1.55, 3.00)	2.16 (1.41, 3.33)

Data Source Table 4: CSR 206280
All values are expressed as adjusted geometric mean ratio (90% CI).
Abbreviations: $AUC_{0-inf,}$ area under the plasma concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; fu, fraction of unbound drug; HI, hepatic impairment; PK, pharmacokinetic; TMR, temsavir.

Conclusions

Plasma total and unbound TMR C_{max} and AUC_{0-inf} were higher in subjects with moderate HI, and severe HI compared with subjects with normal hepatic function. The magnitude of the increase of TMR concentrations in moderate and severe hepatic impairment subjects versus controls is not clinically significant.

Drug Interaction With Darunavir/Cobicistat and Cobicistat (206285)

Study Design

Study 206285 was a Phase 1, nonrandomized, open-label, two-period, single-sequence, crossover trial to evaluate the interaction between FTR and cobicistat (COBI) and between FTR and darunavir (DRV)/COBI in healthy adult subjects and to evaluate the effect of FTR on COBI PK.

Period 1 (Days 1 to 4):

- Treatment A FTR 600 mg BID
- Treatment C FTR 600 mg BID

Period 2 (Days 5 to 14):

- Treatment B FTR 600 mg BID + DRV/COBI 800/150 mg QD
- Treatment D FTR 600 mg BID + COBI 150 mg QD

FTR was administered orally as ER tablets under fed conditions in the morning and evening. Serial plasma PK samples were collected over 12 hours after the last dose in each period for TMR analysis and over 24 hours after the last dose in Period 2 for COBI analysis.

Results

Table 111. Effect of DRV/COBI 800/100 mg QD on Plasma TMR PKs Following Coadministration With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
FTR (Trt A)	2,045 (33)	10,214 (32)	219 (50)
FTR+DRV/COBI (Trt B)	3,768 (30)	20,835 (31)	504 (40)
Trt B vs. Trt A	1.79 (1.62, 1.98)	1.97 (1.78, 2.18)	2.24 (1.75, 2.88)

Data Source: Study 206285 CSR Table 9.2.1.1-1, Table 9.2.1.1-2
All values are expressed as geometric mean (% CV) except those in the last row (Trt B vs. Trt A), which are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; COBI, cobicistat; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; TMR, temsavir; Trt, treatment.

Table 112. Effect of COBI 150 mg QD on Plasma TMR PKs Following Coadministration With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
FTR (Trt C)	2,096 (22)	10,417 (30)	202 (58)
FTR+COBI (Trt D)	3,515 (37)	19.976 (39)	449 (60)
Trt D vs. Trt C	1.71 (1.54, 1.90)	1.93 (1.75, 2.12)	2.36 (2.03, 2.75)

Data Source: Study 206285 CSR Table 9.2.1.2-2
All values are expressed as geometric mean (% CV) except those in the last row (Trt D vs. Trt C), which are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; COBI, cobicistat; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; TMR, temsavir; Trt, treatment.

The effect of FTR on COBI PK Parameters was also evaluated in this study.

Table 113. COBI PK Parameters Following Coadministration of COBI 150 mg QD and DRV/COBI 800/150 mg QD With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
DRV/COBI+FTR (Trt B)	1,038 (22)	7,910 (29)	25.1 (70)
COBI+FTR (Trt D)	1,486 (26)	11,754 (42.)	64.4 (97)

Data Source: Study 206285 CSR Table 9.2.2-1
All values are expressed as geometric mean (% CV).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; COBI, cobicistat; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; Trt, treatment.

Conclusion

The coadministration of COBI or DRV/COBI increased TMR exposure approximately by 2-fold. The use of COBI-boosted protease inhibitors(PIs) was allowed in the Phase 3 trial. The use of COBI or DRV/COBI with FTR is supported by safety and efficacy data observed in the Phase 3 trial.

Drug Interaction with Darunavir/Ritonavir and/or Etravirine

Study Design: Study 206281 was a randomized, open-label, three-period, single- sequence, crossover study to evaluate the interaction between FTR and DRV/r, etravirine (ETR), and ETR + DRV/r in healthy adult subjects. Subjects received following study drugs under fed condition. All subjects received FTR in Period 1, then subjects received two of six other treatments in Periods 2 and 3.

Period 1 (Days 1 to 4):

- Treatment A: FTR 600 mg BID

Period 2 (Days 7 to 16):

- Treatment B: DRV/r 600/100 mg BID
- Treatment C: ETR 200 mg BID
- Treatment B + C: DRV/r 600/100 mg BID + ETR 200 mg BID

Period 3 (Days 17 to 26):

- Treatment A + B: FTR 600 mg BID + DRV/r 600/100 mg BID
- Treatment A + C: FTR 600 mg BID + ETR 200 mg BID
- Treatment A + B + C: FTR 600 mg BID + DRV/r 600/100 mg BID + ETR 200 mg BID

Serial plasma PK samples for TMR, DRV, RTV, and/or ETR analysis were collected over 12 hours after the last dose in each period.

Results

Table 114. Effect of DRV/r on Plasma TMR PKs Following Coadministration of DRV/r 600/100 mg BID With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
FTR	2,033 (50)	12,632 (44)	308 (127)
DRV/r+FTR	3,188 (74)	20,457 (59)	628 (32)
DRV/r+FTR vs. FTR	1.52 (1.28, 1.82)	1.63 (1.42, 1.88)	1.88 (1.09, 3.22)

Data Source: Study 206281 CSR Table 9.2-2
All values are expressed as geometric mean (% CV) except those in the last row (DRV/r+FTR vs FTR), which are expressed as geometric mean ratio (% CV).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve from time zero to 12 hours (over the dosing interval); BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval (12 hours); CV, coefficient of variation; DRV, darunavir; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir; TMR, temsavir.

Table 115. Effect of ETR on Plasma TMR PKs Following Coadministration of ETR 200 mg BID With FTR ER Tablets 600 mg BID Without DRV/r 600/100 mg BID

Treatment	C_{max}	AUC_{tau}	C_{tau}
FTR	1,941 (27)	13,364 (33)	479 (77)
ETR+FTR	1,003 (35)	6,714 (36)	231 (78)
ETR+FTR vs. FTR	0.516 (0.454, 0.587)	0.502 (0.442, 0.571)	0.483 (0.324, 0.720)

Data Source: Study 206281 CSR Table 9.2-4
All values are expressed as geometric mean (% CV) except for those in the last row (ETR+FTR vs. FTR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ER, extended-release; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir; TMR, temsavir.

Table 116. Effect of ETR on Plasma TMR PKs Following Coadministration of ETR 200 mg BID With FTR ER Tablets 600 mg BID and With DRV/r 600/100 mg BID

Treatment	C_{max}	AUC_{tau}	C_{tau}
FTR	1,568 (43)	10,339 (33)	312 (100)
ETR+DRV/r+FTR	2,383 (22)	13,502 (35)	393 (103)
ETR+DRV/r+FTR vs. FTR	1.53 (1.32, 1.77)	1.34 (1.17, 1.53)	1.33 (0.980, 1.81)

Data Source: Study 206281 CSR Table 9.2-6
All values are expressed as geometric mean (% CV) except for those in the last row (ETR + DRVRTV + FTR vs. FTR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ER, extended-release; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir; TMR, temsavir.

Table 117. Effect of FTR on Plasma DRV PKs Following Coadministration of FTR 600 mg BID With DRV/r 600/100 mg BID With ETR 200 mg BID

Treatment	C_{max}	AUC_{tau}	C_{tau}
DRV/r+ETR	10,105 (13)	77,739 (14)	3,672 (30)
FTR+DRV/r+ETR	9,636 (16)	72,907 (20)	3,234 (37)
FTR+DRV/r+ETR vs. DRV/r+ETR	0.954 (0.903, 1.01)	0.938 (0.888, 0.991)	0.881 (0.769, 1.01)

Data Source: Study 206281 CSR Table 9.3-3
All values are expressed as geometric mean (% CV) except for those in the last row (FTR+DRV/r+ETR vs. DRV/r+ETR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ER, extended-release; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir.

Table 118. Effect of FTR on Plasma DRV PKs Following Coadministration of FTR 600 mg BID With DRV/r 600/100 mg BID Without ETR 200 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
DRV/r	8,785 (14)	68,380 (15)	3,633 (22)
FTR+DRV/r	8,567 (15)	63.968 (20)	3,432 (28)
FTR+DRV/r vs. DRV/r	0.983 (0.931, 1.04)	0.944 (0.894, 0.996)	0.948 (0.865, 1.04)

Data Source: Study 206281 CSR Table 9.3-4
All values are expressed as geometric mean (% CV) except for those in the last row (FTR+DRV/r vs. DRV/r), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir.

Table 119. Effect of FTR on Plasma RTV PKs Following Coadministration of FTR 600 mg BID With DRV/r 600/100 mg BID With ETR 200 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
DRV/r+ETR	862 (33)	4,928 (25)	157 (23)
FTR+DRV/r+ETR	982 (32)	5,380 (18)	168 (27)
FTR+DRV/r+ETR vs. DRV/r+ETR	1.14 (0.960, 1.35)	1.09 (0.979, 1.22)	1.07 (0.972, 1.17)

Data Source: Study 206281 CSR Table 9.4-1, Table 9.4-2
All values are expressed as geometric mean (% CV) except for those in the last row (FTR+DRV/r+ETR vs. DRV/r+ETR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir.

Table 120. Effect of FTR on Plasma RTV PKs Following Coadministration of FTR 600 mg BID With DRV/r 600/100 mg BID Without ETR 200 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
DRV/r	1,324 (33)	7,191 (38)	229 (53)
FTR+DRV/r	1,261 (47)	7,675 (45)	248 (49)
FTR+DRV/r vs. DRV/r	0.995 (0.856, 1.16)	1.15 (0.992, 1.33)	1.19 (1.06, 1.35)

Data Source: Study 206281 CSR Table 9.4-3, Table 9.4-4
All values are expressed as geometric mean (% CV) except for those in the last row (FTR+DRV/r vs. DRV/r), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir.

Table 121. Effect of FTR on Plasma ETR PKs Following Coadministration of FTR 600 mg BID With ETR 200 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
ETR	846 (26)	7,825 (28)	457 (36)
FTR+ETR	943 (30)	8,670 (29)	522 (33)
FTR+ETR vs. ETR	1.11 (1.04, 1.19)	1.11 (1.05, 1.17)	1.14 (1.08, 1.21)

Data Source: Study 206281 CSR Table 9.5-1, Table 9.5-2
All values are expressed as geometric mean (% CV) except for those in the last row (FTR+ETR vs. ETR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir.

Table 122. Effect of FTR on Plasma ETR PKs Following Coadministration of FTR 600 mg BID With ETR 200 mg BID and DRV/r 600/100 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
ETR+DRV/r	838 (52)	7,102 (55)	417 (76)
FTR+ETR+DRV/r	989 (62)	9,071 (71)	533 (94)
FTR+ETR+DRV/r vs. ETR	1.18 (1.10, 1.27)	1.28 (1.20, 1.36)	1.28 (1.18, 1.39)

Data Source: Study 206281 CSR Table 9.5-3, Table 9.5-4
All values are expressed as geometric mean (% CV) except for those in the last row (FTR+ETR+DRV/r vs. ETR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; RTV, ritonavir.

Conclusions

Coadministration of DRV/r with FTR resulted in an increase in exposure of TMR, likely due to inhibition of CYP3A.

Coadministration of ETR with FTR decreased plasma TMR C_{max}, AUC_{tau}, and C12 by approximately 50% due to the induction of CYP3A. However, following coadministration of the combination of DRV/r, ETR, and FTR, the effects of ETR on CYP3A4 are nullified. FTR had no effect on plasma DRV or RTV exposures when co-administered with DRV/r or DRV/r + ETR.

Coadministration of FTR with DRV/r and/or ETR did not have a clinically relevant effect on the exposure of ETR.

Drug Interactions with Atazanavir (ATV)/Ritonavir and Ritonavir (206269)

Study Design

Study 206269 was a Phase 1, randomized, open-label, three-period, four-sequence, crossover trial to evaluate the interaction between FTR and atazanavir (ATV)/RTV in healthy adult subjects. Subjects received following study drugs under fed condition. All subjects received FTR in Period 1.

Table 123. Study 206269 Design

Period 1 (Days 1-5)	Period 2 (Days 6-15)	Period 3 (Days 16-25)
Treatment A	Treatment B	Treatment D
	Treatment D	Treatment B
	Treatment C	Treatment D
	Treatment D	Treatment C

Treatment A: FTR 600 mg BID
Treatment B: FTR 600 mg BID+RTV 100 mg QD
Treatment C: ATV/r 300/100 mg QD
Treatment D: FTR 600 mg BID+ATV/r 300/100 mg QD

Serial plasma PK samples were collected over 12 hours after the last dose for TMR analysis and/or over 24 hours after the last dose for ATV and RTV analyses.

Results

Table 124. Effect of RTV on Plasma TMR PKs Following Coadministration of RTV 100 mg QD With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
FTR	1,781 (1,534, 2,067)	11,707 (10,205, 13,429)	362 (283, 464)
FTR+RTV	2,724 (2,259, 3,284)	16,913 (14,055, 20,352)	523 (361, 758)
FTR+RTV vs. FTR	1.53 (1.31, 1.79)	1.45 (1.29, 1.61)	1.44 (1.00, 2.08)

Data Source: Study 206269 CSR Table 9.2.4
All values are expressed as geometric mean (% CV), except for those in the last row (FTR+RTV vs. FTR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; ER, extended-release; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; RTV, ritonavir; TMR, temsavir.

Table 125. Effect of ATV/r on Plasma TMR PKs Following Coadministration of ATV/r 300/100 mg QD With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
FTR	1,878 (1,690, 2,087)	12,040 (10,865, 13,342)	12,040 (10,865, 13,342)
ATV/r+FTR	3,150 (2,808, 3,533)	18,559 (16,412, 20,987)	560 (467, 672)
ATV/r+FTR vs. FTR	1.68 (1.58, 1.79)	1.54 (1.44, 1.65)	1.57 (1.28, 1.91)

Data Source: Study 206269 CSR Table 9.2.2
All values are expressed as geometric mean (% CV), except for those in the last row (ATV/r+FTR vs. FTR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: ATV, atazanavir; AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; ER, extended-release; ETR, etravirine; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; RTV, ritonavir; TMR, temsavir.

Table 126. Effect of FTR on Plasma ATV PKs Following Coadministration of FTR 600 mg BID With ATV/r 300/100 mg QD

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
ATV/r	5,957 (5,518, 6,430)	54,823 (49,532, 60,680)	1,105 (934, 1,308)
FTR+ATV/r	6,121 (5,798, 6,462)	59,674 (55,164, 64,552)	1,318 (1,163, 1,493)
FTR+ATV/r vs. ATV/r	1.03 (0.963, 1.10)	1.09 (1.03, 1.15)	1.19 (1.10, 1.30)

Data Source: Study 206269 CSR Table 9.3.2
All values are expressed as geometric mean (% CV), except for those in the last row (FTR+ATV/r vs. ATV/r), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: ATV, atazanavir; AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; RTV, ritonavir.

Conclusions

The coadministration of ATV/r or RTV alone increased TMR exposure approximately by 50%, which is not considered clinically significant. FTR did not alter the PK of ATV. ATV/r and FTR can be coadministered.

Rifabutin and Rifabutin + Ritonavir Interaction With Repeat Doses of FTR ER Tablets and Effect on PK of Metabolites BMS-646915 and BMS-930644 (206282)

Study Design

Study 206282 was a Phase 1, randomized, open-label, two-period, single-sequence, crossover trial to evaluate the interaction between FTR and rifabutin, with and without RTV, in healthy adult subjects. Subjects were randomized to one of two cohorts; all subjects received FTR in Period 1, then subjects received a combination regimen in Period 2.

- Period 1 (Days 1 to 4):
- Regimen A: FTR 600 mg BID

On Day 5, subjects were randomly assigned to one of the two cohorts as follows.

Period 2 (Days 5 to 15):

- Regimen B (Cohort 1): FTR 600 mg BID +Rifabutin 300 mg QD
- Regimen C (Cohort 2): FTR 600 mg BID +Rifabutin 150 mg QD +RTV 100 mg QD

All study drugs were administered with a standard meal. Serial plasma PK samples were collected over 12 hours after the last dose in each period for analysis of TMR and two metabolites, BMS-646915 (hydrolysis metabolite) and BMS-930644 (N-dealkylation metabolite), and over 24 hours after the last dose in Period 2 for rifabutin analysis.

Results

Table 127. Effect of Rifabutin on Plasma TMR PKs Following Coadministration of Rifabutin 300 mg QD With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
FTR	2,398 (23)	14,736 (27)	387 (74)
FTR+RFB	1,820 (40)	10,418 (33)	225 (78)
FTR+RFB vs. FTR	0.732 (0.647, 0.829)	0.698 (0.642, 0.760)	0.594 (0.461, 0.766)

Data Source: Study 206282 CSR Table 9.2.2-2
All values are expressed as geometric mean (% CV), except for those in the last row (FTR+RFB vs. FTR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; RFB, rifabutin; TMR, temsavir.

Table 128. Effect of Rifabutin on Plasma TMR PKs Following Coadministration of Rifabutin 150 mg QD + RTV 100 mg QD With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
FTR	2,419 (37)	14,097 (38)	328 (85)
FTR+RFB+RTV	3,827 (35)	25,664 (39)	867 (46)
FTR+RFB+RTV vs. FTR	1.50 (1.38, 1.64)	1.66 (1.52, 1.81)	2.58 (1.95, 3.42)

Data Source: Study 206282 CSR Table 9.3.2-2
All values are expressed as geometric mean (% CV), except for those in the last row (FTR+Rifabutin+RTV vs. FTR), in which values are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; RFB, rifabutin; RTV, ritonavir; TMR, temsavir.

PK of BMS-646915 and BMS-930644 following oral administration of FTR alone (600 mg ER tablets BID for 4 days) or administered with rifabutin with or without RTV in Cohort 1 and Cohort 2 are presented in Table 129, Table 130, and Table 131, below.

Table 129. PKs of Metabolite BMS-646915

Cohort	Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)
Cohort 1	FTR	354 (28)	3,276 (34)
	FTR+RFB	299 (38)	2,487 (40)
Cohort 2	FTR	312 (32)	2,838 (33)
	FTR+RFB+RTV	489 (34)	4,683 (36)

Data Source: 206282 CSR Table 9.2.4-1; 206282 CSR Table 9.2.6-1.
All values are expressed as geometric mean (% CV).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; RFB, rifabutin; RTV, ritonavir.

Table 130. PKs of Metabolite BMS-930644

Cohort	Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)
Cohort 1	FTR	412 (34)	4,077 (36)
	FTR+RFB	792 (60)	6,915 (42)
Cohort 2	FTR	458 (39)	4,566 (39)
	FTR+RFB+RTV	114 (40)	1,069 (38)

Data Source: 206282 CSR Table 9.2.4-1; 206282 CSR Table 9.2.6-1.
All values are expressed as geometric mean (% CV).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; RFB, rifabutin; RTV, ritonavir.

Table 131. Metabolite/Parent Ratios Following Administration of FTR ER Tablets 600 mg BID Alone, Coadministered With RFB 300 mg QD, and Coadministered With RFB 150 mg QD + RTV 100 mg QD

	Plasma PK	Cohort 1		Cohort 2	
Metabolite/Parent	Parameter	FTR	FTR+RFB	FTR	FTR+RFB+RTV
BMS-930644/TMR	C_{max} ratio	0.182 (33)	0.460 (48)	0.201 (28)	0.032 (27)
	AUC_{tau} ratio	0.293 (31)	0.702 (36)	0.343 (29)	0.044 (31)
BMS-646915/TMR	C_{max} ratio	0.189 (24)	0.211 (27)	0.165 (26)	0.164 (30)
	AUC_{tau} ratio	0.285 (17)	0.306 (16)	0.258 (26)	0.234 (29)

Data Source: Study 206282 CSR Table 9.2.6-1, Table 9.3.6-1, Table 9.2.4-1, Table 9.3.4-1
All values are expressed as geometric mean (% CV).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; C_{max}, maximum plasma concentration; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; RFB, rifabutin; RTV, ritonavir; TMR, temsavir.

Conclusions

- Coadministration of rifabutin, a CYP3A inducer, with FTR 600 mg BID decreased plasma TMR concentrations; TMR exposure were increased when FTR 600 mg BID was coadministered with the combination of rifabutin 150 mg QD + RTV 100 mg BID.
- Coadministration of rifabutin 300 mg QD with FTR 600 mg BID increased plasma BMS-930644 (N-alkylation metabolite formed by CYP3A) concentrations and the BMS-930644/TMR C_{max} and AUC_{tau} ratios, consistent with rifabutin CYP3A induction. Adding RTV to the regimen decreased plasma BMS-930644 concentrations and the BMS-930644/TMR C_{max} and AUC_{tau} ratios, consistent with RTV CYP3A inhibition. In contrast, the coadministration of rifabutin did not significantly alter the PK of BMS-646965, a metabolite formed by esterases.
- Metabolite BMS-646915 is produced by hydrolysis by an esterase. Therefore, coadministration of rifabutin 300 mg QD with FTR 600 mg BID did not affect plasma BMS-646915 concentrations and the BMS-646915/TMR C_{max} and AUC_{tau} ratios.

Effect of Raltegravir (RAL) +Tenofovir Disoproxil Fumarate (TDF) on Plasma TMR PK Following Coadministration With FTR (205889)

Study Design

Study 205889 was a Phase 2b, randomized, parallel, active-controlled, dose ranging study to Investigate efficacy and Dose-Response of FTR in treatment-experienced HIV-1 patients. Subjects were randomized to 1 of 4 FTR dosage regimens or the active control ATV/r (all in combination with raltegravir [RAL] + tenofovir disoproxil fumarate [TDF]):

- FTR 400 mg BID + RAL 400 mg BID + TDF 300 mg QD
- FTR 800 mg BID + RAL 400 mg BID + TDF 300 mg QD
- FTR 600 mg QD + RAL 400 mg BID + TDF 300 mg QD
- FTR 1,200 mg QD+ RAL 400 mg BID + TDF 300 mg QD

The study also included an assessment of FTR monotherapy for 7 days in a subset of subjects who had not received RAL treatment. FTR was administered as ER tablets with food. Serial plasma PK samples were collected over 24 hours after dosing on Day 7 in the monotherapy substudy and on Week 2 in a subset of subjects receiving FTR combination therapy; samples were analyzed for TMR and RAL from combination therapy study.

Reviewer Comments: *Refer to Section II.6.3 for PK, efficacy and safety findings in this Phase 2 trial.*

Results

Table 132. Plasma TMR and RAL PK Parameters Following Repeat Dose Administration of FTR ER Tablets in the Fed State in HIV-1 Infected Patients With Combination Therapy With RAL 400 mg BID + TDF 300 mg QD

		TMR PK			RAL PK		
Trt Regimen	**N**	**C_{max} (ng/mL)**	**AUC_{tau} (ng·h/mL)**	**C_{tau} (ng/mL)**	**C_{max} (ng/mL)**	**AUC_{tau} (ng·h/mL)**	**C_{tau} (ng/mL)**
Group 1	20	1,400 (44)	8,923 (36)	284 (87)	2,120 (64)	9,825 (57)	259 (182)
Group 2	12	3,290 (42)	20,905 (46)	603 (59)	2,330 (79)	8,776 (77)	149 (73)
Group 3	19	1,480 (44)	14,784 (50)	99.3 (165)	2,760 (72)	11,402 (59)	199 (126)
Group 4	17	4,220 (49)	29,611 (63)	127 (128)	3,370 (65)	14,983 (49)	214 (81)

Source: Study 205889 PK Report Table 5.2.2-1 and Table 5.1.2-2
All values are expressed as geometric mean (% CV).
Group 1: FTR 400 mg BID + RAL 400 mg BID + TDF 300 mg QD
Group 2: FTR 800 mg BID + RAL 400 mg BID + TDF 300 mg QD
Group 3: FTR 600 mg QD + RAL 400 mg BID + TDF 300 mg QD
Group 4: FTR 1,200 mg QD + RAL 400 mg BID + TDF 300 mg QD
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; RAL, raltegravir; RFB, rifabutin; RTV, ritonavir; TDF, tenofovir disoproxil fumarate; TMR, temsavir; Trt, treatment.

Table 133. TMR PK From FTR Monotherapy and Effect of RAL 400 mg BID + TDF 300 mg QD on Plasma TMR PKs Following Coadministration With FTR ER Tablets QD or BID in HIV-1 Infected Subjects and GMR (90% CI)

FTR Dosage		**TMR PK From FTR Monotherapy**			**TMR PK From FTR+RAL+TDF vs. FTR[a]**		
Regimen	**N**	**C_{max} (ng/mL)**	**AUC_{tau} (ng·h/mL)**	**C_{tau} (ng/mL)**	**C_{max}**	**AUC_{tau} (ng·h/mL)**	**C_{tau}**
Group 1	6	1,380 (38)	7,136 (36)	142 (69)	0.824 (0.610, 1.11)	0.979 (0.782, 1.23)	1.92 (0.929, 3.98)
Group 2	4	3,790 (47)	22,138 (38)	733 (32)	0.895 (0.572, 1.40)	0.948 (0.658, 1.37)	0.998 (0.345, 2.89)
Group 3	10	2,000 (45)	12,789 (43)	57.2 (95)	0.960 (0.742, 1.24)	1.16 (0.952, 1.42)	2.06 (1.11, 3.81)
Group 4	9	1,830 (68)	22,622 (49)	83.6 (148)	1.23 (0.923, 1.64)	1.07 (0.844, 1.34)	1.17 (0.587, 2.32)

Source: Study 205889 PK Report Table 5.2.2-1 and Table 5.1.2-2
The TMR PK values from FTR monotherapy are expressed as geometric mean (% CV). The TMR PK values from FTR+RAL+TDF vs. FTR are expressed as geometric mean ratio (90% CI).
[a] Between-subject comparison; All FTR dosage regimens were in combination with RAL 400 mg BID + TDF 300 mg QD except FTR Monotherapy substudy
Group 1: FTR 400 mg BID
Group 2: FTR 800 mg BID
Group 3: FTR 600 mg QD
Group 4: FTR 1,200 mg QD
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; GMR, geometric mean ratio; PK, pharmacokinetic; QD, once a day; RAL, rategravir; RFB, rifabutin; RTV, ritonavir; TDF, tenofovir disoproxil fumarate; TMR, temsavir.

Conclusion

Coadministration of FTR with RAL + TDF did not have clinically significant effect on plasma TMR concentrations over the dose range of FTR and with two different regimens of FTR. RAL exposures observed in this study were within the ranges of historical data

Drug Interaction With Tenofovir Disoproxil Fumarate (206266)

Study Design

Study 206266 was a nonrandomized, open-label, three-period, single-sequence, crossover study to evaluate the interaction between FTR and TDF in healthy adult subjects. All study drug doses were administered with a standard meal.

Period 1: Subjects received FTR 600 mg BID, Days 1 to 5

Period 2: Subjects received TDF 300 mg QD, Days 6 to 12

Period 3: Subjects received TDF 300 mg QD + FTR 600 mg BID for 6 days

Serial plasma PK samples were collected over 12 hours after the last dose in each period for TMR analysis and over 24 hours after the last dose in each period for tenofovir analysis.

Results

Table 134. Effect of TDF on Plasma TMR PKs Following Administration of TDF 300 mg QD With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau}(ng·h/mL)	C_{tau} (ng/mL)
FTR	2,071 (35.6)	12,190 (33.8)	304 (83.6)
FTR+TDF	2,043 (38.3)	12,234 (37.1)	344 (88.1)
FTR+TDF vs. FTR	0.986 (0.861, 1.13)	1.00 (0.910, 1.11)	1.13 (0.773, 1.66)

Source: Study 206266 CSR Table 9
The values are expressed as geometric LS means (% CV) except those in the last row (FTR+TDF vs. FTR), which are expressed as geometric mean ratio (90% CI).
FTR 600 mg BID, TDF 300 mg QD
$C_{tau} = C_{12}$
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; TDF, tenofovir disoproxil fumarate; TMR, temsavir.

Table 135. Effect of FTR on Plasma TFV PKs Following Administration of TDF 300 mg QD With FTR ER Tablets 600 mg BID

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
TDF	315 (24.2)	2,885 (19.2)	56.6 (20.1)
FTR+TDF	372 (22.7)	3,420 (23.5)	72.7 (24.0)
FTR+TDF vs TDF	1.18 (1.12, 1.25)	1.19 (1.12, 1.25)	1.28 (1.20, 1.38)

Source: Study 206266 CSR Table 11
All values are expressed as geometric LS means (% CV) except those in the last row (FTR+TDF vs. TDF), which are expressed as geometric mean ratio (90% CI).
FTR 600 mg BID, TDF 300 mg QD
$C_{tau} = C_{24}$
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; C_{tau}, concentration at the end of the dosing interval; CV, coefficient of variation; ER, extended-release; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TMR, temsavir.

Conclusions

Coadministration of TDF 300 mg QD with FTR 600 mg BID, administered under a fed condition, did not alter plasma TMR concentrations. The increase in tenofovir exposure following coadministration of TDF with FTR is not considered clinically significant.

FTR Interaction With Rosuvastatin (206276)

Study Design

Study 206276 was a Phase 1, open-label, three-period, single-sequence, crossover trial to evaluate the interaction between FTR 600 mg BID and rosuvastatin 10 mg single dose in adult subjects. The study also assessed time to steady state plasma TMR concentrations.

Period 1: Treatment A- Day 1: Rosuvastatin 10 mg single dose

Period 2: Treatment B- Days 5 to 8: FTR 600 mg BID

Period 3: Treatment C- Days 9 to 12: FTR 600 mg BID, Day 9: Rosuvastatin 10 mg single dose

FTR was administered orally as ER tablets were administered with standard meals (morning doses) and snacks (evening doses). Serial plasma PK samples for rosuvastatin analysis were collected up to 96 hours on Days 1 and 9. Plasma trough PK samples for TMR analysis were collected on Days 7, 8, 9, 11, and 13.

Results

Table 136. Effect of FTR on Plasma Rosuvastatin (RSV) PKs Following Administration of FTR 600 mg BID With a Single Dose of Rosuvastatin 10 mg

Treatment	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)
RSV	2.43 (62.41)	35.48 (51.94)
FTR+RSV	4.33 (48.89)	55.08 (33.35)
FTR+RSV vs. RSV	1.79 (1.51, 2.11) [a]	1.65 (1.45, 1.87)[a, b]

Source: [a] Clinical Pharmacology Review Team's analysis
All values are expressed as geometric mean (% CV) except those in the last row (FTR+RSV vs. RSV), which are expressed as geometric mean ratio (90% CI).
[b] There were 7 subjects who showed AUC_{inf}/AUC_{last}>120%.
Treatments: A = rosuvastatin 10 mg SD on day 1; B = FTR 600 mg BID for 4 days (days 5 to 8); C = rosuvastatin 10 mg SD coadministered with FTR 600 mg BID for 1 day (day 9), followed by FTR 600 mg BID alone for 3 days (days 10 to 12).
Abbreviations: AUC_{inf}, area under plasma concentration-time curve from time 0 to infinity; BID, twice a day; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; FTR, fostemsavir; PK, pharmacokinetic; QD, once a day; RSV, rosuvastatin, SD, single dose.

Conclusion

The coadministration of FTR increased rosuvastatin C_{max} and AUC by 70% and 40%, respectively, likely due to the inhibition of OATP1B and breast cancer resistance protein (BCRP) by FTR. The magnitude of interaction is not considered clinically significant. However, the high-dose and high potency statin without titration may lead to AEs such as rhabdomyolysis in few high-risk patients. Therefore, we agree with the Applicant's proposal to use the lowest possible starting dose for statins and monitor for statin associated AEs.

Drug Interaction With Methadone and Buprenorphine (206216)

Study Design

Study 206216 was a Phase 1, open-label, two-part trial to evaluate the interaction between methadone and FTR (Part 1) and between buprenorphine/naloxone and FTR (Part 2) in both male and female subjects receiving stable ongoing maintenance therapy of methadone (Part 1) or buprenorphine/naloxone (in Part 2) throughout the entire study. All study drug doses were administered with standard meal.

Methadone and FTR (Part 1)

- Treatment A: Current dose of methadone (40 to 120 mg) orally QD on Day 1
- Treatment B: Current dose of methadone (40 to120 mg) orally QD + FTR 600 mg ER BID on Days 2 to 9

Buprenorphine/Naloxone and FTR(Part 2)

- Treatment C: Current dose of buprenorphine/naloxone (8/2-24/6 mg) QD on Day 1
- Treatment D: Current dose of buprenorphine/naloxone (8/2 to 24/6 mg) QD + FTR 600 mg BID on Days 2 to 9

Serial plasma PK samples were collected over 24 hours post dose on Day 1 and Day 9 for methadone (Part 1) and buprenorphine (Part 2), and over 12 hours post dose on Day 9 for TMR.

Results

Part 1: DDI Between Methadone and FTR

Table 137. Statistical Analysis of R-Methadone for Methadone Coadministered With FTR

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{24} (ng/mL)
Treatment A	162 [15] (149, 176)	2,707 [14] (2,450, 2,993)	98.5 [14] (86.3, 113)
Treatment B	187 [16] (173, 202)	3,062 [16] (2,804, 3,343)	107 [16] (94.6, 121)
B vs A	1.153 [15] (1.111, 1.196)	1.131 [14] (1.073, 1.193)	1.086 [14] (1.010, 1.168)

Source: Study206216 CSR Table 9.2.1-1.
All values are expressed as adjusted geometric mean [N] (90% CI) except those in the last row (B vs. A), which are expressed as geometric mean ratio [N] (90% CI).
The parameters C_{max}, AUC_{tau}, and C_{24} are normalized relative to the lowest dose administered.
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{24}, concentration at the end of the 24-hour dosing interval; CI, confidence interval; C_{max}, maximum plasma concentration; FTR, fostemsavir.

Table 138. Statistical Analysis of S-Methadone for Methadone Coadministered With FTR

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{24} (ng/mL)
Treatment A	199 [15] (180, 220)	2,967 [14] (2,593, 3,396)	97.3 [14] (80.7, 117)
Treatment B	228 [16] (206,252)	3,412 [16] (2,974, 3,915)	107 [16] (87.8, 131)
B vs A	1.145 [15] (1.100, 1.191)	1.150 [14] (1.091, 1.212)	1.101 [14] (1.017, 1.191)

Source: Study206216 CSR Table 9.2.1-2.
All values are expressed as adjusted geometric mean [N] (90% CI) except those in the last row (B vs. A), which are expressed as geometric mean ratio [N] (90% CI).
The parameters C_{max}, AUC_{tau}, and C_{24} are normalized relative to the lowest dose administered.
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{24}, concentration at the end of the 24-hour dosing interval; CI, confidence interval; C_{max}, maximum plasma concentration; FTR, fostemsavir.

Table 139. Statistical Analysis of Total Methadone for Methadone Coadministered With FTR

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{24} (ng/mL)
Treatment A	362 [15] (332, 395)	5,702 [14] (5,095, 6,380)	197 [14] (170, 230)
Treatment B	415 [16] (382,452)	6,509 [16] (5,849, 7,244)	216 [16] (186, 252)
B vs A	1.148 [15] (1.109, 1.188)	1.142 [14] (1.088, 1.198)	1.095 [14] (1.020, 1.175)

Source: Study206216 CSR Table 9.2.1-3.
All values are expressed as adjusted geometric mean [N] (90% CI) except those in the last row (B vs. A), which are expressed as geometric mean ratio [N] (90% CI).
The parameters C_{max}, AUC_{tau}, and C_{24} are normalized relative to the lowest dose administered.
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{24}, concentration at the end of the 24-hour dosing interval; CI, confidence interval; C_{max}, maximum plasma concentration; FTR, fostemsavir.

Table 140. Summary Statistics of TMR for Methadone Coadministered With FTR

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{12} (ng/mL)
Treatment B	1,498 [16] (41)	9,758 [16] (40)	409 [16] (60)

Source: Study206216 CSR Table 9.2.1-4.
All values are expressed as adjusted geometric mean [N] (% CV).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{12}, concentration at the end of the 12-hour dosing interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; FTR, fostemsavir; TMR, temsavir.

Part 2: DDI Between Buprenorphine/Naloxone and FTR

Table 141. Statistical Analysis of Buprenorphine for Buprenorphine Coadministered With FTR

Treatment	C_{max} (pg/mL)	AUC_{tau} (pg·h/mL)	C_{24} (pg/mL)
Treatment C	4,187 [16] (3835, 4572)	33,867 [16] (30,230, 37,942)	780 [16] (638, 953)
Treatment D	5,206 [16] (4534, 5977)	44,090 [16] (39,652, 49,024)	1,082 [16] (949, 1234)
D vs C	1.243 [16] (1.056, 1.464)	1.302 [16] (1.170, 1.449)	1.388 [16] (1.180, 1.632)

Source: Study206216 CSR Table 9.2.2-1.
All values are expressed as adjusted geometric mean [N] (90% CI) except those in the last row (D vs. C), which are expressed as geometric mean ratio [N] (90% CI).
The parameters C_{max}, AUC_{tau}, and C_{24} are normalized relative to the lowest dose administered.
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{24}, concentration at the end of the 24-hour dosing interval; C_{max}, maximum plasma concentration; CI, confidence interval; FTR, fostemsavir.

Table 142. Summary Statistics of Norbuprenorphine for Buprenorphine Coadministered With FTR

Treatment	C_{max} (pg/mL)	AUC_{tau} (pg·h/mL)	C_{24} (pg/mL)
Treatment C	2,152 [16] (1,644, 2,818)	30,219 [16] (22,688, 40,252)	1,104 [16] (843, 1,447)
Treatment D	2,674 [16] (2,171, 3,295)	41,920 [16] (33,436, 52,557)	1,506 [16] (1,205, 1,883)
D vs C	1.242 [16] (1.025, 1.506)	1.387 [16] (1.155, 1.665)	1.364 [16] (1.103, 1.687)

Source: Study206216 CSR Table 9.2.2-2.
All values are expressed as adjusted geometric mean [N] (90% CI) except those in the last row (D vs. C), which are expressed as geometric mean ratio [N] (90% CI).
The parameters C_{max}, AUC_{tau}, and C_{24} are normalized relative to the lowest dose administered.
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{24}, concentration at the end of the 24-hour dosing interval; C_{max}, maximum plasma concentration; CI, confidence interval; FTR, fostemsavir.

Table 143. Summary Statistics of TMR for Buprenorphine Coadministered With FTR

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{12} (ng/mL)
Treatment D	2,052 [16] (39)	13,176 [16] (35)	468 [16] (80)

Source: Study206216 CSR Table 9.2.2-3.
All values are expressed as adjusted geometric mean [N] (% CV).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{12}, concentration at the end of the 12-hour dosing interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; FTR, fostemsavir; TMR, temsavir.

Discussions/Conclusions:

- Repeat administration of FTR had no effect on the PK of methadone.
- Repeat administration of FTR had no clinically significant effect on the PK of buprenorphine and norbuprenorphine.
- The exposure of TMR when coadministered with methadone or buprenorphine/naloxone was comparable to what has been observed historically in healthy subjects receiving multiple oral doses of FTR.

Drug Interaction with Maraviroc (206278)

Study Design

Study 206278 was a Phase 1, open-label, single-sequence, two-way trial to evaluate the interaction between maraviroc (MVC) and FTR in healthy subjects. All study drug doses were administered with standard meal.

- Treatment A: FTR ER tablet 600 mg orally BID on Day 1 through the morning dose on Day 4 (7 doses).
- Treatment B: MVC 300 mg orally BID on Day 7 through Day 11 (10 doses).
- Treatment C: FTR ER tablet 600 mg and MVC 300 mg orally BID on Day 12 through the morning dose on Day 18 (13 doses).

Serial blood samples for PK analysis of TMR were collected at scheduled time points on Days 4 and 18. Serial blood samples for PK analysis of MVC were collected at scheduled time points on Days 11 and 18.

Results

Table 144. Statistical Analysis of C_{max}, AUC_{tau}, and C_{12} of TMR

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{12} (ng/mL)
Treatment A	1,812 (1,538, 2,136)	10,209 (8,802, 11,842)	287 (216, 383)
Treatment C	2,044 (1,811, 2,308)	11,264 (10,474, 12,113)	259 (212, 316)
C vs A	1.128 (0.962, 1.323)	1.103 (0.993, 1.226)	0.901 (0.691, 1.174)

Source: Study206278 CSR Table 9.2.1-2.
All values are expressed as adjusted geometric mean (90% CI) except those in the last row (C vs. A), which are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{12}, concentration at the end of the 12-hour dosing interval; C_{max}, maximum plasma concentration; CI, confidence interval; TMR, temsavir.

Table 145. Statistical Analysis of C_{max}, AUC_{tau}, and C_{12} of Maraviroc

Treatment	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{12} (ng/mL)
Treatment B	522 (463, 589)	1,914 (1,624, 2,256)	36.5 (30.4, 43.8)
Treatment C	525 (441, 625)	2,382 (2,115, 2,682)	49.9 (41.1, 60.5)
C vs B	1.006 (0.844, 1.199)	1.245 (1.076, 1.440)	1.365 (1.257, 1.483)

Source: Study206278 CSR Table 9.2.2-2.
All values are expressed as adjusted geometric mean (90% CI) except those in the last row (C vs. B), which are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over the dosing interval; C_{12}, concentration at the end of the 12-hour dosing interval; C_{max}, maximum plasma concentration; CI, confidence interval.

Conclusions

- MVC did not alter the PK of TMR.
- FTR slightly increased (24% increase in AUC) MVC exposure, but no dose adjustment is needed for MVC.

Drug Interaction with Rifampin (206277)

Study Design

Study 206277 was a Phase 1, open-label, one sequence, one-way trial to evaluate the interaction between rifampin and FTR in healthy subjects. FTR was administered in the morning with a standard meal and rifampin doses were administered in the evening at least 2 hours after completion of a meal.

- Treatment A: FTR 1,200 mg ER single dose in the morning with standard meal
- Treatment B: Rifampin 600 mg QD in the evening fasted (at least 2 hours after a meal) on Days 6 to 12; FTR 1,200 mg ER single dose on Day 11 in the morning with standard meal.

Serial blood samples for PK analysis of TMR were collected predose and up to 48 hours postdose on Days 1 and 11.

Results

Table 146. Statistical Analysis of C_{max}, AUC_{0-t}, and AUC_{inf} of TMR

Treatment	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	AUC_{inf} (ng·h/mL)
Treatment A	5,470.72	29,827.16	30,024.53
Treatment B	1,319.27	5,287.87	5,427.98
B vs. A	0.241 (0.208, 0.279)	0.177 (0.160, 0.196)	0.181 (0.163, 0.200)

Source: Study206277 CSR Table 6.
All values are expressed as geometric mean (90% CI) except those in the last row (B vs. A), which are expressed as geometric mean ratio (90% CI).
Abbreviations: AUC_{0-t}, area under plasma concentration-time curve from time 0 to time t; AUC_{inf}, area under plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; TMR, temsavir.

Conclusions

- Following administration of a single dose of 1,200 mg FTR after multiple daily doses of 600 mg rifampin, the AUC and C_{max} of TMR were reduced by approximately 82% and 76%, respectively, compared to administration of FTR alone.
- Rifampin should be contraindicated.

Drug Interaction With Oral Contraceptive containing Ethinyl Estradiol and Norethindrone Acetate (206279)

Study Design

Study 206279 was a Phase 1, open-label, single-sequence, 4-cycle, 4-treatment trial to evaluate the effect of FTR on the PKs of ethinyl estradiol (EE) and norethindrone (NE), in healthy female subjects. Subjects are required to fast (nothing but water) for a minimum of 10 hours before and 4 hours after morning drug administration on PK sampling days (Day 1 of Cycle 1, Day 21 of Cycle 2, Days 10 and 21 of Cycle 3, and on Day 21 of Cycle 4).

- Treatment A: Subject's existing combination OC tablet containing EE and progestin administered orally once on Day 1 (21st day of OC cycle) followed by inert or no dosing according to package instructions (acceptable OCs contained EE)
- Treatment B: Subject's existing combination OC tablet containing EE and progestin administered orally QD for 21 days followed by inert or no dosing according to package instructions (acceptable OCs contained EE)
- Treatment C: Loestrin 1.5/30 (norethindrone acetate [NEA] 1.5 mg and EE 30 μg) for 21 days
- Treatment D: Loestrin 1.5/30 (NEA 1.5 mg and EE 30 μg) administered orally QD for 11 days (Days 1 through 11) and then Loestrin 1.5/30 (NEA 1.5 mg and EE 30 μg) QD coadministered with FTR (600-mg tablet administered orally BID) from Days 12 through 21

Serial blood samples for PK analysis of plasma EE, NE, and other progestins were collected prior to dosing (0 hour) through 24 hours after OC administration on Day 1 (21st day of the subjects existing cycle) of Cycle 1, Day 21 of Cycle 2, Days 10 and 21 of Cycle 3, and Day 21 of Cycle 4.

Results

Table 147. Statistical Analysis of C_{max} and AUC_{tau} of EE for Cycle 3 and Cycle 4 (Evaluable PK Analysis Set)

Treatment	C_{max} (pg/mL)	AUC_{tau} (pg·h/mL)
Treatment C (C3D21)	108 (94.3, 124)	1,083 (955, 1,228)
Treatment D (C4D21)	150 (134, 168)	1,514 (1,386, 1,654)
D vs. C	1.39 (1.28, 1.51)	1.40 (1.29, 1.51)

Source: Study206279 CSR Table 5.
All values are expressed as adjusted geometric mean (90% CI) except those in the last row (D vs. C), which are expressed as adjusted geometric mean ratio (90% CI).
Treatment C C3D21, Treatment C Cycle 3 Day 21; Treatment D C4D21, Treatment D Cycle 4 Day 21.
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; C_{max}, maximum plasma concentration; CI, confidence interval; EE, ethinyl estradiol; PK, pharmacokinetic.

Table 148. Statistical Analysis of C_{max} and AUC_{tau} of NE for Cycle 3 and Cycle 4 (Evaluable PK Analysis Set)

Treatment	C_{max} (pg/mL)	AUC_{tau} (pg·h/mL)
Treatment C (C3D21)	23,629 (21,129, 26,424)	170,293 (144,247, 201,042)
Treatment D (C4D21)	25,582 (23,437, 27,923)	184,302 (160,117, 212,140)
D vs. C	1.08 (1.01, 1.16)	1.08 (1.03, 1.14)

Source: Study206279 CSR Table 6.
All values are expressed as adjusted geometric mean (90% CI) except those in the last row (D vs. C), which are expressed as adjusted geometric mean ratio (90% CI).
Treatment C C3D21, Treatment C Cycle 3 Day 21; Treatment D C4D21, Treatment D Cycle 4 Day 21.
Abbreviations: AUC_{tau}, area under plasma concentration-time curve over dosing interval; C_{max}, maximum plasma concentration; CI, confidence interval; NE, norethindrone; PK, pharmacokinetic.

Conclusions

- Coadministration of FTR at steady state with Loestrin 1.5/30 resulted in the following:
  - Increased EE C_{max} and AUC_{tau}, 39% and 40%, respectively, with corresponding 90% CIs of 1.28 to 1.51 and 1.29 to 1.51.
  - No clinically meaningful effect on C_{max} and AUC_{tau} of NE. The 90% CIs were 1.01 to 1.16 and 1.03 to 1.14 for C_{max} and AUC_{tau}, respectively.
- As significant increase in EE exposure can lead to increased risk of venous thromboembolism therefore the max allowed dose of EE when co-administered with FTR is ≤30 μg.

14.3. Pharmacometrics Review

Summary of Applicant's Population Pharmacokinetics Analysis

The Applicant conducted a population pharmacokinetics (PPK) analysis of FTR following administration of FTR tablets using the plasma TMR concentration data from healthy adult subjects and adult patients with HIV-1 enrolled in Phase 1, Phase 2, and Phase 3 trials. A summary of key demographics and covariates for PPK population is presented in Table 149. The final PPK model was a two-compartment model with dual zero and first-order absorption and first-order elimination with CYP3A inducers and CYP3A inhibitors as covariates on apparent total clearance of the drug from plasma after oral administration (CL/F) and allometrically scaled body weight as a covariate on CL/F, V2/F, Q/F and V3/F. Final parameter estimates are listed in

Table 150. The eta shrinkages are 11%, 35%, and 43% for CL/F, V2/F, and Ka, respectively. The standard goodness of fit plots are presented in Figure 9.

Table 149. Summary of Key Demographics and Covariates for Subjects Included in PPK Analysis

Covariate		Subjects Included in the PPK Analysis (N = 764)
		Number of subjects (%)
Population	HIV-1-infected patients	606 (79%)
	Healthy subject	158 (21%)
Age ≥65 years		11 (1.4%)
Gender	Male	548 (72%)
	Female	216 (28%)
Race	White	490 (64%)
	Black / African American	177 (23%)
	Asian	5 (1%)
	Other	92 (12%)
Concomitant Medication	CYP3A Inhibitor[a,b,c]	293 (38%)
	CYP3A Inducer[a,d,e]	37 (5%)
Granulation Method (Formulation PIN)	Dry Granulation (ER Tablet PIN 663068-V-600-007)	50 (7%)
	Wet Granulation (ER Tablet PINs 663068-V600-014 & 663069-V400-015)	337 (44%)
	Twin Screw Granulation/Hot Melt Extrusion (ER Tablet PINs 663068-V600-022 & 663068-V600-027)	377 (49%)
		Median (min-max)
Age (years)		42 (17-73)
Baseline body weight (kg)		72 (38-151)
Baseline BMI (kg/m^2)		24.9 (14.4-52.2)
Baseline CRCL (mL/min)		118 (5.26-271)
Baseline ALT (IU/L)		24 (6-240)
Baseline AST (IU/L)		25 (10-288)
Baseline ALP (IU/L)		80 (36-612)
Baseline BILI (mg/dL)		0.100 (0.00-30.8)

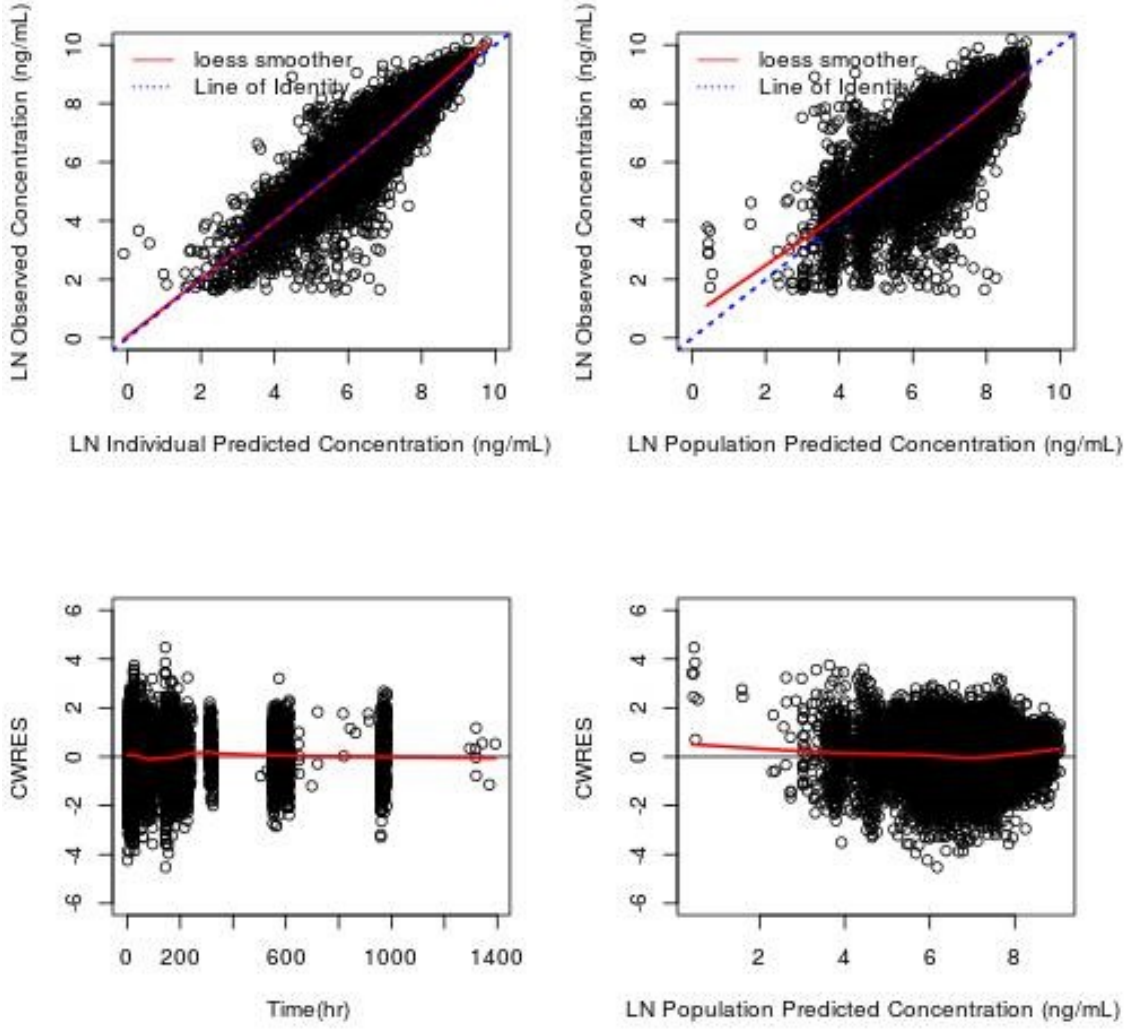
Source: Applicant's report, 2018N392690_00, Table 14
[a] PK observations where both CYP3A inhibitor and CYP3A inducer were co-administered were included in the reference group (i.e., with observations where neither CYP3A inhibitor or CYP3A inducer was co-adminstered).
[b] CYP3A inhibitors included ATV, COBI, DRV, fosamprenavir, indinavir, lopinavir/RTV, nelfinavir, RTV, saquinavir, tipranavir.
[c] RTV and COBI (both strong inhibitors) were co-administered at 85.4% (RTV 82.6%, COBI 2.8%) of PK observations for CYP3A inhibitor group.
[d] CYP3A inducers included desamethasone, ETR, and prednisone.
[e] ETR (moderate inducer) was co-administered at 94.7% of PK observations for the CYP3A inducer group.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; BILI, bilirubin; BMI, body mass index; CRCL, creatinine clearance; ER, extended-release; PPK, population pharmacokinetics.

Table 150. Final TMR Population PK Parameter Estimates (MAP Model 64)

PPK parameter (unit)	Population Estimate			Bootstrap[a]	
	THETA	S.E.	% RSE	Lower 95% CI	Upper 95% CI
CL/F (L/hr)	51.0	1.10	2.16	49.1	52.9
V2/F (L)	257	8.17	3.18	233	279
Q/F (L/hr)	2.58	0.184	7.13	0.973	4.40
V3/F (L)	37.4	1.48	3.95	26.5	65.6
KA (1/hr)	2.33	0.311	13.3	1.84	2.79
DUR (hr)	3.84	0.0965	2.51	3.68	3.99
Effect of CYP3A Inducer on CL/F	1.41	0.0338	2.39	1.25	1.58
Effect of CYP3A Inhibitor on CL/F	0.721	0.0114	1.57	0.687	0.764
Effect of WT on CL/F and Q/F	0.75 Fixed	-	-	-	-
Effect of WT on V2/F and V3/F	1 Fixed	-	-	-	-
ETA(CL/F) %	42.6	0.0137	3.78	39.8	45.5
ETA(V2/F) %	49.0	0.0268	5.59	38.8	56.8
ETA (Ka) %	127	0.274	8.53	112	146
BSC(CL/F, V2/F)	0.609	0.0166	6.54	0.576	0.645
Residual Additive SD on Log Scale	0.613	0.0127	1.69	0.595	0.628
ETA (Residual) %	33.2	0.00789	3.59	30.1	35.8

Source: Applicant's report, 2018N392690_00, Table 15.
Abbreviations: BSC, between-subject covariance; CI, confidence interval; CL/F, apparent total clearance of the drug from plasma after oral administration; DUR, duration; KA, absorption rate constant; PPK, population pharmacokinetics; Q/F, intercompartmental clearance; RSE, relative standard error; SE, standard error; TMR, temsavir; V2/F, volume of distribution for central compartment; V3/F, volume of distribution for peripheral compartment; WT, wild-type.

Figure 9. Goodness of Fit Plots for the Final PPK Model



Source: Applicant's report, 2018N392690_00, Figure 5.
Abbreviations: CWRES, conditional weighted residual; LN, natural log; PPK, population pharmacokinetics.

CYP3A inducers were associated with a 41% increase in CL/F, estimating 53% decrease in C_{tau} and 29% decrease in AUC. ETR comprised 94.7% of the PK observations for the CYP3A inducer group. The Applicant noted that the PPK-estimated impact of moderate CYP3A inducers on plasma TMR C_{tau} was consistent with results of the ETR drug-drug interaction (DDI) study 206281 (52% decrease), but the estimated impact on AUC was less than observed in the ETR DDI study (50% decrease). Strong CYP3A inducers were not evaluated in the PPK analysis because strong inducers were prohibited from the studies of patients with HIV-1.

CYP3A inhibitors were associated with a 28% decrease in CL/F, estimating 79% increase in C_{tau} and 39% increase in AUC_{tau}. CYP3A inhibitors were restricted to HIV PIs and COBI in the final PPK model; RTV and COBI (both strong inhibitors) accounted for 85.4% (RTV 82.6% and COBI 2.8%) of the PK observations in the CYP3A inhibitor group. The PPK-estimated impact of

strong CYP3A inhibitors was consistent with results of RTV, ATV/r, and DRV/r DDI Studies 206269 and 206281 (AUC_{tau} increases of 45 to 63% and C_{tau} increases of 44 to 88%).

Over a body weight range of 40 to 150 kg, plasma TMR C_{tau} was estimated as 1.4 to 0.70-fold the reference exposure for 72 kg. The Applicant's covariate analysis suggests that HIV status, age, gender, race, formulation, and baseline clinical laboratory parameters (CRCL, alanine aminotransferase (ALT), AST, ALP, and direct bilirubin) had no effect on TMR PK. TMR PK data in subjects ≥65 years old (n=11) and some racial groups (i.e., Asians) were limited. Plasma TMR PK parameters for FTR 600 mg BID are summarized based on data collected on Day 8 in subjects with HIV-1 enrolled in the Randomized Cohort of the Phase 3 Trial 205888 (Table 151).

Table 151. Post Hoc Plasma TMR Exposure Estimates

				Geometric Mean (CV%)		
Study	Visit	FTR Regimen	N	Cmax (ng/mL)	AUCtau (ng·hr/mL)	Ctau (ng/mL)
Phase 3 Study 205888 (AI438047)[a,b]	Day 8	600 mg BID	196	1770 (39.9)	12,900 (46.4)	478 (81.5)
Phase 2b Study 205889 (AI438011)[b]	Week 4	400 mg BID	48	1120 (33.7)	7720 (31.8)	304 (46.0)
		800 mg BID	49	2750 (33.5)	18,700 (33.6)	706 (56.2)
		600 mg QD	51	1450 (77.8)	12,400 (74.3)	67.0 (94.4)
		1200 mg QD	48	3270 (55.8)	27,100 (55.0)	133 (104)

Source: Applicant's report, 2018N392690_00, Table 16
PK parameter values were simulated based on individual post-hoc estimates from the final PPK model
[a] Study 205888 (Phase 3) subjects received a wide variety of concurrent medications including CYP3A inducers and CYP3A inhibitors
[b] Study 205888 (Phase 3) subjects received FTR without regard to food and Study 205889 (Phase 2b) subjects received FTR fed.
Abbreviations: AUCtau, area under plasma concentration-time curve over dosing interval; BID, twice a day; Cmax, maximum plasma concentration; Ctau, plasma concentration during a dosing interval; FTR, fostemsavir; CV, coefficient of variation; QD, once a day; TMR, temsavir

The Applicant noted that the PPK dataset is comprised of PK samples following multiple formulations (Table 149) and the formulation was assessed by incorporating as categorical covariates (600 mg, Dry Granulation [663068-V600-007] which was administered in Phase 2a versus all other formulations) for the zero-order absorption duration. As inclusion of the formulation in the model did not improve model, the formulation was not retained in the final model. The Applicant also noted that the following prior data supports that the FTR ER tablet formulations included in the PPK analysis deliver similar plasma TMR exposure:

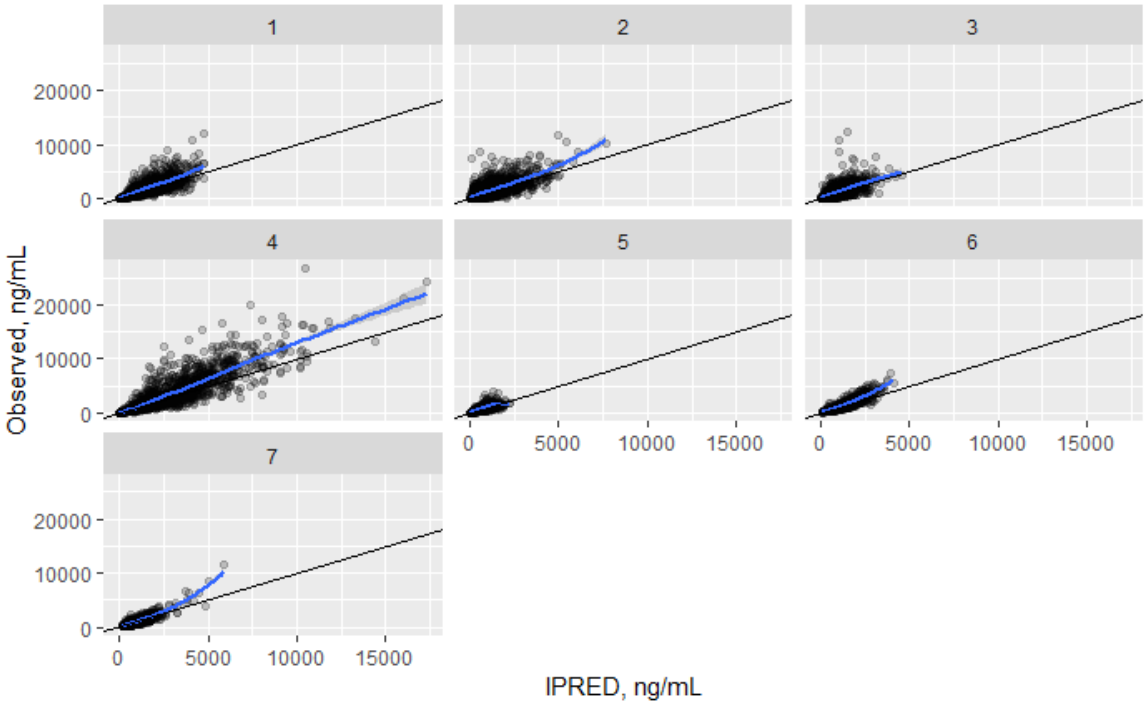
- 663068-V600-022 (Twin-screw Granulation) showed comparable TMR bioavailability to 663068-V600-014 (Wet Granulation), meeting BE criteria (0.80 to 1.25) for both AUC_{inf} and C_{max} in the Relative Bioavailability Study 206274
- 663068-V600-007 (Dry Granulation), 663068-V600-014 (Wet Granulation), and 663068-V600-027 (Twin-screw Granulation, Phase 3 formulation) delivered comparable plasma TMR exposure in healthy adult subjects based on cross-study comparison (Table 24, pg. 74, PopPK report).

Reviewer's Assessment on Population PK Analysis

The Applicant's PPK model adequately describes TMR PK of HIV patients enrolled in Phase 2b and Phase 3 studies based on examination of followings:

- The PK parameters were estimated with acceptable precision (relative standard error <15%) and the shrinkage was modest for plasma clearance (11%) and V2 (35%).
- In the reviewer's GOF plots in linear scale, an underprediction is noted in the high concentrations, which are mostly based on the data from the supratherapeutic concentrations from the thorough QT study. At the therapeutic concentrations observed in the Phase 3 trial, no obvious bias was noted.

Figure 10. Observed vs. Individual Predicted Concentration by Studies



Source: FDA Reviewer's analysis
1 = AI438006, Phase 2a; 2 = AI438011, Phase 2b; 3 = AI438047, Phase 3; 4 = AI438016, Phase 1 - TQT study; 5 = AI438042, Phase 1 - Repeat dose food effect; 6 = AI438044, Phase 1 - DRV/COBI and COBI DDI; 7 = AI438020, Phase 1 - DRV/r and ETR DDI
Abbreviations: IPRED, individual predicted value.

- The Applicant's VPC stratified by studies (Applicant's report, Figure 6 on page 53 to 54) suggests that the simulated profiles are generally in line with the observed profile from Phase 2b, and Phase 3 trials except that a notable overprediction is observed for the Phase 2a trial (Trial 206267) in the later phase (>12 hours) after the dose administration. In that a reasonable prediction is preserved during the proposed dosing interval (<12 hour), the predose concentrations (C_{tau}) and AUC_{tau} are less likely affected by the overprediction.

- The final model reasonably captures the TMR PK for the subjects taking the concomitant medications (CYP3A inhibitors and inducers defined by the Applicant). The reviewer's GOF plots stratified by the concomitant medication categories did not show an obvious bias.
- The Applicant's assessment on the formulations effect is reasonable based on the current data supporting the BE bridging between the two formulations (wet granulation [014] and twin-screw granulation [022]) and the dissolution bridging between the two twin-screw granulation formulations (022 and 027 [the Phase 3 formulation]).

Summary of Applicant's Exposure-Response Analysis for Efficacy

The Applicant performed E-R analyses for efficacy based on the data from the Randomized Cohort of the Phase 3 (Study 205888) which was conducted in the intended population with HIV-1 at the proposed regimen of FTR 600 mg BID. E-R analysis was performed based on the data from 258 subjects (193 on FTR 600 mg BID and 65 on placebo) who had both PK samples and plasma HIV-1 RNA data; The final E-R model was an E_{max} inhibitory model where the response variable was change in plasma HIV-1 RNA from Day 1 to Day 8 and explanatory variables were the exposure metric (post hoc C_{tau}) and the two baseline characteristics (baseline plasma HIV-1 RNA and CD4+ T cell counts >20 cells/mm3). The Applicant noted that age, gender, race, body weight, geographic region, and the following baseline factors: IC_{50}, IC_{50} fold change (FC), number of predefined genotypic substitutions of interest within the gp160 domain, and CD8+ T cell count had no effect on Day 8 virologic response. The Applicant concluded that the final E-R model (Table 152) suggests the E-R relationship between plasma TMR C_{tau} and change in plasma HIV-1 RNA on Day 8 is shallow and highly variable.

Table 152. Parameter Estimates for Exposure-Efficacy Model (C_{tau} - Day 8 Virologic Response)

PK/PD Parameter (unit)	Population Estimate (Mean)			Bootstrap	
	THETA	SE	% RSE	Lower 95% CI	Upper 95% CI
E0 (log_{10} c/mL)	-0.129	0.0851	66.1	-0.268	-0.00665
EC50 (ng/mL)	64.3	63.0	98.0	16.6	250
EMAX (log_{10} c/mL)	1.00	0.171	17.1	0.825	1.28
Effect of Baseline Plasma HIV-1 RNA	0.150	0.044	29.6	0.113	0.197
Effect of Baseline CD4+	0.481	0.0957	19.9	0.293	0.673
ε (log_{10} c/mL)	0.653	0.0350	4.10	0.594	0.699

Source: Applicant's report, 2018N392690_00, Table 18
Parameter estimation:
- Change in plasma HIV-1 from Day 1 to Day 8 = E0-EMAX*(Ctau)/(EC50+Ctau)*(BHIVRNA/44,940)^θ1*θ2^BSL
- Residual error = Y = IPRED+(ε1)

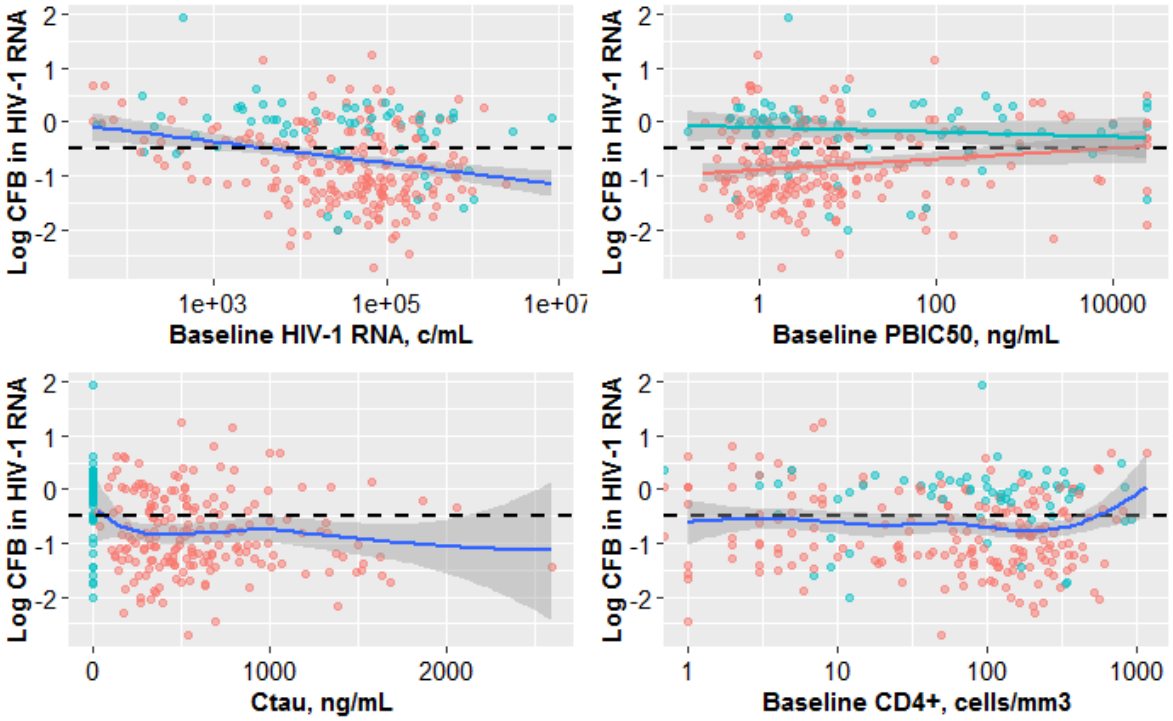
Note: 100% of the 500 bootstrap runs were successful
Abbreviations: %RSE, percent relative standard error of the estimate; BHIVRNA, baseline plasma HIV-1 RNA (copies/mL); BSL, baseline CD4 flag (>20 cells/mm^3 or <20 cells/mm^3); CI, confidence interval; E0, change in plasma HIV-1 RNA from Day 1 to Day 8 for TMR Ctau=0 (i.e., placebo effect); EC50, post-hoc plasma TMR Ctau which results in 50% of maximum effect: EMAX, maximum effect; ε, residual error (additive); IPRED, individual predicted value; PK/PD, pharmacokinetic/pharmacodynamic; SE, standard error of the estimate.

Reviewer's Assessment of E-R for Efficacy

The reviewer agrees with the Applicant's conclusion regarding the relationship between C_{tau} and Day 8 virologic response. The Applicant's final E-R model (Table 152) showed a large additive residual error (SD =0.653) relative to the difference between E0 and E_{max}, which indicates high variability unexplained by the model. EC_{50} estimate (64.3 ng/mL) lays at the lower end of the range of observed C_{tau}, which suggests a shallow relationship at the proposed dosing regimen. The reviewer's graphical examination (Figure 11, bottom left) shows no apparent trend between Ctau and the Day 8 decline at the recommended dosing regimen.

Consistent with the Applicant's E-R model, the lower values of baseline HIV-1 RNA (top left), and the lower baseline CD4+ T cell counts (bottom right) appear to be associated with the reduced decline on Day 8. Inconsistent with the Applicant's conclusion, a positive trend was noted between the high baseline IC_{50} and the reduced response on Day 8 HIV-1 RNA decline (Figure 11, top right).

Figure 11. Potential Covariates for Day 8 Virologic Response

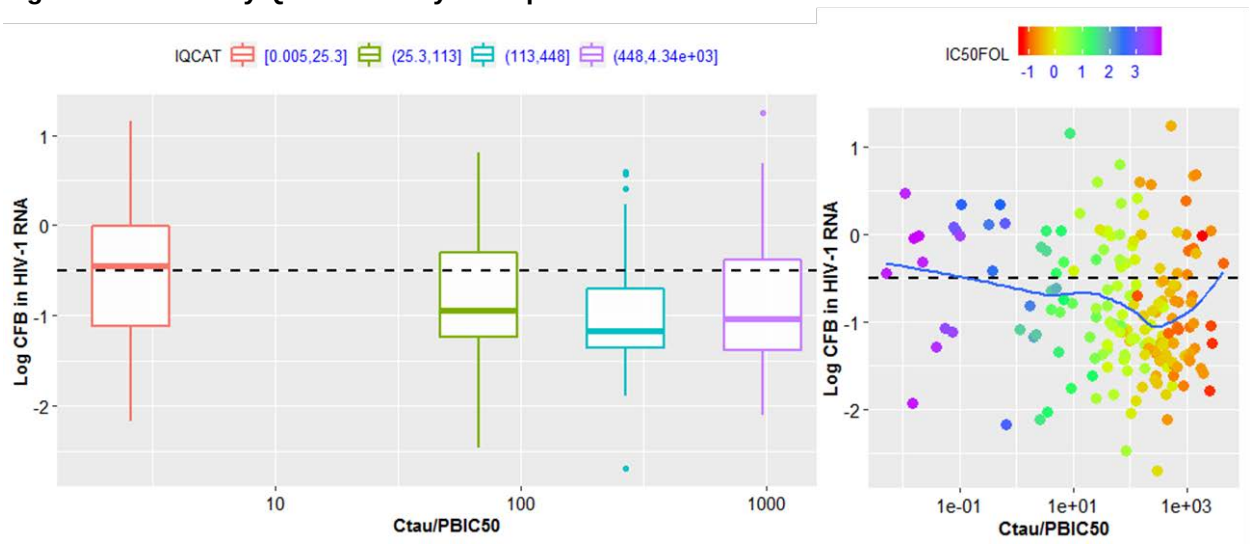


Source: Reviewer's analysis
Note: Blue dots (placebo) and red dots (FTR 600 mg BID)
Abbreviations: CFB: Change from baseline; Ctau, plasma concentration during a dosing interval; $PBIC_{50}$: Baseline IC_{50} adjusted with protein binding.

The IC_{50} (and the derived inhibitory quotients [IQ, derived by $C_{tau}/PBIC_{50}$])) are drug-specific variables, hence the relationship observed in the FTR-treated group (excluding placebo group) is biologically plausible in describing the relationship between IQ and the response. Presented by the quartile plot excluding the placebo data (Figure 12, the left panel), the lowest IQ quartile group (>0.005 to 25.3) had a reduced response on Day 8 HIV-1 RNA decline compared to the

rest of the quartile groups (IQ >25.3). Note that the lowest IQ values (>0.005 to 25.3) are correlated to the significantly high baseline IC_{50} values (Figure 12, right panel). The observed IQ-response relationship is thought to be mainly driven by the IC_{50}-Response relationship (Figure 11, top right) rather than C_{tau}-Response relationship. Furthermore, there is a > 10-fold difference in the median IQ values between the two quartile groups 25.3<IQ ≤113 and 0.005<IQ ≤25.3. This difference is not expected to be overcome by any practical dose increase. Therefore, the review team does not recommend dose adjustment based on the patients' IQ values or baseline IC_{50}.

Figure 12. Inhibitory Quotient - Day 8 Response



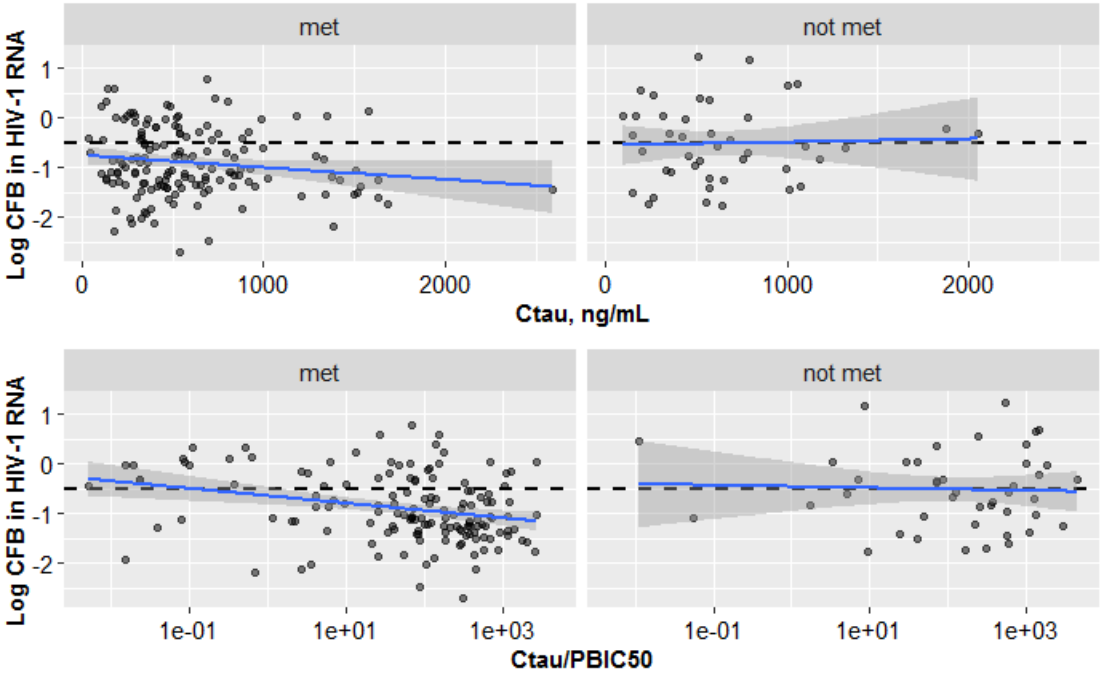
Source: Reviewer's analysis.
Note: IC_{50}FOL is the color scale is based on log-transformed IC_{50} fold change (untransformed IC_{50} ranges from <0.1 (red) to >1,000 (purple)).
Abbreviations: CFB, change from baseline; Ctau, plasma concentration during a dosing interval; IQCAT, IQ categories by IQ quartiles; $PBIC_{50}$, Baseline IC_{50} adjusted with protein binding.

To evaluate confounding effects of other identified covariates such as baseline HIV-1 RNA levels and baseline CD4+ T cell counts, the reviewer performed subgroup analyses.

Baseline HIV-1 RNA

The subjects in the Randomized Cohort from the Phase 3 trial were grouped by meeting/not meeting a criterion (<0.4 $\log_{10}$ decline from screen to baseline, and baseline HIV-1 RNA >400 copies/mL). This criterion was determined to assess the E-R relationship during the "functional monotherapy" of FTR in absence of significant residual activity in the failing regimen. As shown in Figure 13, left panels (meeting the criterion), the result is consistent as the primary analysis: a shallow relationship between C_{tau} and Day 8 response and a positive trend between IQ and the Day 8 response. In the subjects not meeting the criterion, there was generally a reduced decline in Day 8 viral response and no E-R relationship is observed (flat slopes).

Figure 13. E-R Relationships in Subgroups by Based on Baseline HIV-1 RNA Criterion

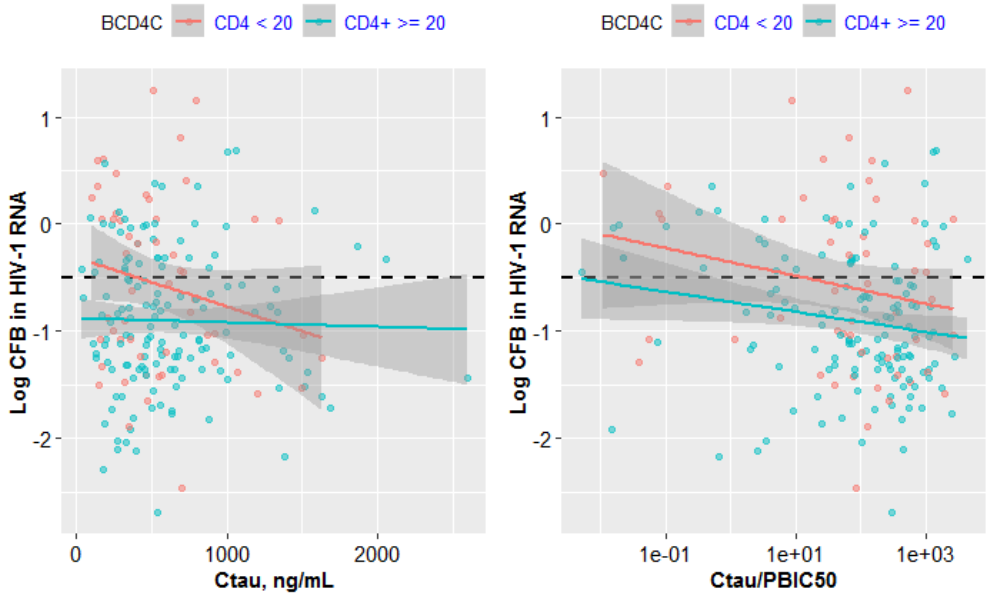


Source: Reviewer's analysis.
Abbreviations: CFB, change from baseline; Ctau, plasma concentration during a dosing interval; E-R, exposure-response.

Baseline CD4+ T Cell Counts

The subgroup analysis was performed based on the baseline CD4+ T cell counts (CD4+ T cell counts ≥20 cells/mm^3 or <20 cells/mm^3). Consistent with the Applicant's E-R model, the lower baseline CD4+ T cell count is associated with the reduced response Day 8 viral load decline. The consistent E-R relationships were observed in the subgroup (CD4+ T cell counts ≥20 cells/mm^3) as the primary analysis.

Figure 14. E-R Relationships in Subgroups by Baseline CD4+ T Cell Counts



Source: Reviewer's figure.
Abbreviations: CFB, change from baseline; Ctau, plasma concentration during a dosing interval; E-R, exposure-response.

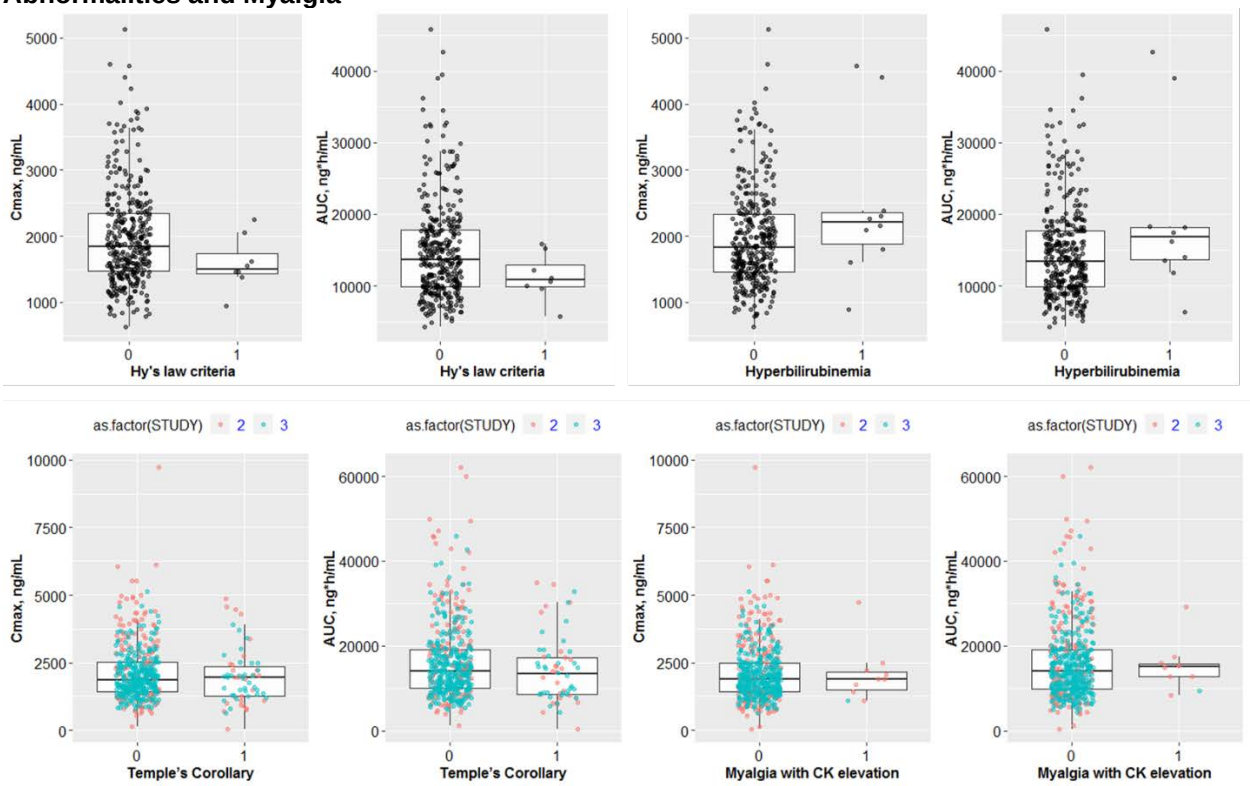
Summary of Applicant's Exposure-Response Analysis for Safety

The Applicant conducted a graphical analysis to evaluate the relationship between post hoc plasma TMR exposure metrics from the final PPK model and select safety parameters. The Applicant concluded that exposure-safety relationships were not evident between TMR exposure metrics (C_{avg} and C_{max}) and safety endpoints of interest, including rash and change from baseline (at each visit through Week 24) in AST, ALT, direct bilirubin, CPK, SCr, and QTcF based on exploratory analysis of data from Phase 2b and Phase 3 trials (FTR 400, 600, and 800 mg BID and 600 and 1,200 mg QD regimens) in ART-experienced subjects with HIV-1.

Reviewer's Assessment of E-R for Safety

The reviewer explored the FTR exposure in patients who experienced drug-induced liver injury (DILI)-related liver lab abnormalities, or the muscle toxicities presented by myalgia and elevated CK (Refer to Clinical Safety). For the liver lab abnormalities, FTR exposure (C_{max},ss and AUCss) were compared between the patients meeting Hy's Law criteria, hyperbilirubinemia (elevated bilirubin without ALT elevation), or Temple's Corollary criteria and the patients who did not meet the respective criteria. Overall, no exposure-dependent signal was identified graphically for the DILI-related liver lab abnormalities. The subjects who experienced myalgia with a graded elevation in CK have similar TMR exposure as the rest of the subjects.

Figure 15. Graphical Comparison of TMR Exposure Between Subjects With and Without Liver Lab Abnormalities and Myalgia



Source: FDA Reviewer's analysis
Note: Top figures for Hy's law criteria, and Hyperbilirubinemia present the data based on subjects from Phase 3 BRIGHTE trial only. Bottom figures for Temple's corollary criteria, and myalgia with CK elevation present the data based on subjects from both the Phase 2b trial (red dots) and the BRIGHTE trial (blue dots).
On the x-axis: 0=without abnormality; 1=with abnormality.
Abbreviations: AUC, area under the curve; CK, creatine kinase; Cmax, maximum plasma concentration; TMR, temsavir.

14.4. Summary of Bioanalytical Method Validation and Performance

The review team reviewed the bioanalytical method validation reports and sample analysis reports for the quantitation of TMR, FTR, and metabolites of TMR in human plasma. Method validation and sample analysis were acceptable. Validation results for bioanalytical methods are summarized in Table 153 and Table 154.

Table 153. Bioanalytical Method Validation for the Determination of FTR and TMR in Human Plasma

Analyte	TMR[a]		FTR	
Bioanalytical method validation report name, study number supported, and hyperlinks	2018N362764_00, 2018N362765_00, 2018N362766_00, 2018N362769_00, 2018N362773_00, 2019N405966_00, 2018N362762_00, 2018N362763_00, 2019N399249_00, 2018N362829_00, 2017N339868_00, 2018N369721_00	206267, 206275, 206276, 206277, 206281, 206283, 206285, 206261, 206262, 206265, 206217, 206280, 206295, 205888, 205889	2017N339865_00	206261, 206262
Method description	Protein precipitation followed by LC-MS/MS		Protein precipitation followed by LC-MS/MS	
Stability in Human Plasma	4 to 5 freeze-thaw cycles at -20°C 637 to729 days at -20°C/-70°C 24 hours at ambient temperature		4 freeze-thaw cycles at -20°C 125 days at -20°C 96 hours at ambient temperature	
Processed Extract stability	117 hours to144 hours at approximately 5°C to 10°C		6 days at approximately 5°C	
Standard calibration curve performance during accuracy and precision runs			Validation parameters	
LLOQ	5 ng/mL		1 ng/mL	
Validated range	5 to 5000 ng/mL		1 to 500 ng/mL	
Within-run Precision (%CV)	≤15%		≤10%	
Between-run Precision (%CV)	≤15%		≤10%	
Accuracy (% Bias)	≤-6.50% 0.8%		≤7.8%	

Source: FDA Reviewer's table
Abbreviations: CV, coefficient of variation; FTR, fostemsavir; LLOQ, lower limit of quantitation; LC-MS/MS, Liquid chromatography–mass spectrometry; TMR, temsavir.

Dilution integrity was verified within each clinical pharmacology study when sample dilutions were performed.

The bioanalytical method validation reports and sample analysis reports for the quantitation of concomitant medications for drug interaction studies and those for TMR in urine and dialysate were reviewed and deemed acceptable.

Table 154. Bioanalytical Method Validation for the Determination of BMS-626529, BMS-646915, and BMS-930644 in Human Plasma

Analyte	TMR	BMS-646915	BMS-930644
Bioanalytical method validation report name, study number supported and hyperlinks	2018N363632_00, 206282, 2018N363652_00, 206269 2018N363633_00, 2018N363661_00	2018N363632_00, 206282 2018N363652_00, 2018N363633_00, 2018N363661_00	2018N363632_00, 206282 2018N363652_00, 2018N363633_00, 2018N363661_00
Method description	Protein precipitation followed by LC-MS/MS	Protein precipitation followed by LC-MS/MS	B Protein precipitation followed by LC-MS/MS
Stability in Human Plasma	5 freeze-thaw cycles at -20/-70°C 15 days at -20/-70°C 24 hours at ambient temperature	5 freeze-thaw cycles at -20/-70°C 15 days at -20/-70°C 24 hours at ambient temperature	5 freeze-thaw cycles at -20/-70°C 15 days at -20/-70°C 24 hours at ambient temperature
Processed Extract stability	145 hours at ambient temperature	145 hours at ambient temperature	145 hours at ambient temperature
Standard calibration curve performance during accuracy and precision runs		Validation parameters	
LLOQ	5 ng/mL	2 ng/mL	2 ng/mL
Validated range	5 to 5000 ng/mL	2 to 1,000 ng/mL	2 to 1,000 ng/mL
Within-run Precision (%CV)	≤15%	≤15%	≤15%
Between-run Precision (%CV)	≤15%	≤10%	≤10%
Accuracy (% Bias)	-8.67% to 5.67%	-3.70% to 3.03%	-6.60% to 3.06%

Source: FDA Reviewer's table

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; LC-MS/MS, Liquid chromatography–mass spectrometry; TMR, temsavir.

15. Trial Design: Additional Information and Assessment

15.1. Applicant's Protocol Synopsis

Clinical Protocol Synopsis for BRIGHTE (AI438047/205888) Trial (Revised Protocol Number 04, Incorporates Amendment 26, Date: December 22, 2014, Revised Date: April 27, 2018)

Protocol Title: A Multiarm Phase 3 Randomized Placebo-Controlled Double-Blind Clinical Trial to Investigate the Efficacy and Safety of Fostemsavir (BMS-663068/GSK3684934) in Heavily Treatment Experienced Subjects Infected with Multidrug Resistant HIV-1 (BRIGHTE Study)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s)

Randomized Cohort

- On Day 1 through Day 8, approximately 105 subjects will begin dosing with blinded FTR 600 mg twice a day (BID), approximately 12 hours apart + current failing ART, and approximately 35 subjects will begin dosing with placebo BID, approximately 12 hours apart + current failing ART.
- After Day 8 subjects are dosed with open-label FTR 600 mg BID, approximately 12 hours apart in combination with an optimized background therapy (OBT).

Non-randomized Cohort

On Day 1, subjects will begin dosing with open-label FTR 600 mg twice a day, approximately 12 hours apart + OBT.

Study Phase: 3

Research Hypothesis

Fostemsavir 600 mg BID has superior antiviral efficacy compared to placebo in a Randomized Cohort of heavily treatment experienced (HTE) subjects infected with multidrug resistance (MDR) HIV-1 when given in combination with a failing background antiretroviral (ARV) regimen over a period of 7 days.

Objectives: Primary Objectives

- To compare the efficacy of FTR relative to placebo, when given on the background of a failing regimen, by determining the mean change in $\log_{10}$ HIV-1 RNA from Day 1 at Day 8 in the Randomized Cohort.

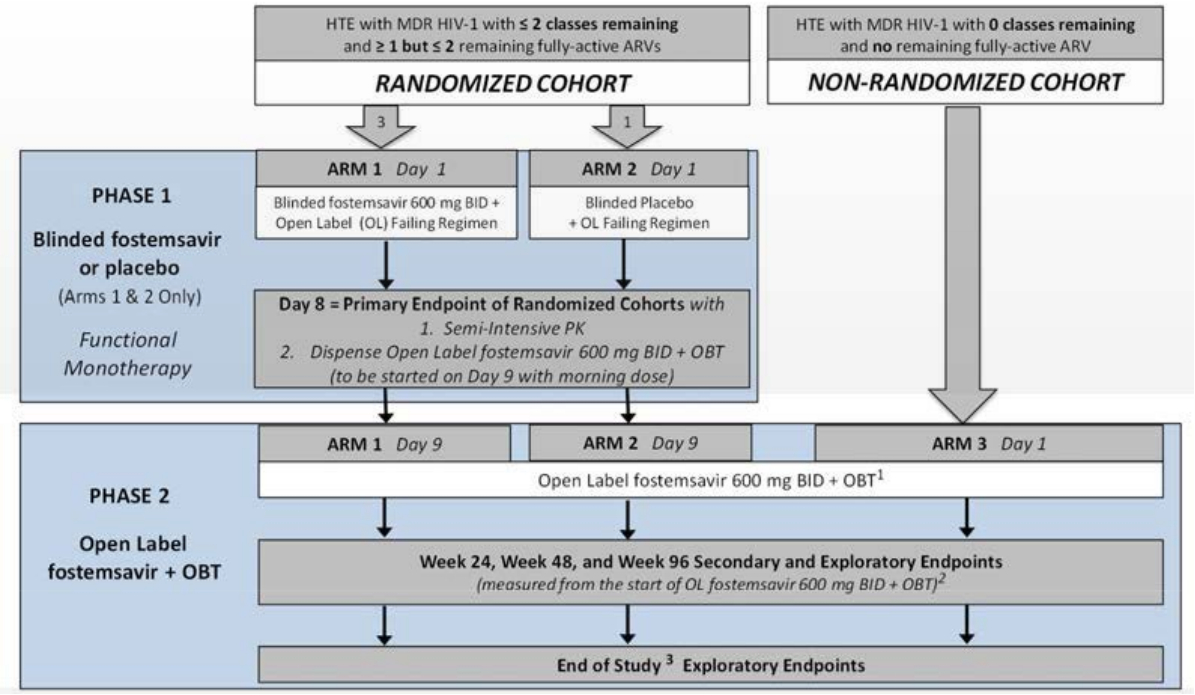
Secondary Objectives

- To assess the efficacy of FTR 600 mg BID relative to placebo, when given on the background of a failing regimen, by determining the proportions of subjects with HIV-1 RNA decreases from Day 1 that exceed 0.5 $\log_{10}$ copies/mL and 1 $\log_{10}$ copies/mL at Day 8 in the Randomized Cohort.
- To assess the durability of the subjects' responses to FTR when given with an OBT by determining the proportion of subjects with plasma HIV-1 RNA <40 copies/mL at Week 24, Week 48, and Week 96 in the Randomized Cohort.
- To assess the safety and tolerability of FTR + OBT in subjects by measuring frequency of serious adverse events (SAEs), AEs leading to discontinuation, and Grade 3-4 laboratory abnormalities in the Randomized Cohort.
- To assess disease progression during OBT as measured by the occurrence of new AIDS-defining events (Centers for Disease Control [CDC] Class C events) or death in the Randomized Cohort.
- To assess the emergence of ARV drug resistance among subjects with protocol-defined virologic failure in the Randomized Cohort.
- To assess the efficacy of FTR functional monotherapy, and placebo, by examining the changes from Day 1 in CD4 + T cell counts, and the percentage of CD4 + T cell counts at Day 8 in the Randomized Cohort.
- To assess the efficacy of FTR + OBT, by examining the changes from baseline in $\log_{10}$ HIV-1 RNA, CD4 + T cell counts, and the percentage of CD4 + T cell counts through Week 24, Week 48, and Week 96 in the Randomized Cohort.

Study Design

This two-cohort Phase 3 trial will be conducted in HTE patients with HIV-1 (total N across both Randomized and Non-randomized Cohorts at least 260) infected with MDR HIV-1 in either a Randomized Cohort (at least 140 subjects) or a Non-randomized Cohort; participation in the Randomized Cohort or Non-randomized Cohort will be dictated by the number of fully active ARVs which can be used to construct a background regimen.

Figure 16. Study Design for the BRIGHTE Trial



Source: Figure 3.1-1 of the Clinical Study Protocol
[1] Subjects in the Randomized Cohort begin open label dosing on Day 9. Subjects in the Non-randomized Cohort begin open label dosing on Day 1.
[2] The start of the open label fostemsavir 600 mg BID is used as the marker from which all other visits will be measured, i.e., the Week 4 visit for subjects in the Randomized Cohort will occur 4 weeks after the Day 8 visit; the Week 4 visit for subjects in the Non-randomized Cohort will occur 4 weeks after the Day 1 visit.
[3] The study is expected to be conducted until an additional option, a rollover study or marketing approval, is in place (as outlined in Section 3.2).
Abbreviations: ARV, antiretroviral; BID, twice a day; HTE, heavily treatment experienced; MDR, multidrug resistance; OBT, optimized background therapy.

Study Population

Male and female subjects with HIV-1 ≥18 years of age with documented resistance, intolerability, and/or contraindication to ARVs in at least 3 classes, and who are failing their current ARV regimen with confirmed plasma HIV-1 RNA ≥400 copies/mL. For the Randomized Cohort, subjects must have ≤2 classes with at least 1 but no more than 2 fully-active ARVs remaining, which can be effectively combined to form a viable new regimen. Subjects without any remaining fully-active approved ARVs may be enrolled in the Non-randomized Cohort.

Study Drug

Includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) and can consist of any OBT and the following:

Table 155. Study Treatments, Phase 1 of BRIGHTE Trial, Randomized Cohort

Product Name and Dosage Form[a]	Potency	IP/ Non-IP	Blinded or Open-Label
BMS-663068-03 (GSK3684934) Extended-release Tablet	600 mg (as the free acid)	IP	Blinded
Placebo for BMS-663068-03 (GSK3684934) Extended-release Tablet	N/A	IP	Blinded
BMS-663068-03 (GSK3684934) Extended-release Tablet	600 mg (as the free acid)	IP	Open-Label

Source: Table 4-1 of the Clinical Study Report
[a] May also be referenced as BMS-663068-03 (GSK3684934/Fostemsavir) Extended-release Tablets or as BMS-663068-03 Extended-release Tablets (name used by BMS, the previous study sponsor).
Abbreviations: IP, investigational product.

Study Assessments

The primary measure of efficacy is the change from Day 1 in $\log_{10}$ HIV-1 RNA at Day 8 in the Randomized Cohort. The difference between FTR and placebo, when given with a failing ARV regimen in the background, is estimated using analysis of covariance (ANCOVA). An important secondary measure of efficacy is the durability of response at Week 24, Week 48, and Week 96. This is assessed by determining the proportion of subjects with HIV-1 RNA <40 copies/mL using a modified Intent-to-Treat analysis based on treated subjects. Safety is assessed through the frequency of SAEs, AEs leading to discontinuation, and Grade 3-4 laboratory abnormalities.

Statistical Considerations: Sample Size

The primary endpoint is assessed in the Randomized Cohort with a sample size of at least 140 subjects. The power of a single superiority comparison between FTR and placebo is more than 95% assuming: a two-sided test; an alpha level of 0.05; a 0.5 $\log_{10}$ difference between the treatment groups; and a common standard deviation of 0.6 $\log_{10}$.

Endpoints: Primary Endpoint

The efficacy of FTR, relative to placebo, is assessed using the mean change in $\log_{10}$ HIV-1 RNA from Day 1 at Day 8 as determined by ANCOVA in the Randomized Cohort.

Secondary Endpoints

- The proportions of subjects in the Randomized Cohort with HIV-1 RNA decreases from Day 1 that exceed 0.5 $\log_{10}$ copies/mL and 1 $\log_{10}$ copies/mL are determined by comparing each subject's HIV-1 RNA Day 1 measurement to their Day 8 measurement. This is a modified Intent-to-Treat analysis based on treated subjects who classifies subjects without HIV-1 RNA at Day 1 or Day 8 as failures.
- The durability of response (HIV-1 RNA <40 copies/mL) at Week 24, Week 48, and Week 96 of OBT in the Randomized Cohort is assessed using the FDA snapshot algorithm (November 2015). This is a modified Intent-to-Treat analysis based on treated subjects who classifies subjects without HIV-1 RNA at Week 24, Week 48, or Week 96, or those who changed OBT due to lack of efficacy through Week 24, Week 48, or Week 96 as failures.

- The frequency of SAEs, AEs leading to discontinuation, and Grade 3-4 laboratory abnormalities during OBT are tabulated from Case Report Forms and laboratory data.
- Disease progression during OBT is assessed using the occurrence of new AIDS-defining events (Centers for Disease Control Class C events) or death as tabulated from Case Report Forms.
- Drug resistance is assessed through phenotypic and genotypic resistance testing of isolates from subjects identified as meeting the criteria for virologic failure.
- The changes in CD4+ T cell counts and percentages, for FTR and placebo when given with failing background therapies, are determined using the mean changes from Day 1 at Day 8 with ANCOVA in the Randomized Cohort.
- The changes from baseline in HIV-1 RNA, CD4+ T cell counts, and percentage of CD4+ T cell counts

T-cells, for FTR when given with OBT, are assessed using laboratory results collected through Week 24, Week 48, and Week 96 in the Randomized Cohort.

Analyses

There are 4 planned analyses of efficacy, resistance, and safety data:

- The first interim analysis is conducted after the last subject (randomized or nonrandomized) completes the Week 24 visit. This analysis covers the primary endpoint and other endpoints based on the change from Day 1 at Day 8 for subjects in the Randomized Cohort.

The second interim analysis is conducted after the last subject (randomized or nonrandomized) completes the Week 48 visit.

- The third interim analysis is conducted after the last subject (randomized or nonrandomized) completes the Week 96 visit.
- The final analysis occurs at the close of the study. Note: One or more optional interim analyses may be conducted after the Week 96 interim analysis and before the final analysis.

15.2. BRIGHTE Study Design: Full Eligibility Criteria

Abbreviated eligibility criteria were provided in Section II.6.2.1 and 15.1 The full list of inclusion and exclusion criteria are provided below.

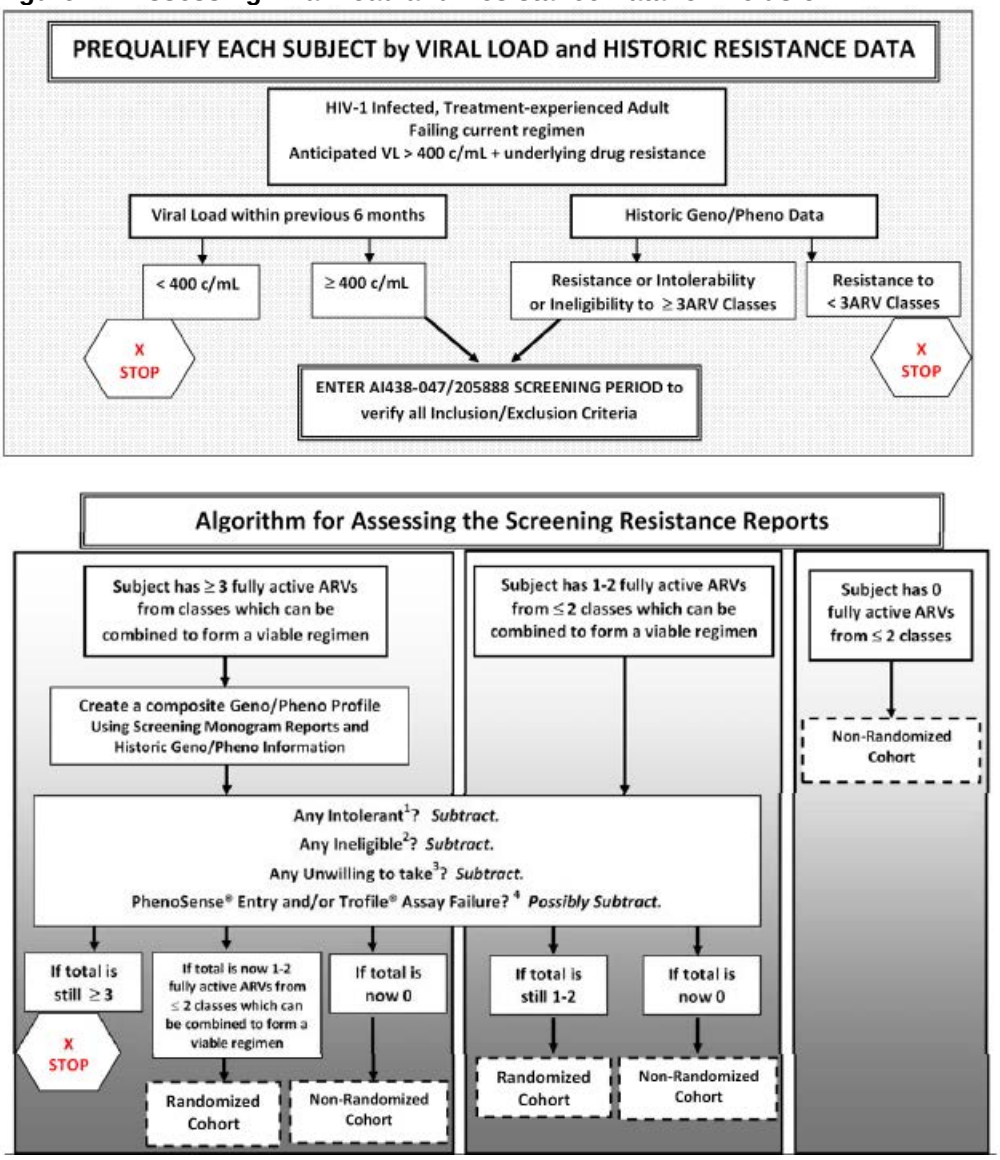
Inclusion Criteria

- Ability to understand and sign a written informed consent form
- Men and nonpregnant women with chronic HIV-1 infection
- Age 18 years and older, (or minimum age as determined by local regulatory/legal requirements)

- Subject Re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pretreatment failure (i.e., subject has not been randomized /has not been treated). If re-enrolled, the subject must be reconsented.
- Antiretroviral-experienced with documented historical or baseline resistance, intolerability, and/or contraindications to ARVs in at least three classes
- Failing current ARV regimen with a confirmed plasma HIV-1 RNA ≥400 copies/mL (first value from Investigator within 6 months of Screening visit, with the second value obtained from Screening labs). Subjects with a Screening HIV-1 RNA <400 copies/mL should be counted as screen failures; repeat testing is not permissible.
- Must have at least 1 fully active and available agent in ≤2 ARV classes, based on current and/or documented historical resistance testing, taking into account tolerability, and other safety concerns.
- A fully active agent is one that meets any of the following criteria:
  - "Sensitive" on the Net Assessment of the Phenosense GT Plus Integrase ®. If assay is nonreportable due to assay failure, a new sample should be drawn from the subject and the assay repeated.
  - "Yes", on the anticipated activity of the CCR5 coreceptor in HIV entry per the Trofile® Co-Receptor Tropism Assay. If the Trofile Assay® is nonreportable, retest with a new sample drawn from the patient. However, if the subject has a history of non-R5 using virus on prior tropism testing, consider MVC a nonactive ARV; in such circumstances repeat Trofile testing is not required prior to Day 1. If a repeat Trofile test is required and is nonreportable, the subject should be screen failed.
  - "Susceptible" on the Phenosense® Entry Assay for Fuzeon. If the Fuzeon entry assay is nonreportable repeat the test, except in the following circumstances:
    - the subject has no prior exposure to Fuzeon (consider Fuzeon as fully active)
    - the subject has no prior history of virologic failure on Fuzeon (consider Fuzeon as fully active)
    - the subject is unwilling to include Fuzeon as a part of their OBT (consider Fuzeon unavailable for OBT). Note: Subjects requiring repeat resistance assays due to assay failure may be enrolled later than 42 days post Screening visit but should be rescreened if screening period exceeds 60 days.
  - Partially active ARVs are not considered fully active and do not apply towards number of active remaining ARVs
  - Documented ARVs or drug classes which subjects are either intolerant of, ineligible for, or unwilling to take (e.g., enfuvirtide [ENF] in a subject unwilling to receive an injectable agent) do not apply towards number of active remaining ARVs
  - Able to receive 1 to 2 fully active approved antiretroviral as part of the OBT from Day 9 onwards in the Randomized Cohort
  - Subjects without any remaining fully active approved ARVs may be enrolled in the Non-randomized Cohort

The algorithm for determining eligibility based on treatment options is summarized in Figure 17.

Figure 17. Assessing Viral Load and Resistance Data for Inclusion



Source: Figure 3.3.1-1 of the Clinical Study Protocol
[1] Intolerant = Prior clinical and/or adverse event due to an ARV
[2] Ineligible = Unable to take an ARV due to current medical condition
[3] Unwilling to take = Patient refusal to self-administer an ARV
[4] If PhenoSense Entry Assay is non-reportable, consider T20 an active ARV if no history of treatment or treatment failure on T20. If Trofile Assay is non-reportable, retest with a new patient sample (if there is a history of non R5 using virus on prior tropism testing, consider maraviroc a non-active ARV). If a second Trofile test is non-reportable, the subject should be screen failed.
Abbreviations: ARV, antiretroviral; VL, viral load

- Age and Reproductive Status
  - Willingness to use approved highly effective methods of contraception to avoid pregnancy (men and women of child bearing potential only).
  - Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

  - Women must not be breastfeeding
  - Men and women must agree to follow instructions for method(s) of contraception for the duration of treatment and for at least 60 hours after drug exposure.

Exclusion Criteria

- Any other clinical condition (including but not limited to substance use) or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study; unable to comply with dosing requirements; or unable to comply with study visits; or a condition that could affect the ADME of the drug.
- Physical and Laboratory Test Findings
  - Chronic untreated hepatitis B virus (HBV) (however, patients with chronic treated HBV are eligible)
  - HIV-2 infection
  - ALT or AST >7 x upper limit of normal (ULN)
  - ALP >5 x ULN
  - Bilirubin ≥1.5 x ULN (unless subject has Gilbert's disease, and/or is currently on ATV, and has predominantly unconjugated hyperbilirubinemia)
  - History of decompensated cirrhosis or active decompensated cirrhosis
  - History of congestive heart failure or congenital prolonged QT syndrome
  - Hemoglobin <8.0 g/dL (Randomized Cohort); Hemoglobin <6.0 g/dL (Non-randomized Cohort)
  - Platelets <50,000 cells/mm3 (Randomized Cohort); Platelets <20,000 cells/mm^3 (Non-randomized Cohort);
  - Confirmed QT value >500 msec at Screening or Day 1
  - Confirmed QTcF value >470 msec for women and >450 msec for men at Screening or Day 1
  - Confirmed PR Interval >260 msec (severe 1st degree AV block) at Screening or Day 1
  - Confirmed second or third degree heart block at Screening or Day 1
  - Current or anticipated treatment with any of the following medications: rifampin, Hypericum perforatum (St. John's wort), efavirenz, nevirapine, carbamazepine, phenobarbital, phenytoin, grapefruit juice, amiodarone disopyramide, dofetilide, ibutilide, procainamide, sotalol, and quinidine. Simvastatin and lovastatin should not be co-administered with boosted PIs.
  - Participation in an experimental drug and/or HIV-1 vaccine trial(s) within the previous 30 days (Randomized Cohort only)
- Other Exclusion Criteria
  - Prisoners or subjects who are involuntarily incarcerated
  - Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

16. Efficacy Assessment Additional Information and Assessment

16.1. Additional Analyses of the Primary Endpoint

The section supplements the analyses and interpretation presented in Section II.6.3.2. Several subgroup analyses were performed to identify baseline demographic and clinical characteristics impacting response to FTR.

Baseline HIV-1 RNA and CD4+ T Cell Count

Subgroup analyses were conducted to assess FTR efficacy in subjects with baseline HIV-1 RNA >1,000 copies/mL compared to ≤1,000 copies/mL (Table 156). A much greater difference in the unadjusted mean change was observed in subjects with baseline HIV-1 RNA >1,000 copies/mL. One explanation is that subjects with low baseline viral loads may not be able to achieve a reduction in HIV-1 RNA of at least one $\log_{10}$ before reaching the testing method's lower limit of quantification.

Table 156. Plasma HIV-1 RNA $\log_{10}$ (copies/mL) Change From Day 1 at Day 8 in Subjects by Baseline HIV-1 RNA ≤1,000 and >1,000 copies/mL (Randomized Cohort)—ITT-E Population, BRIGHTE Trial

Baseline HIV-1 RNA (c/mL)	Placebo			FTR 600 mg BID		
	n	Mean (SD)	Median	n	Mean (SD)	Median
>1000	59	-0.202 (0.5969)	0.000	180	-0.861 (0.7148)	-1.015
≤1000	10	0.099 (0.7182)	-0.060	21	-0.219 (0.5137)	-0.143

Source: Table 21 of the Clinical Study Report
Note: Missing Day 8 HIV-1 RNA values are imputed with D1OCF/LOCF.
Abbreviations: BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; SD, standard deviation.

The Applicant proposed including the median decline in HIV-1 RNA at Day 8 with FTR or placebo in subjects with baseline HIV-1 RNA >1,000 copies/mL in Section 14 of labeling. The review team favored removing this information from the label because the impact of FTR on the primary endpoint is otherwise adequately conveyed. However, the review team agreed to include the results from this subgroup analysis if (1) they were reported as the mean change rather than the median change to maintain consistency with the primary endpoint presentation, and (2) the mean change at Day 8 was also reported for subjects with baseline HIV-1 RNA <1,000 copies/mL for completeness. The Applicant agreed.

Additional subgroup analyses were conducted to assess FTR efficacy in subjects with four categories of baseline HIV-1 RNA, as prespecified in the statistical analysis plan (Table 157). In both treatment groups, an increased reduction of HIV-1 RNA from baseline was observed with increasing baseline HIV-1 RNA levels.

Table 157. Plasma HIV-1 RNA log_{10} (copies/mL) Change From Day 1 at Day 8 in Subjects by Baseline HIV-1 RNA (Randomized Cohort)—ITT-E Population, BRIGHTE Trial

Baseline HIV-1 RNA (copies/mL)	Placebo			FTR 600 mg BID		
	n	Mean (SE)	Median	n	Mean (SE)	Median
<1,000	10	+0.10 (0.23)	-0.06	21	-0.22 (0.11)	-0.14
1,000-<10,000	14	+0.10 (0.08)	+0.05	29	-0.71 (0.14)	-0.44
10,000-<100,000	21	-0.26 (0.15)	-0.01	96	-0.87 (0.07)	-1.04
≥100,000	24	-0.33 (0.12)	-0.02	55	-0.92 (0.09)	-1.04

Source: Statistics Reviewer's table
Abbreviations: BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; SE, standard error.

Table 158 summarizes adjusted mean changes in HIV-1 RNA from Day 1 to Day 8 according to baseline HIV-1 RNA or baseline CD4+ T cell count. For subjects with high baseline HIV-1 RNA levels ≥100,000 copies/mL even the placebo group had statistically significant decreases from baseline. In the placebo group, subjects with baseline HIV-1 RNA ≥10,000 copies/mL had greater declines from Day 1 to Day 8, leading to smaller observed treatment group differences than for moderate baseline HIV-1 RNA between 1,000 and 10,000 copies/mL.

In the placebo group, HIV-1 RNA decline from Day 1 to Day 8 was greatest in subjects with baseline CD4+ T cell count <20 cells/mm^3 compared to other categories of baseline CD4+ T cell count. In contrast, FTR-treated subjects with baseline CD4+ T cell count <20 cells/mm^3 had the lowest reduction in HIV-1 RNA from Day 1 to Day 8. As a result, a smaller treatment difference was observed between FTR and placebo in subjects with CD4+ T cell count <20 cells/mm^3. Other categories of baseline CD4+ T cell count had less of a clinically meaningful impact on response.

Table 158. Plasma HIV-1 RNA log_{10} (copies/mL) Change From Day 1 to Day 8 in Subjects by Additional Key Baseline Characteristics (Randomized Cohort)—ITT-E Population (CD4+ T Cell Count and HIV-1 RNA Level), BRIGHTE Trial

Baseline Characteristic	Placebo		FTR 600 mg BID		Treatment Difference (95%CI)[c]
	n	Adjusted Mean[a] (95%CI)	n[b]	Adjusted Mean[a] (95%CI)	
Baseline CD4+ cell count (cells/mm³)					
<20	17	-0.319 (-0.711, 0.072)	53	-0.582 (-0.803, -0.362)	-0.263 (-0.714,0.188)
20 to <50	6	0.069 (-0.314, 0.452)	17	-0.820 (-1.047, -0.592)	-0.888 (-1.334, -0.443)
50 to <100	10	0.136 (-0.289, 0.560)	28	-0.880 (-1.133, -0.627)	-1.016 (-1.511, -0.521)
100 to <200	16	-0.209 (-0.485, 0.067)	46	-0.930 (-1.091, -0.768)	-0.720 (-1.042, -0.398)
≥200	20	-0.197 (-0.462, 0.068)	52	-0.810 (-0.975, -0.646)	-0.614 (-0.926, -0.302)
Baseline HIV-1 RNA (c/mL)					
<1000	10	0.107 (-0.260, 0.473)	21	-0.222 (-0.475, 0.031)	-0.329 (-0.775, 0.116)
1000 to <10,000	14	0.073 (-0.257, 0.403)	29	-0.700 (-0.929, -0.471)	-0.773 (-1.175, -0.370)
10,000 to <100,000	21	-0.263 (-0.574 ,0.047)	96	-0.867 (-1.012, -0.722)	-0.604 (-0.947, -0.261)
≥100,000	24	-0.332 (-0.609, -0.054)	55	-0.926 (-1.108, -0.744)	-0.594 (-0.928, -0.260)

Source: Table 24 of the Clinical Study Report
Note: Day 1 values are absolute values, Day 8 values are changes from Day 1.
Note: Missing Day 8 HIV-1 RNA values are imputed with Day 1 observation carried forward/LOCF.
[a] Mean Adjusted by Day 1 log_{10} HIV-1 RNA
[b] Subjects AI438047.000476 and AI438047.000527 did not have an HIV-1 RNA result at Day 1 and have been excluded from this summary
[c] FTR – Placebo
Abbreviations: BID, twice a day; CI, confidence interval; FTR, fostemsavir; ITT-E, intent-to-treat, exposed

ARV Treatment History

Fostemsavir subjects had consistently greater rates of decline from Day 1 to Day 8 in HIV-1 RNA across subgroups of PK enhancing ("boosting") agents in the failing regimen, number of prior ARV regimens, number of years of HIV therapy, and history of AIDS.

Table 159. Plasma HIV-1 RNA log_{10} (copies/mL) Change From Day 1 at Day 8 in Subjects by Key Baseline Characteristics (Randomized Cohort)—ITT-E Population, BRIGHTE Trial

Baseline Characteristic	Placebo			FTR 600 mg BID		
	n	Mean (SD)	Median	n[a]	Mean (SD)	Median
Boosting Agent in the Failing Regimen						
Boosting Agent (Yes)	50	-0.163 (0.6207)	-0.051	142	-0.774 (0.7141)	-0.893
Boosting Agent (No)	19	-0.147 (0.6325)	0.039	59	-0.842 (0.7477)	-0.787
Number of Prior ARV Regimens						
2 Prior Regimens	3	-0.308 (0.4095)	-0.496	7	-0.668 (0.5304)	-0.839
3 Prior Regimens	5	0.198 (0.1726)	0.237	8	-0.756 (0.4455)	-0.774
4 Prior Regimens	4	-0.169 (0.5605)	0.023	16	-0.872 (0.5618)	-0.983
≥5 Prior Regimens	57	-0.181 (0.6540)	-0.015	167	-0.803 (0.7564)	-0.877
Number of Years on HIV Therapy						
1-5 Years	8	0.026 (0.2734)	0.060	11	-0.814 (0.5583)	-0.839
6-10 Years	6	-0.350 (0.5165)	-0.324	16	-0.706 (0.5729)	-0.793
11-15 Years	14	-0.210 (0.5070)	0.013	30	-0.893 (0.6835)	-1.086
16-20 Years	18	-0.444 (0.7723)	-0.045	70	-0.850 (0.7521)	-0.930
>20 Years	22	0.094 (0.5916)	0.058	70	-0.721 (0.7675)	-0.819
History of AIDS						
History of AIDS (Yes)	61	-0.176 (0.6461)	-0.015	168	-0.767 (0.7371)	-0.821
History of AIDS (No)	8	-0.026 (0.3545)	0.091	33	-0.933 (0.6379)	-1.043

Source: Table 23 of the Clinical Study Report
Note: Day 1 values are absolute values, Day 8 values are changes from Day 1.
Note: Missing Day 8 HIV-1 RNA values are imputed with Day 1 observation carried forward/LOCF.
[a] Subjects AI438047.000476 and AI438047.000527, from the Randomized Cohort, did not have an HIV-1 RNA result at Day 1 and have been excluded from this summary.
Abbreviations: ARV, antiretroviral; BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; SD, standard deviation.

Demographic Subgroups

As demonstrated in Table 160, Table 161, Table 162, Table 163, and Table 164, below, the treatment effect of FTR compared to placebo appeared to be consistent across demographic subgroups of age, gender, race, ethnicity, and geographic region in the BRIGHTE trial.

Table 160. Primary Analysis by Age Group, BRIGHTE Trial

	Placebo		FTR 600 mg BID			
Age Group	n	Adjusted Mean (95% CI)	n	Adjusted Mean (95% CI)	Difference (95%CI)	p-value
<35	16	-0.24 (-0.56, +0.07)	45	-0.75 (-0.94, -0.57)	-0.51 (-0.87, -0.15)	0.007
35-49	30	-0.05 (-0.33, +0.23)	70	-0.82 (-1.00, -0.64)	-0.77 (-1.10, -0.44)	<0.0001
50+	23	-0.22 (-0.48, +0.03)	86	-0.80 (-0.93, -0.67)	-0.58 (-0.87, -0.29)	0.0001

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; CI, confidence interval; FTR, fostemsavir.

Table 161. Primary Analysis by Gender, BRIGHTE Trial

	Placebo		FTR 600 mg BID			
Gender	n	Adjusted Mean (95% CI)	n	Adjusted Mean (95% CI)	Difference (95%CI)	p-value
Female	12	-0.29 (-0.71, +0.14)	60	-0.74 (-0.93, -0.55)	-0.45 (-0.92, +0.01)	0.057
Male	57	-0.14 (-0.31, +0.03)	141	-0.82 (-0.92, -0.71)	-0.68 (-0.88, -0.48)	<0.0001

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; CI, confidence interval; FTR, fostemsavir.

Table 162. Primary Analysis by Race, BRIGHTE Trial

	Placebo		FTR 600 mg BID			
Region	n	Adjusted Mean (95% CI)	n	Adjusted Mean (95% CI)	Difference (95%CI)	p-value
Black or African American	18	-0.05 (-0.34, +0.23)	42	-0.82 (-1.00, -0.63)	-0.76 (-1.1, -0.42)	<0.0001
White	48	-0.20 (-0.41, -0.00)	135	-0.76 (-0.88, -0.64)	-0.56 (-0.80, -0.33)	<0.0001
Other	3	-0.11 (-0.84, +0.62)	24	-0.92 (-1.18, -0.66)	-0.81 (-1.58, -0.03)	0.043

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; CI, confidence interval; FTR, fostemsavir.

Table 163. Primary Analysis by Ethnicity, BRIGHTE Trial

	Placebo		FTR 600 mg BID			
Ethnicity	n	Adjusted Mean (95% CI)	n	Adjusted Mean (95% CI)	Difference (95%CI)	p-value
Hispanic or Latino	18	-0.10 (-0.39, +0.20)	60	-0.87 (-1.03, -0.71)	-0.77 (-1.11, -0.43)	<0.0001
Other	26	+0.01 (-0.25, +0.27)	76	-0.63 (-0.78, -0.48)	-0.64 (-0.94, -0.34)	<0.0001

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; CI, confidence interval; FTR, fostemsavir.

Table 164. Primary Analysis by Geographic Region, BRIGHTE Trial

	Placebo		FTR 600 mg BID			
Region	n	Adjusted Mean (95% CI)	n	Adjusted Mean (95% CI)	Difference (95%CI)	p-value
Europe	13	-0.32 (-0.70, +0.05)	38	-0.79 (-1.01, -0.56)	-0.46 (-0.90, -0.02)	0.04
North America	29	-0.12 (-0.39, +0.14)	79	-0.74 (-0.90, -0.58)	-0.62 (-0.93, -0.31)	0.0001
South America	25	-0.21 (-0.45, +0.03)	78	-0.84 (-0.97, -0.70)	-0.63 (-0.91, -0.36)	<0.0001

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; CI, confidence interval; FTR, fostemsavir.

16.2. Durability of Virologic Response

Please refer to Section II.6.3.2 for the main discussion pertaining to durability of virologic response. This section presents additional analyses to support the conclusion that efficacy of FTR is durable over 96 weeks. As shown in Table 165, decreases from baseline of HIV-1 RNA over time in the open-label phase of the trial were approximately 2.0 $\log_{10}$ copies/mL at Week 4 for subjects in the Randomized Cohort when most of the subjects had available HIV-1 RNA measurements. Subjects with missing data were excluded at subsequent weeks where the decrease from baseline was slightly over 2.0 $\log_{10}$ copies/mL through Week 96 in the Randomized Cohort. Mean decreases from baseline measured in $\log_{10}$ copies/mL were slightly lower in the Non-randomized Cohort than decreases in the Randomized Cohort.

Table 165. HIV-1 RNA log_{10} (copies/mL) Change From Baseline Over Time—ITT-E Population, BRIGHTE Trial

	Randomized Cohort						Non-Randomized Cohort FTR 600 mg BID (N=99)	
	Placebo[a] (N=69)		FTR 600 mg BID (N=203)		Total (N=272)			
	n	Mean	n	Mean	n	Mean	n	Mean
Baseline	69	4.380	203	4.438	272	4.423	99	4.203
Week 4	66	-1.948	196	-2.085	262	-2.051	98	-1.339
Week 12	61	-2.151	187	-2.265	248	-2.237	93	-1.371
Week 24	64	-2.218	182	-2.325	246	-2.297	89	-1.162
Week 48	60	-2.411	173	-2.293	233	-2.324	83	-1.272
Week 60	55	-2.482	168	-2.398	223	-2.419	77	-1.384
Week 72	58	-2.400	163	-2.437	221	-2.427	75	-1.401
Week 84	56	-2.362	159	-2.488	215	-2.455	70	-1.411
Week 96	55	-2.471	159	-2.478	214	-2.476	66	-1.546

Source: Table 37 in the Clinical Study Report
Note: Baseline is defined as the last non-missing value on or before the date of first dose of study treatment.
Note: Baseline values are absolute values. Postbaseline values are changes from baseline.
[a] Subjects randomized to the placebo arm received FTR 600 mg BID during the open-label phase.
Abbreviations: BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed.

As shown in Table 166, time to initial virologic response (HIV-1 RNA <40 copies/mL) occurred in 29% and 18% of the subjects by Week 4 during the open-label phase in the Randomized and Non-randomized Cohorts with the next biggest increases occurring by Weeks 8 and 12.

Table 166. Time to Initial HIV-1 Virologic Response (<40 copies/mL), BRIGHTE Trial

Visit	Rand Cohort FTR 600 mg BID (N=272)	Non-Randomized Cohort FTR 600 mg BID (N=99)	Total (N=371)
Day 8	4 (1)		4 (1)
Week 4	80 (29)	18 (18)	98 (26)
Week 8	44 (16)	15 (15)	59 (16)
Week 12	25 (9)	11 (11)	36 (10)
Week 16	12 (4)	4 (4)	16 (4)
Week 24	16 (6)	2 (2)	18 (5)
Week 36	9 (3)	1 (1)	10 (3)
Week 48	6 (2)	2 (2)	8 (2)
Week 60	15 (6)	0	15 (4)
Week 72	3 (1)	3 (3)	6 (2)
Week 84	2 (<1)	1 (1)	3 (<1)
Week 96	4 (1)	0	4 (1)
Week 108	3 (1)	0	3 (<1)
Week 120	1 (<1)	0	1 (<1)
Week 132	1 (<1)	0	1 (<1)
Week 144	0	0	0

Source: Table 38 in the Clinical Study Report
Abbreviations: BID, twice a day; FTR, fostemsavir.

Response rates were durable over 24, 48, and 96 weeks of open-label FTR 600 mg BID + OBT treatment. Note that subjects randomized to the placebo group were also taking FTR after the end of the double-blind phase (Day 9 onwards). However, these associations should be interpreted in the context that the initial failing background drugs were reoptimized after the end of the double-blind phase.

Table 167. Response Rate by Treatment Arm, BRIGHTE Trial

Treatment Group HIV-1 RNA (copies/mL)	Baseline n (%)	Day 8 n (%)	Week 24 n (%)	Week 48 n (%)	Week 96 n (%)
Placebo (N=69)					
<40	0	1 (1)	31 (45)	31 (45)	39 (57)
<200	4 (6)	5 (7)	43 (62)	48 (70)	42 (61)
<400	7 (10)	10 (14)	51 (74)	48 (70)	42 (61)
FTR 600 mg BID (N=203)					
<40	2 (1)	3 (1)	113 (56)	115 (57)	124 (61)
<200	9 (4)	22 (11)	143 (70)	139 (68)	132 (65)
<400	14 (7)	34 (17)	152 (75)	142 (70)	133 (66)
Total randomized cohort (N=272)					
<40	2 (1)	4 (1)	144 (53)	146 (54)	163 (60)
<200	13 (5)	27 (10)	186 (68)	187 (69)	174 (64)
<400	21 (8)	44 (16)	203 (75)	190 (70)	175 (64)

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; FTR, fostemsavir.

Outcomes by FDA Snapshot Algorithm

The FDA Snapshot algorithm was used to summarize Week 24, 48, and 96 Study Outcomes for virologic response of HIV-1 RNA <40 copies/mL. The tables in this section include a separation of FTR and placebo groups in the Randomized Cohort; all subjects received FTR after the Day 8 primary efficacy endpoint assessment.

The overall percentage of randomized subjects with HIV-1 RNA results <40 copies/mL occurring during the Week 24 window (open-label study days 127 to 210, study days 135 to 218) was 53% with somewhat higher response rates in subjects randomized to the FTR group than for those randomized to the placebo group (56% versus 45%, respectively). Compared to randomized subjects, the response rate was lower in nonrandomized subjects (37%).

Table 168. BRIGHTE Trial Study Outcomes (<40 copies/mL) at Week 24 – Snapshot Analysis, OBT Change Due to Lack of Efficacy as Failure (Open-Label Phase)—ITT-E Population

	Randomized Cohort			Non-randomized Cohort
Week 24 Outcomes	**Placebo N=69 n (%)**	**Fostemsavir N=203 n (%)**	**Total N=272 n (%)**	**Fostemsavir +OBT N=99 n (%)**
HIV-1 RNA <40 copies/mL	31 (45)	113 (56)	144 (53)	37 (37)
HIV-1 RNA ≥40 copies/mL	34 (49)	74 (36)	108 (40)	54 (55)
Data in window not below threshold	28 (41)	60 (30)	88 (32)	44 (44)
Discontinued for lack of efficacy	0	1 (<1)	1 (<1)	0
Discontinued for other reason while not below threshold	1 (1)	3 (1)	4 (1)	2 (2)
Change in ART	5 (7)	10 (5)	15 (6)	8 (8)
No Virologic Data	4 (6)	16 (8)	20 (7)	8 (8)
Discontinued study due to AE or death	4 (6)	7 (3)	11 (4)	4 (4)
Discontinued study for other reasons	0	5 (2)	5 (2)	0
Missing data during window but on study	0	4 (2)	4 (1)	4 (4)

Source: Statistics Reviewer's analysis
Abbreviations: AE, adverse event; ART, antiretroviral therapy; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy.

The overall percentage of randomized subjects with HIV-1 RNA results <40 copies/mL occurring during the Week 48 window (open-label study days 295 to 378, study days 303 to 386) was 54% with somewhat higher response rates in subjects randomized to the FTR group than for those randomized to the placebo group (57% versus 45%, respectively). Compared to randomized subjects, the response rate was lower in nonrandomized subjects (38%).

Table 169. Study Outcomes (<40 copies/mL) at Week 48 – Snapshot Analysis, OBT Change Due to Lack of Efficacy as Failure (Open-Label Phase)—ITT-E Population, BRIGHTE Trial

	Randomized Cohort			Non-randomized Cohort
Week 48 Outcomes	Placebo N=69 n (%)	Fostemsavir N=203 n (%)	Total N=272 n (%)	Fostemsavir +OBT N=99 n (%)
HIV-1 RNA <40 copies/mL	31 (45)	115 (57)	146 (54)	38 (38)
HIV-1 RNA ≥40 copies/mL	33 (48)	71 (35)	104 (38)	52 (53)
Data in window not below threshold	22 (32)	49 (24)	71 (26)	33 (33)
Discontinued for lack of efficacy	2 (3)	4 (2)	6 (2)	2 (2)
Discontinued for other reason while not below threshold	2 (3)	7 (3)	9 (3)	3 (3)
Change in ART	7 (10)	11 (5)	18 (7)	14 (14)
No Virologic Data	5 (7)	17 (8)	22 (8)	9 (9)
Discontinued study due to AE or death	5 (7)	8 (4)	13 (5)	7 (7)
Discontinued study for other reasons	0	7 (3)	7 (3)	2 (2)
Missing data during window but on study	0	2 (1)	2 (1)	0

Source: Statistics Reviewer's analysis
Abbreviations: AE, adverse event; ART, antiretroviral therapy; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy.

The overall percentage of randomized subjects with HIV-1 RNA results <40 copies/mL occurring during the Week 96 window (open-label study days 631 to 714, study days 639 to 722) was 60% with a similar response rate in subjects randomized to the FTR group than for those randomized to the placebo group (61% versus 57%, respectively). Compared to randomized subjects, the response rate was lower in nonrandomized subjects (37%).

Table 170. Study Outcomes (<40 copies/mL) at Week 96 – Snapshot Analysis, OBT Change Due to Lack of Efficacy as Failure (Open-Label Phase)—ITT-E Population, BRIGHTE Trial

	Randomized Cohort			Non-randomized Cohort
Week 96 Outcomes	Placebo N=69 n (%)	Fostemsavir N=203 n (%)	Total N=272 n (%)	Fostemsavir +OBT N=99 n (%)
HIV-1 RNA <40 copies/mL	39 (57)	124 (61)	163 (60)	37 (37)
HIV-1 RNA ≥40 copies/mL	24 (35)	57 (28)	81 (30)	43 (43)
Data in window not below threshold	9 (13)	24 (12)	33 (12)	15 (15)
Discontinued for lack of efficacy	2 (3)	8 (4)	10 (4)	3 (3)
Discontinued for other reason while not below threshold	6 (9)	11 (5)	17 (6)	6 (6)
Change in ART	7 (10)	14 (7)	21 (8)	19 (19)
No virologic data	6 (9)	22 (11)	28 (10)	19 (19)
Discontinued study due to AE or death	5 (7)	10 (5)	15 (6)	14 (14)
Discontinued study for other reasons	0	8 (4)	8 (3)	4 (4)
Missing data during window but on study	1 (1)	4 (2)	5 (2)	1 (1)

Source: Statistics Reviewer's analysis
Abbreviations: AE, adverse event; ART, antiretroviral therapy; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy.

Immunologic Response by Baseline CD4+ T Cell Count

The Applicant proposed inclusion of a subgroup analysis of the Randomized Cohort in Section 14 of the label to state that subjects with the lowest baseline CD4+ T cell counts (<20 cells/mm^3) had a similar increase in CD4+ T cell counts over time compared with subjects with higher baseline CD4+ T cell counts (>200 cells/mm^3). However, this finding was only observed with baseline CD4+ T cell counts up to 499 cells/mm^3; subjects with baseline CD4+ T cell count ≥500 cells/mm^3 had much lower mean increases in CD4+ T cell counts. The statement in the label was edited accordingly.

Table 171. Mean Change From Baseline in CD4+ T Cell Count (cells/mm^3) by Visit and by Baseline CD4+ T Cell Category – Observed (Randomized Cohort) in the ITT-E Population, BRIGHTE Trial

	Randomized Cohort FTR 600 mg BID (N=272)													
Baseline CD4+ T Cell Count Category:	<20 cells/mm^3		20 to <50 cells/mm^3		50 to <100 cells/mm^3		100 to <200 cells/mm^3		200 to <350 cells/mm^3		350 to <500 cells/mm^3		≥500 cells/mm^3	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Baseline	72	6.1	25	31.9	39	74.7	63	147.3	44	265.1	14	401.6	15	717.7
Day 8	67	5.1	22	18.4	38	24.3	58	35.2	42	26.9	13	-6.4	15	19.3
Week 4	70	62.1	23	74.5	35	44.6	62	57.0	41	37.2	13	48.1	15	-43.2
Week 8	67	58.0	23	88.4	35	68.5	60	68.7	41	79.3	13	61.9	15	-58.4
Week 12	65	76.9	23	80.0	35	75.7	59	79.6	41	72.9	11	186.3	15	29.9
Week 16	65	83.2	23	94.4	35	84.2	57	89.8	41	104.3	11	91.0	13	-24.5
Week 24	64	96.6	24	100.3	33	84.1	59	101.7	41	87.9	12	122.0	14	-8.2
Week 36	61	121.8	21	120.1	31	99.1	57	112.6	39	137.7	11	69.1	14	7.1
Week 48	58	145.2	20	149.0	30	126.4	57	123.1	39	193.5	11	138.0	13	29.6
Week 60	53	193.9	21	133.3	25	149.6	51	136.3	40	218.3	11	187.2	14	32.9
Week 72	56	191.7	18	163.7	27	179.4	52	155.0	39	234.8	11	195.6	14	-39.8
Week 84	52	221.2	18	173.4	25	176.2	49	192.6	36	196.4	9	229.9	14	80.1
Week 96	54	239.8	17	200.9	26	198.8	52	172.3	39	234.5	11	271.4	14	70.5

Source: Table 53 of the Clinical Study Report
Note: Baseline is defined as the last non-missing value on or before the date of first dose of study treatment.
Note: Baseline values are absolute values. Postbaseline values are changes from baseline.
Abbreviations: BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed.

A similar pattern was difficult to discern for the Non-randomized Cohort given the small number of subjects in categories with baseline CD4+ T cell counts ≥20 cells/mm^3. However, subjects in with <20 cells/mm^3 at baseline had increases that were less than half the corresponding increases that were observed for the Randomized Cohort.

Table 172. Mean Change From Baseline in CD4+ T Cell Count (cells/mm³) by Visit and by Baseline CD4+ T Cell Category–Observed (Non-randomized Cohort) in the ITT-E Population, BRIGHTE Trial

	Non-Randomized Cohort FTR 600 mg BID (N=99)													
Baseline CD4+ T Cell Count Category:	<20 cells/mm³		20 to <50 cells/mm³		50 to <100 cells/mm³		100 to <200 cells/mm³		200 to <350 cells/mm³		350 to <500 cells/mm³		≥500 cells/mm³	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Baseline	40	5.8	14	35.1	14	74.1	11	150.5	15	269.2	3	406.7	2	581.0
Week 4	40	18.3	14	20.4	13	34.8	11	71.9	15	45.1	3	-28.3	2	94.5
Week 8	39	22.6	12	24.3	13	37.5	10	63.6	15	41.2	3	0	2	123.0
Week 12	39	30.7	11	30.0	12	46.8	9	82.7	15	53.1	3	-41.3	1	131.0
Week 16	38	28.4	11	38.5	13	40.8	10	89.2	15	44.5	3	-30.3	1	399.0
Week 24	36	31.8	11	34.6	11	49.2	10	84.1	14	27.9	3	-27.7	2	177.0
Week 36	35	45.8	9	54.7	11	72.8	10	99.4	13	49.0	3	-9.7	2	249.5
Week 48	33	59.5	10	66.5	11	75.5	9	92.9	15	21.9	3	-37.3	2	380.5
Week 60	27	66.7	9	72.4	11	43.2	9	81.4	12	56.9	3	4.3	2	551.0
Week 72	27	88.4	9	73.8	11	81.2	9	135.7	11	67.4	3	34.7	2	434.0
Week 84	27	102.9	7	65.6	10	84.9	7	204.1	12	3.8	3	49.7	2	885.0
Week 96	22	120.5	8	79.9	9	91.0	8	178.5	13	15.2	3	49.7	2	929.0

Source: Table 54 of the Clinical Study Report
Note: Baseline is defined as the last non-missing value on or before the date of first dose of study treatment.
Note: Baseline values are absolute values. Postbaseline values are changes from baseline.
Abbreviations: BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed

16.3. Additional Analyses for Benefit Issue: Evaluating efficacy at Week 24 in Subjects With DTG- and/or boosted DRV-Containing OBT

This section supplements the discussion on efficacy with dolutegravir (DTG)- and/or boosted darunavir (DRV/r or DRV/c)-containing OBT started in Section II.6.4.4.

Prior to initial OBT assignment, the proportion of subjects with at least a 0.5 $\log_{10}$ decrease from baseline was consistently lower in the placebo group than in the FTR group for each DTG/DRV subgroup. The percentage of subjects in both groups combined with at least a 0.5 $\log_{10}$ decrease from baseline appeared comparable in the four DTG/DRV subgroups ranging from 47% in subjects without DTG and with boosted DRV to 54% in subjects with DTG without boosted DRV and in subjects without DTG or boosted DRV.

Table 173. Double-Blind Efficacy at Day 8: Randomized Cohort, ITT-E Population for Subjects Who Used DTG and/or boosted DRV[a] in Optimized Background Therapy, Proportion With >0.5 $\log_{10}$ Decrease From Day 1 to Day 8 in HIV-1 RNA (copies/mL), BRIGHTE Trial

OBT	Placebo	FTR 600 mg BID	Randomized Groups Combined
With DTG and DRV	5/29 (17%)	57/88 (65%)	62/117 (53%)
With DTG, without DRV	7/26 (27%)	54/86 (63%)	61/112 (54%)
Without DTG, with DRV	1/8 (13%)	6/9 (67%)	8/17 (47%)
Without DTG or DRV	0/6	14/20 (70%)	14/26 (54%)

Source: Statistics Reviewer's analysis
[a] Darunavir boosted with ritonavir or cobicistat
Abbreviations: BID, twice a day; DTG, dolutegravir; DRV, darunavir; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy.

Prior to initial OBT assignment, the proportion of subjects with at least a 1.0 log_{10} decrease from baseline was consistently lower in the placebo group than in the FTR group for each DTG/DRV subgroup. The percentage of subjects in both groups combined with at least a 1.0 log_{10} decrease from baseline appeared comparable in the four DTG/DRV subgroups ranging from 29% in subjects without DTG and with boosted DRV to 42% in subjects without DTG or boosted DRV.

Table 174. Double-Blind Efficacy at Day 8: Randomized Cohort, ITT-E Population for subjects Who Used DTG and/or boosted DRV [a] in Optimized Background Therapy, Proportion With >1.0 log_{10} Decrease From Day 1 to Day 8 in HIV-1 RNA (copies/mL), BRIGHTE Trial

OBT	Placebo	FTR 600 mg BID	Randomized Groups Combined
With DTG and DRV	3/29 (10%)	40/88 (45%)	43/117 (37%)
With DTG, without DRV	4/26 (15%)	37/86 (43%)	41/112 (37%)
Without DTG, with DRV	0/8	5/9 (56%)	5/17 (29%)
Without DTG or DRV	0/6	11/20 (55%)	11/26 (42%)

Source: Statistics Reviewer's analysis
[a] Darunavir boosted with ritonavir or cobicistat
Abbreviations: BID, twice a day; DTG, dolutegravir; DRV, darunavir; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy.

16.4. Evaluating Efficacy at Week 24 in Subjects With ETR-Containing OBT

Additional analyses were performed to assess whether ETR, with or without PIs, affects the durability of FTR's response. This analysis helped determine the effects of coadministration of moderate CYP3A inducers, such as ETR, on efficacy of FTR. Please refer to Section II.8.2.2 for a detailed discussion about PK drug interactions. The same approach used to assess the impact of DTG and/or boosted DRV was used for ETR/PI analyses.

As was observed in the DTG/DRV analysis, baseline viral loads were comparable by use of ETR with or without a PI in the OBT, as shown in Table 175. In addition, there was comparable improvement from baseline to Day 8 in these groups (Table 176 and Table 177). Therefore, differences in response rates at Week 24 and beyond are unlikely to be related to imbalances in baseline HIV-1 RNA or observed improvements at the end of the double-blind phase of the trial.

Table 175. Baseline Viral Loads (log_{10} copies/mL) by Use of Etravirine With and Without a Protease Inhibitor in the Initial OBT—TT-E Population, BRIGHTE Trial

OBT	Placebo	FTR 600 mg BID	Randomized Groups Combined
Without Etravirine			
n	57	161	218
Mean (SE)	4.3 (0.2)	4.4 (0.1)	4.4 (0.1)
Median	4.5	4.7	4.7
Min, max	1.6, 6.5	1.6, 6.4	1.6, 6.5
Etravirine without PI			
n	1	12	13
Mean (SE)	7.0	4.5 (0.3)	4.7 (0.3)
Median	7.0	4.6	4.6
Min, max	7.0, 7.0	2.2, 5.6	2.2, 6.9
Etravirine and PI			
n	11	30	41
Mean (SE)	4.4 (0.3)	4.4 (0.2)	4.4 (0.1)
Median	4.8	4.7	4.7
Min, max	2.7, 5.8	2.2, 5.6	2.2, 5.8

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy; PI, protease inhibitor; SE, standard error.

Prior to OBT assignment, the proportion of subjects with at least a 0.5 log_{10} decrease from baseline was consistently lower in the placebo group than in the FTR group for each ETR subgroup. The percentage of subjects in both groups combined with at least 0.5 log_{10} decrease from baseline appeared relatively comparable in the three ETR subgroups ranging from 46% in subjects with ETR and a PI to 62% in subjects with ETR and without a PI.

Table 176. Double-Blind Efficacy at Day 8: Randomized Cohort, ITT-E Population for Subjects Who Used ETR With/Without a PI in Optimized Background Therapy, Proportion With >0.5 log_{10} Decrease from Day 1 to Day 8 in HIV-1 RNA (copies/mL), BRIGHTE Trial

OBT	Placebo	FTR 600 mg BID	Randomized Groups Combined
Without etravirine	13/57 (23%)	104/161 (65%)	117/218 (54%)
Etravirine without PI	0/1	8/12 (67%)	8/13 (62%)
Etravirine with PI	0/11	19/30 (63%)	19/41 (46%)

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; FTR, fostemsavir; OBT, optimized background therapy; PI, protease inhibitor.

Prior to OBT assignment, the proportion of subjects with at least a 1.0 log_{10} decrease from baseline was consistently lower in the placebo group than in the FTR group for each ETR subgroup. The percentage of subjects in both groups combined with at least a 1.0 log_{10} decrease from baseline appeared comparable in the three ETR subgroups ranging from 34% in subjects with ETR and a PI to 46% in subjects with ETR and without a PI.

Table 177. Double-Blind Efficacy at Day 8: Randomized Cohort, ITT-E Population for Subjects Who Used ETR With/Without a PI in Optimized Background Therapy, Proportion With >1.0 log_{10} Decrease from Day 1 to Day 8 in HIV-1 RNA (copies/mL), BRIGHTE Trial

OBT	Placebo	FTR 600 mg BID	Randomized Groups Combined
Without etravirine	7/57 (12%)	73/161 (45%)	80/218 (37%)
Etravirine without PI	0/1	6/12 (50%)	6/13 (46%)
Etravirine with PI	0/11	14/30 (47%)	14/41 (34%)

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy; PI, protease inhibitor.

Use of ETR, with or without a PI in the OBT did not appear to be associated with lower response rates over time in the originally randomized FTR 600 mg BID subjects. The number of subjects initially randomized to placebo was too small to make any statements about the association of ETR on response rates (Table 178).

Table 178. BRIGHTE Trial Response (HIV-1 RNA <40 copies/mL) at Week 24 by Use of Etravirine With and Without a PI in the Initial OBT—ITT-E Population, BRIGHTE Trial

OBT	Placebo	FTR 600 mg BID	Randomized Groups Combined
Without Etravirine	28/57 (49%)	88/161 (55%)	116/218 (53%)
Etravirine without PI	0/1	7/12 (58%)	7/13 (54%)
Etravirine and PI	3/11 (27%)	18/30 (60%)	21/41 (51%)

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice a day; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; OBT, optimized background therapy; PI, protease inhibitor.

16.5. Health Outcomes Endpoints

A predefined exploratory endpoint was to assess the impact of FTR + OBT on quality of life measures using three different instruments: the EQ-5D-3L, the Functional Assessment of HIV Infection (FAHI), and the M-MASRI Questionnaire on Adherence. These quality of life instruments are not validated for use in evaluating treatment effect in patients living with HIV-1 infection and findings from these analyses are not intended for labeling purposes. FDA did not independently analyze the results of these quality of life instruments, and therefore, the Applicant's results are briefly summarized in this section.

- The EQ-5D-3L is a generic measure of health status/utility that consists of 5 questions covering domains of mobility, pain, self-care, usual activities, and anxiety/depression. Scores on these 5 dimensions can be converted to a single summary index utility score.
  - Results: Baseline scores in the Randomized Cohort were slightly higher than scores in the Non-randomized Cohort, indicating better overall health status among subjects in the in the Randomized Cohort. There was a modest positive trend from baseline to Week 96 in both cohorts.

- The FAHI is a 47-item questionnaire grouped into 5 subscales; physical well-being, global/functional well-being, emotional well-being/living with HIV, social well-being, and cognitive function. Higher scores are associated with better health-related quality of life.
  - Results: Similar to the EQ-5D-3L, subjects in the Non-randomized Cohort had lower baseline scores compared to the Randomized Cohort, reflecting poorer health status among nonrandomized subjects. In the Randomized Cohort, there was a positive change from Baseline to Week 96 in the FAHI total score, physical well-being, and emotional well-being subscales, with no appreciable change in function/global well-being score, social well-being, or cognitive function Similar trends were observed for the Non-randomized Cohort but with more modest change from baseline scores.
- The M-MASRI questionnaire is a self-reported questionnaire regarding medication adherence. The M-MASRI Questionnaire was administered at baseline, Day 8 and Week 24, in both the Randomized as well as Non-randomized Cohorts.
  - Results: Baseline adherence was high and improved during the study.

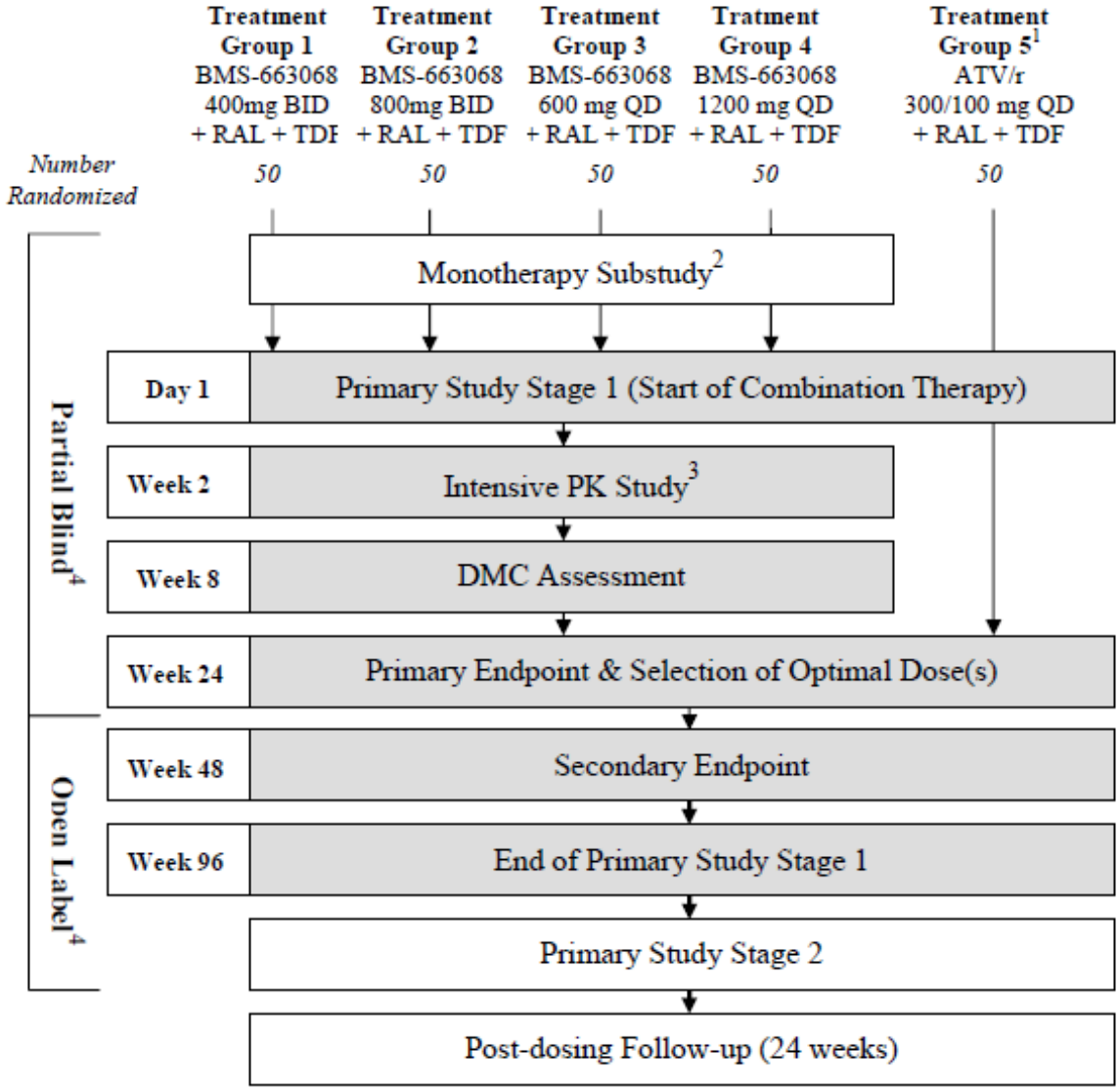
17. Clinical Safety Assessment Additional Information and Assessment

17.1. Phase 2b Trial 205889: Supplementary Information

As noted in Section II.7, the Phase 2b trial (AI438011/205889) provides important supplementary safety data. Overall, subjects in this trial were younger and had higher baseline CD4+ T cell counts compared to the Phase 3 BRIGHTE population. Consequently, this healthier population allowed for a “cleaner” assessment of the safety profile of FTR because there was less confounding from comorbid conditions.

The design of the trial is briefly discussed in Section II.7.4 and additional details are provided here. The following study schematic provides a summary of the study flow including the 5 dosing groups.

Figure 18. Phase 2b Trial Schema



Source: Figure 1, AI438011 Clinical Study Protocol
BMS-663068 is FTR.
[1] Reference treatment group. Subjects will not participate in the Monotherapy Substudy nor Intensive PK; Week 8 Assessment does not apply.
[2] Monotherapy Substudy will last 7 days and include a subset of subjects per BMS-663068 treatment group.
[3] Week 2 Intensive PK will include a subset of subjects per BMS-663068 treatment group.
[4] Unless unblinded at the Week 8 Assessment, subjects in BMS-663068 Treatment Groups (1-4) remain blinded to study therapy until all subjects have reached Week 24 and the optimal dose(s) has/have been selected. Some subjects, then, will be beyond Week 24 when the unblinding occurs.
Abbreviations: ATV, atazanavir; BID, twice a day; PK, pharmacokinetic; QD, once a day; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

17.1.1. Eligibility Criteria

Key Inclusion Criteria

- Plasma HIV-1 RNA ≥1,000 copies/mL
- Men and women at least 18 years of age, (or minimum age as determined by local regulatory or as legal requirements dictate, whichever is higher)
- Antiretroviral treatment-experienced as defined in this protocol
- Susceptibility to study drugs by genotype/phenotype/PhenoSense®
- CD4+ T cell count >50 cells/mm^3

Key Exclusion Criteria

- Chronic HBV/hepatitis C virus (HCV) infection
- Contraindications to any of study drugs
- History of resistance to any component of the study regimen (TDF, ATV, RAL)

17.1.2. Data Analysis and Endpoints

Efficacy assessments included plasma HIV-1 RNA measurements at every visit. Safety assessments included vital signs and physical measurements, SAEs and AEs leading to discontinuations. Intensive PK assessments were conducted in selected individuals receiving FTR (BMS-663068). Sparse PK assessments were conducted in all study participants.

Statistical Methods

Safety and efficacy endpoints were assessed for all treated subjects. Efficacy analyses focused on the proportions of treated subjects with HIV-1 RNA <50 copies/mL at Week 24. Response rates were presented by treatment regimen with exact binomial 95% confidence intervals (CIs).

- An interim analysis was conducted after the last randomized subject received combination treatment for 8 weeks to evaluate early antiviral activity and key safety endpoints
- The primary analysis was conducted after the last randomized subject received combination treatment for 24 weeks
- Another interim analysis was conducted after the last randomized subject received combination treatment for 48 weeks
- The final analysis for Stage 1 was conducted after the last randomized subject received combination treatment for 96 weeks
- The final Stage 2 analyses occurred at the end of the study.

Efficacy Endpoints

- Primary Endpoint: Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 24.

Secondary Endpoints

Monotherapy Substudy

- Changes from monotherapy Baseline (monotherapy Day 1) in log_{10} HIV-1 RNA by study day during monotherapy.
- Maximum decrease from monotherapy Baseline in log_{10} plasma HIV-1 RNA during monotherapy.
- Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Baseline (combination therapy Day 1).
- Changes from monotherapy Baseline in CD4+ and CD8+ T cell counts and percents at baseline (Combination Therapy Day 1).

Primary Study

- Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Weeks 48 and 96.
- Changes from Baseline in CD4+ T cell count at Weeks 24, 48, and 96.
- Frequency of newly-emergent genotypic substitutions and IC_{50} fold changes from Baseline among subjects with virologic failure through Weeks 24, 48, and 96.

Safety Endpoints

Primary Endpoint

- Frequency of SAEs and discontinuations due to AEs through Week 24.

Secondary Endpoints

- Monotherapy Substudy: Frequency of SAEs and discontinuations due to AEs during the Monotherapy period.
- Primary Study: Frequency of SAEs and discontinuations due to AEs through Weeks 48 and 96.

17.1.3. Baseline Characteristics and Subject Disposition

A total of 251 subjects participated in the trial across 45 investigational sites. Baseline demographics are presented in Table 179. For the purposes of this review, the two lower dose cohorts have been consolidated and the two higher dose cohorts have been consolidated.

Table 179. Baseline Demographic and Clinical Characteristics, Safety Population, Phase 2b Trial

Characteristic	≥1,200 mg FTR N=99	≤800 mg FTR N=101	ATV/r N=51
Sex, n (%)			
Male	37 (37.4)	41 (40.6)	22 (43.1)
Female	62 (62.6)	60 (59.4)	29 (56.9)
Age, years			
Mean (SD)	38.8 (10.5)	39.1 (8.9)	39.7 (10.6)
Median (min, max)	40.0 (20.0, 67.0)	39.0 (22.0, 58.0)	39.0 (20.0, 69.0)
Age group, years, n (%)			
35-49	42 (42.4)	52 (51.5)	27 (52.9)
<35	38 (38.4)	38 (37.6)	15 (29.4)
>=50	19 (19.2)	11 (10.9)	9 (17.6)

Characteristic	≥1,200 mg FTR N=99	≤800 mg FTR N=101	ATV/r N=51
Age group, years, n (%)			
19-64	97 (98.0)	101 (100.0)	49 (96.1)
>=65	2 (2.0)	0 (0.0)	2 (3.9)
Race, n (%)			
American Indian or Alaska Native	1 (1.0)	1 (1.0)	1 (2.0)
Asian	2 (2.0)	0 (0.0)	0 (0.0)
Black or African American	33 (33.3)	30 (29.7)	13 (25.5)
Other	28 (28.3)	33 (32.7)	14 (27.5)
White	35 (35.4)	37 (36.6)	23 (45.1)
Ethnicity, n (%)			
Hispanic or Latino	11 (11.1)	12 (11.9)	9 (17.6)
Not Hispanic or Latino	28 (28.3)	31 (30.7)	15 (29.4)
Country of participation, n (%)			
Argentina	7 (7.1)	6 (5.9)	5 (9.8)
Colombia	4 (4.0)	5 (5.0)	3 (5.9)
Germany	4 (4.0)	6 (5.9)	1 (2.0)
Mexico	10 (10.1)	7 (6.9)	9 (17.6)
Peru	17 (17.2)	24 (23.8)	8 (15.7)
Romania	3 (3.0)	1 (1.0)	2 (3.9)
Russian federation	7 (7.1)	9 (8.9)	2 (3.9)
South Africa	30 (30.3)	24 (23.8)	12 (23.5)
Spain	1 (1.0)	0 (0.0)	0 (0.0)
United states	16 (16.2)	19 (18.8)	9 (17.6)

Source: adsl.xpt; Software: Python
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation.

At Week 96, 44% of subjects had completed treatment, 13% withdrew, 12% discontinued due to lack of efficacy, 8% were lost to follow-up, and 6% discontinued to an AE. Disposition by group is summarized in Table 180.

Table 180. Patient Disposition, Phase 2b Trial

Disposition Outcome	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Patients randomized			
ITT/mITT population	99	101	51
Safety population	99	101	51
Discontinued study drug			
Completed	38 (38.4)	54 (53.5)	19 (37.3)
Lack of efficacy	16 (16.2)	8 (7.9)	4 (7.8)
Withdrawal by subject	12 (12.1)	10 (9.9)	9 (17.6)
Lost to follow-up	10 (10.1)	7 (6.9)	4 (7.8)
Other	8 (8.1)	6 (5.9)	2 (3.9)
Adverse event	6 (6.1)	1 (1.0)	7 (13.7)
Non-compliance with study drug	4 (4.0)	10 (9.9)	3 (5.9)
Pregnancy	3 (3.0)	1 (1.0)	2 (3.9)
Did not meet continuation criteria	2 (2.0)	2 (2.0)	0 (0.0)
Death	0 (0.0)	2 (2.0)	0 (0.0)
Sponsor terminated study treatment	0 (0.0)	0 (0.0)	1 (2.0)

Source: adds.xpt; Software: Python
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group.

Similar to the BRIGHTE trial, the duration of FTR exposure in the Phase 2b trial was quite long at nearly 3 years. This allowed for detection of both acute and late-onset AEs.

Table 181. Duration of Exposure, Safety Population, Phase 2b Trial

Variable	≥1,200 mg FTR N=99	≤800 mg FTR N=101	ATV/r N=51
Duration of exposure (weeks)			
Mean (SD)	158.0 (102.8)	189.9 (91.5)	153.6 (102.6)
Median (min, max)	215.6 (0.1, 292.0)	245.7 (0.1, 293.1)	151.7 (0.1, 288.7)
Subjects treated, by duration, n (%)			
Any duration (at least 1 dose)			
<100	42 (42.4)	25 (24.8)	21 (41.2)
100-200	6 (6.1)	15 (14.9)	7 (13.7)
200-250	20 (20.2)	15 (14.9)	4 (7.8)
≥250	31 (31.3)	46 (45.5)	19 (37.3)

Source: adex.xpt; Software: Python
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation.

17.2. Supplemental Data for the Safety Review: Results from the BRIGHTE and Phase 2b Trials

The key elements of the safety review are communicated in Section II.7. This section is intended to provide additional data analyses and the clinical review team's interpretation of the more detailed data that helped support the conclusions outlined in Section II.7.

17.2.1. BRIGHTE Trial: Adverse Events by Demographic Subgroup

Table 182 and Table 183 summarize the frequency of AEs by demographic subgroups. As noted in Section II.7, older, white, male, North American subjects had numerically higher proportions of AEs. However, this population was also the most heavily represented in the BRIGHTE trial. Some demographic subgroups had small numbers of subjects, which limits the ability to draw meaningful conclusions.

Table 182. Adverse Events by Patient Demographics, Randomized Cohort, Safety Population, BRIGHTE Trial

	Age (year) n (%)			Sex n (%)		Race n (%)			Total
Parameter	<35 N=61	35-49 N=101	≥50 N=110	Male N=200	Female N=72	White N=185	Black N=60	Other N=27	n (%) N=272
Any AE	55 (90.2)	90 (89.1)	104 (94.5)	182 (91.0)	67 (93.1)	170 (91.9)	55 (91.7)	24 (88.9)	249 (91.5)
Moderate or severe AEs (Grade 3-4)	15 (24.6)	24 (23.8)	40 (36.4)	62 (31.0)	17 (23.6)	59 (31.9)	14 (23.3)	6 (22.2)	79 (29.0)
SAE	18 (29.5)	28 (27.7)	46 (41.8)	73 (36.5)	19 (26.4)	63 (34.1)	21 (35.0)	8 (29.6)	92 (33.8)
SAEs with fatal outcome	3 (4.9)	3 (3.0)	4 (3.6)	7 (3.5)	3 (4.2)	10 (5.4)	0 (0.0)	0 (0.0)	10 (3.7)
AE leading to discontinuation of study drug	2 (3.3)	6 (5.9)	6 (5.5)	11 (5.5)	3 (4.2)	14 (7.6)	0 (0.0)	0 (0.0)	14 (5.1)
AE leading to dose modification of study drug	9 (14.8)	11 (10.9)	15 (13.6)	26 (13.0)	9 (12.5)	25 (13.5)	7 (11.7)	3 (11.1)	35 (12.9)
AE leading to interruption of study drug	8 (13.1)	11 (10.9)	14 (12.7)	24 (12.0)	9 (12.5)	23 (12.4)	7 (11.7)	3 (11.1)	33 (12.1)
AE leading to reduction of study drug	1 (1.6)	0 (0.0)	1 (0.9)	2 (1.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.7)
AE leading to dose delay of study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: adae.xpt;
For Race, the Other Category includes Asian, American Indian Or Alaska Native, Native Hawaiian Or Other Pacific Islander, and Others.
Abbreviations: AE, adverse event; N, number of subjects in treatment group; n, number of subjects with given treatment duration.

Table 183. Adverse Events by Region, Randomized Cohort, Safety Population, BRIGHTE Trial

	Region n (%)				
Parameter	**North America N=92**	**Latin America N=121**	**Europe N=51**	**Other N=8**	**Total n (%) N=272**
Any AE	85 (92.4)	108 (89.3)	48 (94.1)	8 (100.0)	249 (91.5)
Moderate or severe AEs (Grade 3-4)	34 (37.0)	30 (24.8)	13 (25.5)	2 (25.0)	79 (29.0)
SAE	40 (43.5)	31 (25.6)	16 (31.4)	5 (62.5)	92 (33.8)
SAEs with fatal outcome	5 (5.4)	3 (2.5)	2 (3.9)	0 (0.0)	10 (3.7)
AE leading to discontinuation of study drug	4 (4.3)	6 (5.0)	4 (7.8)	0 (0.0)	14 (5.1)
AE leading to dose modification of study drug	17 (18.5)	14 (11.6)	4 (7.8)	0 (0.0)	35 (12.9)
AE leading to interruption of study drug	16 (17.4)	13 (10.7)	4 (7.8)	0 (0.0)	33 (12.1)
AE leading to reduction of study drug	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)	2 (0.7)
AE leading to dose delay of study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: adae.xpt;
Region is a derived geographic variable that includes categories of North America (Canada and United States), Latin America (Argentina, Brazil, Chile, Colombia, Mexico, Peru, Puerto Rico), Europe (Belgium, France, Germany, Greece, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Russian Federation, Spain, United Kingdom), and Other (Australia, South Africa, Taiwan).
Abbreviations: AE, adverse event; N, number of subjects in treatment group; n, number of subjects with given treatment duration; SAE, serious adverse event; SD, standard deviation

17.2.2. Deaths

An overview of deaths that occurred in the BRIGHTE trial was provided in Section II.7.6. A more detailed list is provided in Table 184.

Table 184. Treatment-Emergent Deaths, Safety Population, BRIGHTE Trial

Study Group Subject ID	Age	Sex	Cause of Death	Study Day of Death	Duration of Exposure (Days)
Non-randomized					
AI438047.000787	48	M	Septic rash	392	392
AI438047.000647	28	M	Sepsis	504	503
AI438047.000141	51	M	Hodgkin's disease	660	659
AI438047.000106	56	M	Clostridium difficile colitis	511	488
AI438047.000559	52	M	Disseminated cytomegaloviral infection	661	661
AI438047.000094	56	M	Hepatic failure	537	513
AI438047.000096	53	M	Tonsil cancer	515	509
AI438047.000091	26	M	Kaposi's sarcoma	160	126
AI438047.000075	61	M	Lymphoma	33	27
AI438047.000057	64	F	Acute kidney injury	350	350
AI438047.000012	28	M	Hodgkin's disease	1,094	1,020
AI438047.000006	58	M	Sepsis	580	567
AI438047.000093	44	M	Hepatic failure	142	141
AI438047.000552	62	M	Cardiovascular disorder	530	530
AI438047.000463[a]	51	M	CMV Colitis	355	276
AI438047.000303[a]	47	F	CMV Encephalitis	158	108
AI438047.000126[a]	68	M	MCA Stroke	879	840
Randomized					
AI438047.000694	31	M	Immune reconstitution inflammatory syndrome	32	31
AI438047.000668	65	M	Pseudomonal sepsis	603	597
AI438047.000655	57	F	Progressive multifocal leukoencephalopathy	287	120
AI438047.000734	49	F	Septic shock	334	334
AI438047.000001	50	M	Squamous cell carcinoma	535	483
AI438047.000474	62	M	Staphylococcal sepsis	466	452
AI438047.000293	45	M	Meningoencephalitis viral	101	101
AI438047.000117	26	M	Cholangiocarcinoma	875	874
AI438047.000113	37	M	Anal squamous cell carcinoma	765	736
AI438047.000008	26	F	Pneumonia	199	199
AI438047.000550 [a]	20	M	Pneumonia	228	178

Source: adae.xpt; Software: Python, supplemented by AE narratives
[a] Non treatment-emergent: Subject discontinued from study prior to fatal event
Abbreviations: N, number of subjects in treatment group; n, number of deaths.

Deaths occurred infrequently in the Phase 2b trial, as summarized in Table 185. Three fatal AEs occurred during the study, all of which occurred in FTR-treated subjects. There is no pattern to these events to suggest contribution of FTR to the fatal event.

Table 185. Adverse Events Leading to Death, Safety Population, Phase 2b Trial

Study Group Subject ID	Age	Sex	Preferred Term	Verbatim Term	Study Day of Death	Study Day of AE Onset	Duration of AE (Days)	Duration of Exposure (Days)	Relatedness
High dosage									
AI438011.000436	29	F	Sepsis	Septicaemia	855	854.4	0.2	854	N
Low dosage									
AI438011.000535	36	F	Gunshot wound	Death-gunshot wound	704	703.4	0	685	N
AI438011.000536	46	M	Completed suicide	Suicide	1125	1124	0	1125	N

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; ID, identification.

17.2.3. Serious Adverse Events

As noted in Section II.7.6, the majority of SAEs in the BRIGHTE trial were infections, malignancy, or GI events. Events that occurred in at least two subjects are summarized in Table 186.

Table 186. Serious Adverse Events, All Cause, All Grade, Safety Population, BRIGHTE Trial

Serious Adverse Event[a,b]	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Pneumonia	12 (4.4)	3 (3.0)	15 (4.0)
Cellulitis	5 (1.8)	3 (3.0)	8 (2.2)
Diarrhoea	4 (1.5)	0 (0.0)	4 (1.1)
Acute myocardial infarction	3 (1.1)	1 (1.0)	4 (1.1)
Anal squamous cell carcinoma	3 (1.1)	1 (1.0)	4 (1.1)
Oesophageal candidiasis	3 (1.1)	1 (1.0)	4 (1.1)
Cholelithiasis	3 (1.1)	0 (0.0)	3 (0.8)
Acute kidney injury	2 (0.7)	4 (4.0)	6 (1.6)
Chronic sinusitis	2 (0.7)	1 (1.0)	3 (0.8)
Squamous cell carcinoma	2 (0.7)	1 (1.0)	3 (0.8)
Angina pectoris	2 (0.7)	0 (0.0)	2 (0.5)
Cervical dysplasia	2 (0.7)	0 (0.0)	2 (0.5)
Gastroenteritis	2 (0.7)	0 (0.0)	2 (0.5)
Hepatitis a	2 (0.7)	0 (0.0)	2 (0.5)
HIV-associated neurocognitive disorder	2 (0.7)	0 (0.0)	2 (0.5)
Immune reconstitution inflammatory syndrome	2 (0.7)	0 (0.0)	2 (0.5)
Penile squamous cell carcinoma	2 (0.7)	0 (0.0)	2 (0.5)
Progressive multifocal leukoencephalopathy	2 (0.7)	0 (0.0)	2 (0.5)
Small intestinal obstruction	2 (0.7)	0 (0.0)	2 (0.5)
Suicidal ideation	2 (0.7)	0 (0.0)	2 (0.5)
Hodgkin's disease	1 (0.4)	3 (3.0)	4 (1.1)
Pneumocystis jirovecii pneumonia	1 (0.4)	3 (3.0)	4 (1.1)
Sepsis	1 (0.4)	3 (3.0)	4 (1.1)
Deep vein thrombosis	1 (0.4)	2 (2.0)	3 (0.8)
Pyrexia	1 (0.4)	2 (2.0)	3 (0.8)
Seizure	1 (0.4)	2 (2.0)	3 (0.8)
Anogenital warts	1 (0.4)	1 (1.0)	2 (0.5)
Clostridium difficile colitis	1 (0.4)	1 (1.0)	2 (0.5)
Coronary artery disease	1 (0.4)	1 (1.0)	2 (0.5)
Escherichia bacteraemia	1 (0.4)	1 (1.0)	2 (0.5)
Iron deficiency anaemia	1 (0.4)	1 (1.0)	2 (0.5)
Mucosal inflammation	1 (0.4)	1 (1.0)	2 (0.5)
Nephrolithiasis	1 (0.4)	1 (1.0)	2 (0.5)
Oral candidiasis	1 (0.4)	1 (1.0)	2 (0.5)
Prostatitis	1 (0.4)	1 (1.0)	2 (0.5)
Pseudomonal sepsis	1 (0.4)	1 (1.0)	2 (0.5)
Septic shock	1 (0.4)	1 (1.0)	2 (0.5)
Squamous cell carcinoma of skin	1 (0.4)	1 (1.0)	2 (0.5)

Source: adae.xpt; Software: Python
[a] Coded as MedDRA preferred terms
[b] Terms included are those that occurred in at least two subjects.
Abbreviations: N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term.

Although no clear pattern emerged to suggest contribution of FTR, the large number of events made it difficult to identify patterns. Several analyses were conducted to narrow the number of events evaluated. Table 187 is an example of one analysis focusing on nonfatal SAEs leading to discontinuation. As shown, these events were infrequent. The potential for hepatic and muscle toxicities are discussed in more depth in Section II.7.6.6.

Table 187. Non-Fatal SAEs Leading to Discontinuation, All Cause, All Grade, Safety Population, BRIGHTE Trial

Adverse Event[a]	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Patients with at least 1 AE leading to discontinuation	3 (1.1)	2 (2.0)	5 (1.3)
Hepatocellular injury	1 (0.4)	0 (0)	1 (0.3)
Progressive multifocal leukoencephalopathy	1 (0.4)	0 (0)	1 (0.3)
Rhabdomyolysis	1 (0.4)	0 (0)	1 (0.3)
Cytomegalovirus colitis	0 (0)	1 (1.0)	1 (0.3)
Hepatitis B reactivation	0 (0)	1 (1.0)	1 (0.3)

Source: adae.xpt; Software: Python
[a] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with adverse event; SAE, serious adverse event.

SAEs from the Phase 2b trial were reviewed to improve the ability of the clinical team to find patterns in a less ill population. As summarized in Table 188, very few events occurred in more than one subject. The most common event was overdose in 3 FTR subjects. One SAE of overdose in the 400 mg BID group was considered FTR-related, whereas the other two events were classified as unrelated (by investigator and FDA clinical reviewer assessment). No concerning trends were found from this analysis.

Table 188. Serious Adverse Events, All Cause, All Grade, Safety Population, Phase 2b Trial

Serious Adverse Event	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Total SAEs	20 (20.2)	15 (14.9)	8 (15.7)
Abdominal pain	2 (2.0)	0 (0.0)	0 (0.0)
Bone tuberculosis	2 (2.0)	0 (0.0)	0 (0.0)
Overdose	1 (1.0)	2 (2.0)	1 (2.0)
Diarrhoea	1 (1.0)	0 (0.0)	1 (2.0)
Abortion spontaneous	1 (1.0)	0 (0.0)	0 (0.0)
Acute kidney injury	1 (1.0)	0 (0.0)	0 (0.0)
Acute stress disorder	1 (1.0)	0 (0.0)	0 (0.0)
Back pain	1 (1.0)	0 (0.0)	0 (0.0)
Cellulitis staphylococcal	1 (1.0)	0 (0.0)	0 (0.0)
Decreased appetite	1 (1.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	1 (1.0)	0 (0.0)	0 (0.0)
Depression	1 (1.0)	0 (0.0)	0 (0.0)
Disseminated tuberculosis	1 (1.0)	0 (0.0)	0 (0.0)
Herpes zoster	1 (1.0)	0 (0.0)	0 (0.0)
Intervertebral disc protrusion	1 (1.0)	0 (0.0)	0 (0.0)
Myalgia	1 (1.0)	0 (0.0)	0 (0.0)
Neutropenia	1 (1.0)	0 (0.0)	0 (0.0)
Obstructive airways disorder	1 (1.0)	0 (0.0)	0 (0.0)
Oral candidiasis	1 (1.0)	0 (0.0)	0 (0.0)
Osteonecrosis	1 (1.0)	0 (0.0)	0 (0.0)
Post herpetic neuralgia	1 (1.0)	0 (0.0)	0 (0.0)
Sepsis	1 (1.0)	0 (0.0)	0 (0.0)
Syncope	1 (1.0)	0 (0.0)	0 (0.0)
Vertigo	1 (1.0)	0 (0.0)	0 (0.0)
Accidental overdose	0 (0.0)	2 (2.0)	0 (0.0)
Adenocarcinoma of salivary gland	0 (0.0)	1 (1.0)	0 (0.0)
Anal abscess	0 (0.0)	1 (1.0)	0 (0.0)
Blood creatine phosphokinase increased	0 (0.0)	1 (1.0)	0 (0.0)
Cellulitis	0 (0.0)	1 (1.0)	0 (0.0)
Cholecystitis chronic	0 (0.0)	1 (1.0)	0 (0.0)
Completed suicide	0 (0.0)	1 (1.0)	0 (0.0)
Gunshot wound	0 (0.0)	1 (1.0)	0 (0.0)
Hysterectomy	0 (0.0)	1 (1.0)	0 (0.0)
Lymphangitis	0 (0.0)	1 (1.0)	0 (0.0)
Meningoencephalitis herpetic	0 (0.0)	1 (1.0)	0 (0.0)
Oesophageal varices haemorrhage	0 (0.0)	1 (1.0)	0 (0.0)
Ovarian neoplasm	0 (0.0)	1 (1.0)	0 (0.0)
Suicide attempt	0 (0.0)	1 (1.0)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	1 (2.0)
Ankle fracture	0 (0.0)	0 (0.0)	1 (2.0)
Cholelithiasis	0 (0.0)	0 (0.0)	1 (2.0)
Influenza	0 (0.0)	0 (0.0)	1 (2.0)
Migraine	0 (0.0)	0 (0.0)	1 (2.0)
Pneumonia	0 (0.0)	0 (0.0)	1 (2.0)
Pyelonephritis acute	0 (0.0)	0 (0.0)	1 (2.0)

Source: adsl.xpt and addd.xpt; Software: Python
Abbreviations: ATV/r, ritonavir-boosted atazanavir; CI, confidence interval; FTR, fostemsavir; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term; SAE, serious adverse event.

17.2.4. Discontinuations Due To AEs

Table 189 summarizes AEs leading to discontinuation in the BRIGHTE trial. Many of the AEs that led to FTR discontinuation were fatal events or events that occurred in subjects who ultimately had fatal events. In some cases, the same subject had multiple nonserious events, often at the same time, that seemed to reflect poor tolerability of FTR in these subjects.

Table 189. Adverse Events Leading to Discontinuation, All Cause, All Grade, Safety Population, BRIGHTE Trial

Study Group Subject ID	Age	Sex	Preferred Term	Verbatim Term	SAE[a]	Study Day of AE Onset	Duration of AE (Days)	Duration of Exposure (Days)	Relatedness[b]
Non-randomized									
AI438047.000006[c]	58	M	Sepsis	Sepsis	Y	506	75	567	N
AI438047.000057[c]	64	F	Acute kidney injury	Acute kidney injury	Y	344	7	350	N
AI438047.000062	50	M	Sinusitis	Sinusitis	N	176	38	211	N
AI438047.000062	50	M	Headache	Headage	N	176	38	211	N
AI438047.000062	50	M	Stomatitis	Irritative buccal mucous membrane	N	176	43	211	N
AI438047.000075[c]	61	M	Lymphoma	Lymphoma	Y	27	7	27	N
AI438047.000091[c]	26	M	Kaposi's sarcoma	Kaposi sarcoma	Y	104	57	126	N
AI438047.000093[c]	44	M	Hepatic failure	Hepatic failure	Y	24	119	141	N
AI438047.000093[c]	44	M	Ascites	Ascites	N	137	6	141	N
AI438047.000093[c]	44	M	Iron deficiency	Iron deficiency	N	137	6	141	N
AI438047.000093[c]	44	M	Generalised oedema	Anasorca	N	137	6	141	N
AI438047.000093[c]	44	M	Hepatorenal syndrome	Hepatorenal syndrome	N	139	4	141	N
AI438047.000094[c]	56	M	Hepatitis B reactivation	Reactivation of hepatitis b	Y	477		513	N
AI438047.000094[c]	56	M	Hepatic failure	Liver failure	Y	477	61	513	N
AI438047.000094[c]	56	M	Hepatic enzyme increased	Elevated liver enzymes	N	480		513	Y
AI438047.000141[c]	51	M	Hodgkin's disease	Hodgkins lymphoma	Y	652	9	659	N
AI438047.000463[c]	51	M	Cytomegalovirus colitis	Cmv, colitis	Y	106		276	N
AI438047.000559[c]	52	M	Disseminated cytomegaloviral disease	Disseminated cytomegalovirus disease	Y	469	193	661	N
AI438047.000648	23	M	Tachycardia	Tachychardia	N	47	3	47	Y
AI438047.000648	23	M	Non-cardiac chest pain	Chest pain non cardiac	N	47	3	47	Y
AI438047.000753	72	M	Electrocardiogram QT prolonged	Prolongation of qt interval	N	69	176	243	Y

Study Group Subject ID	Age	Sex	Preferred Term	Verbatim Term	SAE[a]	Study Day of AE Onset	Duration of AE (Days)	Duration of Exposure (Days)	Relatedness[b]
Randomized									
AI438047.000008[c]	26	F	Pneumonia	Pneumonia	Y	192	8	199	N
AI438047.000050	53	F	Hepatocellular injury	Liver cytolysis	Y	66	55	104	Y
AI438047.000113[c]	37	M	Anal squamous cell carcinoma	Anal squamous cell carcinoma metastatic	Y	57	709	736	N
AI438047.000166	53	M	Electrocardiogram QT prolonged	Prolonged qt interval	N	1		14	N
AI438047.000201	48	F	Hepatitis B	Hepatitis b flare	N	10	30	7	N
AI438047.000290	52	M	Dyspepsia	Indigestion	N	2	8	5	Y
AI438047.000290	52	M	Flatulence	Flatulence	N	2	8	5	Y
AI438047.000290	52	M	Abdominal pain	Abdominal pain	N	2	8	5	Y
AI438047.000290	52	M	Nausea	Nausea	N	2	8	5	Y
AI438047.000293[c]	45	M	Meningoencephalitis viral	Viral meningoencephalitis	Y	80	22	101	N
AI438047.000608	50	M	Progressive multifocal leukoencephal	Progressive multifocal leukoencephalopathy	Y	94	20	95	N
AI438047.000620	61	M	Rhabdomyolysis	Rhabdomyolysis	Y	91	196	95	Y
AI438047.000694[c]	31	M	Mycobacterial infection	Probable mycobacterial infection	N	31		31	Y
AI438047.000706	60	M	Electrocardiogram QT prolonged	Qtc prolongation	N	120		119	Y
AI438047.000210	47	M	Asthenia	Generalized weakness	N	1	10	9	Y
AI438047.000210	47	M	Fatigue	Fatigue	N	1	10	9	Y
AI438047.000210	47	M	Dizziness	Dizziness	N	1	10	9	Y
AI438047.000210	47	M	Neck pain	Pain in the neck,	N	1	10	9	Y
AI438047.000210	47	M	Non-cardiac chest pain	Non cardiac thoracic pain	N	9	2	9	Y
AI438047.000427	41	M	Abdominal distension	Abdominal distention	N	31	14	35	N
AI438047.000427	41	M	Abdominal pain	Abdominal colic	N	34	1	35	N
AI438047.000427	41	M	Vomiting	Vomiting	N	34	1	35	N
AI438047.000650	48	M	Rash	Cutaneous rash	N	17	13	20	Y

Source: adsl.xpt and addd.xpt; Software: Python
[a] Serious adverse events classified by Applicant in adae.xpt
[b] Five-point scale: highly likely, likely, possible, unlikely, highly unlikely, investigator's assessment
[c] Subjects who died
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with adverse event; ID, identifier; PT, preferred term; SAE, serious adverse event.

As shown in Table 190, only one event was assessed as FTR-related in the Phase 2b trial. This event of acute kidney injury was attributed to TDF rather than FTR; given the known association between TDF and renal AEs, the clinical reviewer agrees with this assessment.

Table 190. Adverse Events Leading to Discontinuation, Safety Population, Phase 2b Trial

Study Group Subject ID	Age	Sex	Preferred Term	Verbatim Term	SAE[a]	Study Day of AE Onset	Duration of AE (Days)	Duration of Exposure (Days)	Relatedness[b]
ATV/r									
AI438011.000007	49	M	Flatulence	Abdominal gas	N	58	13	69	Y
AI438011.000007	49	M	Abdominal distension	Abdominal bloating	N	58	13	69	Y
AI438011.000237	37	M	Jaundice	Jaundice	N	7	6	10	Y
AI438011.000425	36	F	Chorea	Progression of chorea	N	956		924	N
AI438011.000477	32	M	Hyperbilirubinaemia	Hyperbilirubinemia	N	1,039	27	1,062	Y
AI438011.000621	44	M	Hypertransaminasaemia	Hypertransaminasaemia	N	561		643	Y
AI438011.000630	39	M	Hepatic steatosis	Hepatic steatosis	N	505		658	Y
AI438011.000631	35	M	Blood bilirubin increased	Intermittent elevated bilirubin	N	331	253	567	Y
FTR ≥1,200 mg									
AI438011.000077	51	M	Acute kidney injury	Tenofovir-induced acute renal failure	N	93	1	93	Y
AI438011.000121	42	M	Lymph node tuberculosis	Tuberculosis lymphadenitis	N	387	185	417	N
AI438011.000233	58	M	Disseminated tuberculosis	Disseminated tuberculosis	Y	113		115	N
AI438011.000479	29	F	Bone tuberculosis	Tb spondylitis	N	35	5	35	N
AI438011.000593	26	F	Bone tuberculosis	Tb mastoiditis	Y	1,529		1,541	N
FTR ≤800 mg									
AI438011.000536	46	M	Completed suicide	Suicide	Y	1,125	1	1,125	N
AI438011.000556	34	M	Ischaemia	Possible ischemia likely related to history of IVDU (cocaine use)	N	30		39	N

Source: adae.xpt; Software: Python
[a] Serious adverse events classified by Applicant in adae.xpt
[b] Five-point scale: highly likely, likely, possible, unlikely, highly unlikely
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; ID, identifier; IVDU, intravenous drug use; SAE, serious adverse event.

17.2.5. Adverse Events

Nearly all subjects in the BRIGHTE trial experienced AEs during the 96-week study period: 91% in the Randomized Cohort and 99% in the Non-randomized Cohort. Grade 3/4 events were reported in approximately a third of the subjects overall; as noted in previous safety analyses, subjects in the Non-randomized Cohort were more likely to have high grade safety events (49%) compared to the Randomized Cohort (29%). AEs were also reported in >90% of subjects in the Phase 2b trial (93% of FTR subjects and 98% of ritonavir-boosted atazanavir [ATV/r] subjects) but Grade 3/4 events were less common than the BRIGHTE trial overall and occurred in higher proportions of ATV/r (33%) subjects compared to FTR subjects (18%).

Table 191 and Table 192 provide a high level overview of common AEs by System Organ Class (SOC) in the BRIGHTE trial and Phase 2b trial, respectively. Infections and GI disorders were predominant in both trials.

Table 191. AEs by SOC Occurring in at Least 10% of Subjects, All Cause, All Grade, Safety Population, BRIGHTE Trial

System Organ Class	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Infections and infestations	190 (69.9)	78 (78.8)	268 (72.2)
Gastrointestinal disorders	155 (57.0)	53 (53.5)	208 (56.1)
General disorders and administration site conditions	88 (32.4)	48 (48.5)	136 (36.7)
Nervous system disorders	92 (33.8)	34 (34.3)	126 (34.0)
Skin and subcutaneous tissue disorders	83 (30.5)	42 (42.4)	125 (33.7)
Musculoskeletal and connective tissue disorders	82 (30.1)	41 (41.4)	123 (33.2)
Respiratory, thoracic and mediastinal disorders	80 (29.4)	27 (27.3)	107 (28.8)
Investigations	60 (22.1)	20 (20.2)	80 (21.6)
Metabolism and nutrition disorders	53 (19.5)	25 (25.3)	78 (21.0)
Psychiatric disorders	57 (21.0)	14 (14.1)	71 (19.1)
Neoplasms benign, malignant and unspecified[a]	44 (16.2)	27 (27.3)	71 (19.1)
Injury, poisoning and procedural complications	42 (15.4)	15 (15.2)	57 (15.4)
Renal and urinary disorders	32 (11.8)	21 (21.2)	53 (14.3)
Blood and lymphatic system disorders	23 (8.5)	18 (18.2)	41 (11.1)
Eye disorders	29 (10.7)	9 (9.1)	38 (10.2)
Reproductive system and breast disorders	29 (10.7)	9 (9.1)	38 (10.2)
Vascular disorders	25 (9.2)	11 (11.1)	36 (9.7)

Source: adae.xpt; Software: Python
[a] Includes cysts and polyps
Abbreviations: AE, adverse event; ATV, atazanavir; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with at least one event; SOC, system organ class.

Table 192. AEs by SOC Occurring in at Least 10% of Subjects in Any FTR Group, All Cause, All Grade, Safety Population, Phase 2b Trial

System Organ Class	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Infections and infestations	71 (71.7)	83 (82.2)	36 (70.6)
Gastrointestinal disorders	47 (47.5)	46 (45.5)	25 (49.0)
Nervous system disorders	28 (28.3)	43 (42.6)	14 (27.5)
Skin and subcutaneous tissue disorders	28 (28.3)	39 (38.6)	9 (17.6)
Musculoskeletal and connective tissue disorders	26 (26.3)	36 (35.6)	8 (15.7)
Respiratory, thoracic and mediastinal disorders	16 (16.2)	24 (23.8)	5 (9.8)
Metabolism and nutrition disorders	15 (15.2)	14 (13.9)	8 (15.7)
General disorders and administration site conditions	13 (13.1)	18 (17.8)	6 (11.8)
Renal and urinary disorders	11 (11.1)	13 (12.9)	8 (15.7)
Injury, poisoning and procedural complications	10 (10.1)	28 (27.7)	6 (11.8)
Investigations	10 (10.1)	25 (24.8)	10 (19.6)
Reproductive system and breast disorders	10 (10.1)	17 (16.8)	6 (11.8)
Psychiatric disorders	10 (10.1)	15 (14.9)	8 (15.7)
Vascular disorders	7 (7.1)	17 (16.8)	4 (7.8)
Blood and lymphatic system disorders	7 (7.1)	13 (12.9)	0 (0.0)

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment arm; n, number of subjects with at least one event; SOC, system organ class.

The most commonly reported AEs by preferred term (PT) are shown in Table 193 and Table 194 for the BRIGHTE trial and Phase 2b trial, respectively. Diarrhea was the most commonly reported PT in both trials; of note, the proportion of subjects reporting diarrhea is comparable between the FTR and ATV/r cohorts of the Phase 2b trial.

Table 193. Adverse Events Reported in ≥5%, Safety Population, BRIGHTE Trial

Adverse Event[a,b]	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Diarrhoea	62 (22.8)	25 (25.3)	87 (23.5)
Nausea	46 (16.9)	21 (21.2)	67 (18.1)
Upper respiratory tract infection	42 (15.4)	15 (15.2)	57 (15.4)
Headache	40 (14.7)	12 (12.1)	52 (14.0)
Nasopharyngitis	34 (12.5)	19 (19.2)	53 (14.3)
Cough	34 (12.5)	11 (11.1)	45 (12.1)
Bronchitis	34 (12.5)	6 (6.1)	40 (10.8)
Pyrexia	30 (11.0)	18 (18.2)	48 (12.9)
Vomiting	30 (11.0)	9 (9.1)	39 (10.5)
Influenza	26 (9.6)	13 (13.1)	39 (10.5)
Arthralgia	23 (8.5)	9 (9.1)	32 (8.6)
Constipation	23 (8.5)	6 (6.1)	29 (7.8)
Sinusitis	22 (8.1)	11 (11.1)	33 (8.9)
Abdominal pain	22 (8.1)	5 (5.1)	27 (7.3)
Pneumonia	21 (7.7)	8 (8.1)	29 (7.8)
Depression	19 (7.0)	3 (3.0)	22 (5.9)
Fatigue	18 (6.6)	16 (16.2)	34 (9.2)
Oral candidiasis	18 (6.6)	11 (11.1)	29 (7.8)
Dizziness	18 (6.6)	5 (5.1)	23 (6.2)
Insomnia	18 (6.6)	2 (2.0)	20 (5.4)
Back pain	16 (5.9)	13 (13.1)	29 (7.8)

Adverse Event[a,b]	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Urinary tract infection	16 (5.9)	10 (10.1)	26 (7.0)
Pain in extremity	14 (5.1)	7 (7.1)	21 (5.7)
Anogenital warts	13 (4.8)	6 (6.1)	19 (5.1)
Gastroenteritis	13 (4.8)	6 (6.1)	19 (5.1)
Abdominal pain upper	13 (4.8)	4 (4.0)	17 (4.6)
Asthenia	12 (4.4)	14 (14.1)	26 (7.0)

Source: adae.xpt; Software: Python
[a] Terms included are those that occurred in Randomized Cohort and at least 5% of subjects.
[b] Coded as MedDRA preferred terms
Abbreviations: N, number of subjects in treatment group; n, number of subjects with at least one event.

Table 194. Adverse Events Reported in ≥5% of FTR Subjects, Safety Population, Phase 2b Trial

Adverse Event	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Diarrhoea	16 (16.2)	21 (20.8)	11 (21.6)
Urinary tract infection	14 (14.1)	14 (13.9)	6 (11.8)
Headache	13 (13.1)	25 (24.8)	6 (11.8)
Nasopharyngitis	13 (13.1)	19 (18.8)	5 (9.8)
Herpes zoster	11 (11.1)	7 (6.9)	2 (3.9)
Influenza	10 (10.1)	12 (11.9)	8 (15.7)
Nausea	10 (10.1)	9 (8.9)	6 (11.8)
Bronchitis	9 (9.1)	13 (12.9)	4 (7.8)
Pharyngitis	9 (9.1)	8 (7.9)	5 (9.8)
Vomiting	9 (9.1)	7 (6.9)	6 (11.8)
Upper respiratory tract infection	8 (8.1)	19 (18.8)	7 (13.7)
Back pain	8 (8.1)	12 (11.9)	3 (5.9)
Dyspepsia	8 (8.1)	4 (4.0)	2 (3.9)
Cough	7 (7.1)	10 (9.9)	2 (3.9)
Abdominal pain	7 (7.1)	6 (5.9)	4 (7.8)
Rash	6 (6.1)	9 (8.9)	0 (0.0)
Gastroenteritis	6 (6.1)	5 (5.0)	6 (11.8)
Fatigue	6 (6.1)	5 (5.0)	4 (7.8)
Lower respiratory tract infection	6 (6.1)	4 (4.0)	1 (2.0)
Arthralgia	5 (5.1)	13 (12.9)	1 (2.0)
Hypertension	5 (5.1)	10 (9.9)	3 (5.9)
Pain in extremity	5 (5.1)	9 (8.9)	1 (2.0)
Insomnia	5 (5.1)	8 (7.9)	2 (3.9)
Respiratory tract infection	5 (5.1)	4 (4.0)	2 (3.9)
Gastritis	5 (5.1)	2 (2.0)	2 (3.9)
Sciatica	5 (5.1)	1 (1.0)	1 (2.0)
Oral candidiasis	5 (5.1)	0 (0.0)	0 (0.0)
Constipation	4 (4.0)	7 (6.9)	0 (0.0)
Blood creatine phosphokinase increased	4 (4.0)	6 (5.9)	3 (5.9)
Myalgia	4 (4.0)	6 (5.9)	0 (0.0)
Dizziness	4 (4.0)	5 (5.0)	4 (7.8)
Onychomycosis	3 (3.0)	5 (5.0)	3 (5.9)
Flatulence	3 (3.0)	5 (5.0)	2 (3.9)
Oral herpes	3 (3.0)	5 (5.0)	2 (3.9)
Toothache	3 (3.0)	5 (5.0)	2 (3.9)
Anaemia	3 (3.0)	5 (5.0)	0 (0.0)
Syphilis	3 (3.0)	5 (5.0)	0 (0.0)

Adverse Event	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Sinusitis	3 (3.0)	2 (2.0)	4 (7.8)
Abdominal pain upper	3 (3.0)	2 (2.0)	3 (5.9)
Pyrexia	2 (2.0)	6 (5.9)	2 (3.9)
Eczema	2 (2.0)	6 (5.9)	1 (2.0)
Paraesthesia	2 (2.0)	6 (5.9)	1 (2.0)
Limb injury	2 (2.0)	5 (5.0)	0 (0.0)
Aspartate aminotransferase increased	1 (1.0)	6 (5.9)	2 (3.9)
Arthropod bite	1 (1.0)	6 (5.9)	0 (0.0)
Musculoskeletal pain	1 (1.0)	6 (5.9)	0 (0.0)
Rhinitis	1 (1.0)	5 (5.0)	1 (2.0)
Rash pruritic	1 (1.0)	5 (5.0)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	6 (5.9)	4 (7.8)
Pneumonia	0 (0.0)	5 (5.0)	1 (2.0)
Night sweats	0 (0.0)	5 (5.0)	0 (0.0)

Source: adae.xpt; Software: Python
Abbreviations: ATV/r, ritonavir-boosted atazanavir; CI, confidence interval; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with adverse event; PT, preferred term.

***Medical Officer Assessment**: Commonly reported AEs that are potentially FTR-related are discussed in Section II.7. No concerning trends were found to suggest FTR-related toxicity. However, interpretation of all-cause AEs in the BRIGHTE trial is difficult due to the absence of a control group for comparison.*

17.2.6. Adverse Events of Special Interest

The purpose of this section is to provide a more detailed discussion regarding safety signals that were observed early in the FTR development program or were noted early in the NDA review to occur at high frequency or be associated with serious outcomes. The analyses provided here were used to support the conclusions presented in Section II.7.

17.2.6.1. Prolongation of the QT Interval

To assess the arrhythmogenic potential of FTR, AEs were identified in two pertinent MedDRA Standardized Medical Query (SMQ) categories: Cardiac Arrhythmias (broad and narrow) and Torsade de pointes/QT prolongation (broad and narrow). These analyses are presented in a consolidated format in Table 195; only the narrow analyses are shown, as these are more sensitive for signal detection. Of note, it is unclear why discrepant values were detected for the same PT when analyzed in different SMQs. Subjects with loss of consciousness and syncope had other cardiac abnormalities (e.g., history of rheumatic fever, ECG abnormalities, history of myocardium insufficiency) or noncardiac risk factors (e.g., seizure disorder) which provide alternate causality for the events. No new concerns were identified from these analyses.

Table 195. Adverse Events by Arrhythmia Standardized MedDRA Query and Preferred Term, All Cause, All Grade, Safety Population, BRIGHTE Trial and Phase 2b Trial

	BRIGHTE Trial			Phase 2b Trial		
Standardized MedDRA Query Preferred Term	**Randomized Cohort N=272 n (%)**	**Non-randomized Cohort N=99 n (%)**	**Phase 3 Overall N=371 n (%)**	**≥1,200 mg FTR N=99 n (%)**	**≤800 mg FTR N=101 n (%)**	**ATV/r N=51 n (%)**
Cardiac arrhythmias (SMQ), Broad	4 (1.5)	6 (6.1)	10 (2.7)	0 (0.0)	0 (0.0)	2 (3.9)
Loss of consciousness	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (2.0)
Palpitations	1 (0.4)	3 (3.0)	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (2.0)
Tachycardia	1 (0.4)	3 (3.0)	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrhythmias (SMQ), Narrow	6 (2.2)	4 (4.0)	10 (2.7)	2 (2.0)	2 (2.0)	1 (2.0)
Bundle branch block right	2 (0.7)	1 (1.0)	3 (0.8)	0 (0.0)	0 (0.0)	1 (2.0)
Atrial fibrillation	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Atrial flutter	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram QT prolonged	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)
Sinus bradycardia	1 (0.4)	0 (0.0)	1 (0.3)	1 (1.0)	1 (1.0)	0 (0.0)
Ventricular extrasystoles	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pulseless electrical activity	0 (0.0)	1 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	2 (2.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Torsade de pointes/QT prolongation (SMQ), Broad	3 (1.1)	0 (0.0)	3 (0.8)	1 (1.0)	0 (0.0)	2 (3.9)
Syncope	2 (0.7)	0 (0.0)	2 (0.5)	1 (1.0)	0 (0.0)	1 (2.0)
Loss of consciousness	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (2.0)
Torsade de pointes/QT prolongation (SMQ), Narrow	5 (1.8)	1 (1.0)	6 (1.6)	0 (0.0)	1 (1.0)	0 (0.0)
Electrocardiogram QT prolonged	5 (1.8)	1 (1.0)	6 (1.6)	0 (0.0)	1 (1.0)	0 (0.0)

Source: adae.xpt for each trial; Software: Python
SMQ version: 22.1.
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment group; n, number of subjects with at least one event; SMQ, standardized MedDRA query.

17.2.6.2. Rash and HSRs

As summarized in Section II.7, there is evidence of a relationship between rash events and FTR exposure, demonstrated by an imbalance in frequencies between the FTR and ATV/r group of the Phase 2b trial. Rash events occurred at similar frequencies in the Phase 3 BRIGHTE trial and Phase 2b trial, also supporting a relationship with FTR. A broader query for dermatologic events was performed to identify additional cutaneous events, some of which could be suggestive of HSRs. The MedDRA HLGT Epidermal and dermal conditions was used for this analysis, which is summarized in Table 196 and Table 197 for the BRIGHTE trial and Phase 2b trial, respectively.

It is notable that skin abnormalities not typically suggestive of drug rashes (e.g., eczema, nonspecific dermatitis) again occurred at notably higher rates in the FTR group of the Phase 2b trial, and at similar frequencies among FTR subjects in the two trials.

Table 196. Pooled Skin AEs, All Cause, All Grade, Safety Population, BRIGHTE Trial

Grouped Query Preferred Term	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Rash (Grouped query)	61 (22.4)	32 (32.3)	93 (25.1)
Dermatitis allergic	8 (2.9)	2 (2.0)	10 (2.7)
Rash	7 (2.6)	3 (3.0)	10 (2.7)
Skin lesion	7 (2.6)	2 (2.0)	9 (2.4)
Pruritus	6 (2.2)	3 (3.0)	9 (2.4)
Rash pruritic	5 (1.8)	4 (4.0)	9 (2.4)
Eczema	4 (1.5)	5 (5.1)	9 (2.4)
Rash maculo-papular	4 (1.5)	1 (1.0)	5 (1.3)
Rash papular	4 (1.5)	5 (5.1)	9 (2.4)
Seborrhoeic dermatitis	4 (1.5)	2 (2.0)	6 (1.6)
Dermatitis	3 (1.1)	1 (1.0)	4 (1.1)
Dry skin	3 (1.1)	2 (2.0)	5 (1.3)
Prurigo	3 (1.1)	2 (2.0)	5 (1.3)
Pruritus generalized	3 (1.1)	1 (1.0)	4 (1.1)
Rash generalized	3 (1.1)	4 (4.0)	7 (1.9)
Erythema	2 (0.7)	3 (3.0)	5 (1.3)
Skin exfoliation	2 (0.7)	1 (1.0)	3 (0.8)
Skin plaque	2 (0.7)	0 (0.0)	2 (0.5)
Dermatitis contact	1 (0.4)	0 (0.0)	1 (0.3)
Dyshidrotic eczema	1 (0.4)	1 (1.0)	2 (0.5)
Eczema nummular	1 (0.4)	0 (0.0)	1 (0.3)
Hand dermatitis	1 (0.4)	0 (0.0)	1 (0.3)
Neurodermatitis	1 (0.4)	0 (0.0)	1 (0.3)
Palmar erythema	1 (0.4)	0 (0.0)	1 (0.3)
Rash macular	1 (0.4)	2 (2.0)	3 (0.8)
Rash vesicular	1 (0.4)	0 (0.0)	1 (0.3)
Skin fissures	1 (0.4)	0 (0.0)	1 (0.3)
Solar dermatitis	1 (0.4)	0 (0.0)	1 (0.3)
Stasis dermatitis	1 (0.4)	0 (0.0)	1 (0.3)
Blister	0 (0.0)	1 (1.0)	1 (0.3)
Cutaneous lupus erythematosus	0 (0.0)	1 (1.0)	1 (0.3)
Dermatomyositis	0 (0.0)	1 (1.0)	1 (0.3)
Intertrigo	0 (0.0)	1 (1.0)	1 (0.3)
Koebner phenomenon	0 (0.0)	1 (1.0)	1 (0.3)

Grouped Query Preferred Term	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Psoriasis	0 (0.0)	1 (1.0)	1 (0.3)
Rash erythematous	0 (0.0)	1 (1.0)	1 (0.3)
Skin discoloration	0 (0.0)	1 (1.0)	1 (0.3)

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; N, number of subjects in treatment group; n, number of subjects with at least one event.

Table 197. Pooled Skin AEs, All Cause, All Grade, Safety Population, Phase 2b Trial

Grouped Query Preferred Term	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Rash	20 (20.2)	28 (27.7)	6 (11.8)
Rash	6 (6.1)	9 (8.9)	0 (0.0)
Eczema	2 (2.0)	6 (5.9)	1 (2.0)
Prurigo	2 (2.0)	1 (1.0)	1 (2.0)
Pruritus	2 (2.0)	2 (2.0)	0 (0.0)
Skin exfoliation	2 (2.0)	0 (0.0)	0 (0.0)
Dermatitis	1 (1.0)	4 (4.0)	0 (0.0)
Dry skin	1 (1.0)	2 (2.0)	0 (0.0)
Macule	1 (1.0)	1 (1.0)	0 (0.0)
Pruritus generalised	1 (1.0)	0 (0.0)	1 (2.0)
Rash generalised	1 (1.0)	0 (0.0)	0 (0.0)
Rash macular	1 (1.0)	0 (0.0)	0 (0.0)
Rash maculo-papular	1 (1.0)	0 (0.0)	0 (0.0)
Rash papular	1 (1.0)	3 (3.0)	1 (2.0)
Rash pruritic	1 (1.0)	5 (5.0)	0 (0.0)
Seborrhoeic dermatitis	1 (1.0)	2 (2.0)	1 (2.0)
Dermatitis allergic	0 (0.0)	2 (2.0)	0 (0.0)
Dermatitis contact	0 (0.0)	3 (3.0)	1 (2.0)
Drug eruption	0 (0.0)	1 (1.0)	0 (0.0)
Erythema	0 (0.0)	2 (2.0)	0 (0.0)
Psoriasis	0 (0.0)	1 (1.0)	0 (0.0)
Skin irritation	0 (0.0)	1 (1.0)	0 (0.0)
Skin lesion	0 (0.0)	1 (1.0)	0 (0.0)
Solar dermatitis	0 (0.0)	1 (1.0)	0 (0.0)

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with at least one event.

Rash events were the most frequently reported events in the Hypersensitivity SMQ (Table 198 and Table 199 for BRIGHTE and Phase 2b, respectively). The narratives for events were reviewed as available, and no pattern of events emerged to suspect a pattern of true FTR-related HSRs.

Table 198. HSR SMQ Narrow, All Cause, All Grade, Safety Population, BRIGHTE Trial

Standardized MedDRA Query Preferred Term	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Hypersensitivity (SMQ), Narrow	53 (19.5)	20 (20.2)	73 (19.7)
Dermatitis allergic	8 (2.9)	2 (2.0)	10 (2.7)
Rash	6 (2.2)	3 (3.0)	9 (2.4)

Standardized MedDRA Query Preferred Term	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Rash pruritic	5 (1.8)	3 (3.0)	8 (2.2)
Rhinitis allergic	5 (1.8)	1 (1.0)	6 (1.6)
Drug hypersensitivity	4 (1.5)	2 (2.0)	6 (1.6)
Eczema	4 (1.5)	5 (5.1)	9 (2.4)
Rash maculo-papular	4 (1.5)	1 (1.0)	5 (1.3)
Allergic cough	3 (1.1)	0 (0.0)	3 (0.8)
Dermatitis	3 (1.1)	1 (1.0)	4 (1.1)
Hypersensitivity	3 (1.1)	0 (0.0)	3 (0.8)
Urticaria	3 (1.1)	2 (2.0)	5 (1.3)
Bronchospasm	1 (0.4)	0 (0.0)	1 (0.3)
Conjunctivitis allergic	1 (0.4)	0 (0.0)	1 (0.3)
Dermatitis acneiform	1 (0.4)	2 (2.0)	3 (0.8)
Dermatitis contact	1 (0.4)	0 (0.0)	1 (0.3)
Eczema nummular	1 (0.4)	0 (0.0)	1 (0.3)
Erythema nodosum	1 (0.4)	0 (0.0)	1 (0.3)
Eyelid oedema	1 (0.4)	0 (0.0)	1 (0.3)
Hand dermatitis	1 (0.4)	0 (0.0)	1 (0.3)
Injection site hypersensitivity	1 (0.4)	0 (0.0)	1 (0.3)
Lip oedema	1 (0.4)	0 (0.0)	1 (0.3)
Pharyngeal oedema	1 (0.4)	0 (0.0)	1 (0.3)
Rash macular	1 (0.4)	2 (2.0)	3 (0.8)
Rash vesicular	1 (0.4)	0 (0.0)	1 (0.3)
Rash erythematous	0 (0.0)	1 (1.0)	1 (0.3)
Swelling face	0 (0.0)	1 (1.0)	1 (0.3)

Source: adae.xpt; Software: Python
SMQ version: 22.1.
Abbreviations: HSR, hypersensitivity reaction; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment group; n, number of subjects with at least one event; SMQ, Standardized MedDRA Query.

Table 199. HSR SMQ Narrow, All Cause, All Grade, Safety Population, Phase 2b Trial

Standardized MedDRA Query Preferred Term	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Hypersensitivity (SMQ), Narrow	14 (14.1)	29 (28.7)	3 (5.9)
Rash	5 (5.1)	9 (8.9)	0 (0.0)
Eczema	2 (2.0)	6 (5.9)	1 (2.0)
Rhinitis allergic	2 (2.0)	2 (2.0)	0 (0.0)
Conjunctivitis allergic	1 (1.0)	1 (1.0)	0 (0.0)
Dermatitis	1 (1.0)	4 (4.0)	0 (0.0)
Rash macular	1 (1.0)	0 (0.0)	0 (0.0)
Rash maculo-papular	1 (1.0)	0 (0.0)	0 (0.0)
Rash pruritic	1 (1.0)	5 (5.0)	0 (0.0)
Rash pustular	1 (1.0)	1 (1.0)	0 (0.0)
Urticaria	1 (1.0)	3 (3.0)	0 (0.0)
Urticaria physical	1 (1.0)	0 (0.0)	0 (0.0)
Allergic bronchitis	0 (0.0)	1 (1.0)	0 (0.0)
Allergic sinusitis	0 (0.0)	1 (1.0)	0 (0.0)
Angioedema	0 (0.0)	1 (1.0)	0 (0.0)
Bronchospasm	0 (0.0)	1 (1.0)	0 (0.0)
Dermatitis allergic	0 (0.0)	2 (2.0)	0 (0.0)
Dermatitis contact	0 (0.0)	3 (3.0)	1 (2.0)
Drug eruption	0 (0.0)	1 (1.0)	0 (0.0)

Standardized MedDRA Query Preferred Term	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Hypersensitivity	0 (0.0)	0 (0.0)	1 (2.0)
Scrotal oedema	0 (0.0)	1 (1.0)	0 (0.0)

Source: adae.xpt; Software: Python
SMQ version: 22.1.
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; HSR, hypersensitivity reaction; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; SMQ, Standardized MedDRA Query.

17.2.6.3. Hepatobiliary Events

This section provides supplementary analyses to support the conclusions presented in Section II.7.

Table 200 and Table 201 summarize hepatobiliary AEs and laboratory abnormalities, respectively, that occurred in the Phase 2b trial. The majority of events (clinical and laboratory) occurred in the ATV/r group, which is consistent with the known safety profile of ATV. One subject interrupted FTR due to the SAE cholecystitis chronic. None of the other events in FTR subjects were serious or resulted in interruption of FTR treatment.

Table 200. Hepatobiliary AEs, All Cause, All Grade, Safety Population, Phase 2b Trial

Adverse Event by PT	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Hyperbilirubinaemia	0 (0.0)	0 (0.0)	11 (21.6)
Ocular icterus	0 (0.0)	1 (1.0)	7 (13.7)
Jaundice	0 (0.0)	0 (0.0)	8 (15.7)
Hypertransaminasaemia	1 (1.0)	2 (2.0)	2 (3.9)
Hepatic steatosis	2 (2.0)	1 (1.0)	2 (3.9)
Cholecystitis chronic	0 (0.0)	1 (1.0)	0 (0.0)
Cirrhosis alcoholic	0 (0.0)	1 (1.0)	0 (0.0)
Drug-induced liver injury	0 (0.0)	0 (0.0)	1 (2.0)
Cholelithiasis	0 (0.0)	0 (0.0)	1 (2.0)
Hepatic cyst	0 (0.0)	0 (0.0)	1 (2.0)

Source: adae.xpt; Software: JReview
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; PT, preferred term.

Table 201. Maximum Postbaseline Hepatic Laboratory Abnormalities, Safety Population, Phase 2b Trial

Laboratory Test	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Alanine aminotransferase (U/L) (Sum)	29 (29)	39 (39)	17 (33)
Grade 1 (<3 × ULN)	17 (17)	24 (24)	9 (18)
Grade 2 (≥3 – <5 × ULN)	10 (10)	14 (14)	3 (6)
Grade 3 (≥5 – <10 × ULN)	1 (1)	1 (1)	3 (6)
Grade 4 (≥10 × ULN)	1 (1)	0 (0)	2 (4)

Laboratory Test	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Aspartate aminotransferase (U/L) (Sum)	33 (33)	41 (41)	18 (35)
Grade 1 (<3× ULN)	19 (19)	27 (27)	8 (16)
Grade 2 (≥3– <5 × ULN)	9 (9)	12 (12)	5 (10)
Grade 3 (≥5 – <10 × ULN)	4 (4)	2 (2)	4 (8)
Grade 4 (≥10 × ULN)	1 (1)	0 (0)	1 (2)
Bilirubin (umol/L) (Sum)	6 (6)	19 (19)	46 (90)
Grade 1 (1.1 to <1.6 × ULN)	6 (6)	16 (16)	4 (8)
Grade 2 (1.6 to <2.6 × ULN)	0 (0)	3 (3)	11 (22)
Grade 3 (2.6 to <5.0 × ULN)	0 (0)	0 (0)	24 (47)
Grade 4 (≥5.0 × ULN)	0 (0)	0 (0)	7 (14)

Source: adlb.xpt; Software: Python
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; ULN, upper limit of normal.

17.2.6.4. Elevations in Serum Creatine Kinase and Correlation With Myalgia

The review team evaluated the correlation between laboratory and clinical events reflective of muscle disorders to determine whether FTR has a deleterious effect of muscle health. A summary of clinical AEs by PT is summarized in Table 202 and laboratory abnormalities are provided in Table 201. Elevations in serum creatine kinase (CK) were more commonly reported than clinical AEs in the BRIGHTE trial.

Table 202. Ph 3 HLGT Muscle Disorders, All Cause, All Grade, Safety Population, BRIGHTE Trial

Adverse Event by PT	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Total subjects with muscle AE	17 (6.3)	10 (10.1)	27 (7.3)
Myalgia	11 (4.0)	6 (6.1)	17 (4.6)
Muscle spasms	6 (2.2)	3 (3.1)	9 (2.4)
Muscular weakness	3 (1.1)	0 (0.0)	3 (0.8)
Muscle tightness	1 (0.4)	0 (0.0)	1 (0.3)
Muscle twitching	1 (0.4)	0 (0.0)	1 (0.3)
Myalgia intercostal	0 (0.0)	1 (1.0)	1 (0.3)
Rhabdomyolysis	1 (0.4)	0 (0.0)	1 (0.3)
Torticollis	1 (0.4)	0 (0.0)	1 (0.3)

Source: adae.xpt; Software: JReview
Abbreviations: AE, adverse event; HLGT, high level grouped term; N, number of subjects in treatment arm; n, number of subjects with at least one event; PT, preferred term.

Table 203. Postbaseline Laboratory Abnormalities, Safety Population, BRIGHTE Trial

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Creatine kinase (U/L), Sum	22 (8)	11 (11)	33 (9)
Grade 1 (3 to <6 × ULN)	13 (5)	4 (4)	17 (5)
Grade 2 (6 to <10 × ULN)	2 (1)	4 (4)	6 (2)
Grade 3 (10 to <20 × ULN)	7 (3)	3 (3)	10 (3)

Source: adlb.xpt; Software: Python
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; ULN, upper limit of normal.

The same analyses were performed for the Phase 2b trial to determine whether a similar trend was seen between the two study populations (Table 204 and Table 205). There was an imbalance in clinical events, with more occurring in the FTR arms compared to ATV/r, suggesting contribution of FTR to these events. Laboratory abnormalities were similar between groups.

Table 204. HLGT Muscle Disorders, All Cause All Grade, Phase 2b Trial

Adverse Event by PT	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Total subjects with Muscle AE	5 (5.1)	9 (8.9)	2 (3.9)
Myalgia	4 (4.0)	6 (5.9)	0 (0.0)
Muscle spasms	0 (0.0)	2 (2.0)	2 (3.9)
Muscular weakness	0 (0.0)	2 (2.0)	0 (0.0)
Myositis	0 (0.0)	1 (1.0)	0 (0.0)
Muscle disorder	1 (1.0)	0 (0.0)	0 (0.0)

Source: adae.xpt; Software: Jreview
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; HLGT, high level grouped term; N, number of subjects in treatment arm; n, number of subjects with at least one event; PT, preferred term.

Table 205. Laboratory Abnormalities, Postbaseline Clinical Chemistry, Safety Population, Phase 2b Trial

Laboratory Test	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Creatine kinase (U/L) (Sum)	14 (14)	27 (27)	12 (24)
Grade 1 (3 to <6 × ULN)	6 (6)	19 (19)	6 (12)
Grade 2 (6 to <10 × ULN)	2 (2)	5 (5)	1 (2)
Grade 3 (10 to <20 × ULN)	5 (5)	2 (2)	1 (2)
Grade 4 (≥20 × ULN)	1 (1)	1 (1)	4 (8)

Source: adlb.xpt; Software: Python
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment arm; n, number of subjects with at least one event.

17.2.6.5. Neuropsychiatric AEs

For the purpose of this analysis, events were pooled from several HLGTs from both the neurologic disorders and psychiatric disorders SOCs, as follows:

- HLGT Mental impairment disorders
- HLGT Anxiety disorders and symptoms
- HLGT Cognitive and attention disorders and disturbances
- HLGT Communication disorders and disturbances
- HLGT Depressed mood disorders and disturbances
- HLGT Disturbances in thinking and perception
- HLGT Manic and bipolar mood disorders and disturbances
- HLGT Schizophrenia and other psychotic disorders
- HLGT Mood disorders and disturbances NEC
- HLGT Suicidal and self-injurious behaviours NEC

Similarly, PTs for sleep disorders were pooled as follows:

- HLGT sleep disturbances (incl subtypes), (neuro SOC)
- HLGT Sleep disorders and disturbances (psych SOC)

The full list of events is provided in Table 206 and Table 207 for the BRIGHTE trial and Phase 2b trial, respectively. The PTs have not been pooled by the clinical reviewer in these analyses.

Table 206. Pooled Neuropsychiatric AEs, All Cause, All Grade, Safety Population, BRIGHTE Trial

Grouped Query Preferred Term	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Neuropsychiatric events	39 (14.3)	11 (11.1)	50 (13.5)
Depression	19 (7.0)	3 (3.0)	22 (5.9)
Anxiety	7 (2.6)	4 (4.0)	11 (3.0)
Memory impairment	5 (1.8)	0 (0.0)	5 (1.3)
Irritability	3 (1.1)	0 (0.0)	3 (0.8)
Suicidal ideation	3 (1.1)	1 (1.0)	4 (1.1)
Major depression	2 (0.7)	0 (0.0)	2 (0.5)
Psychotic disorder	2 (0.7)	0 (0.0)	2 (0.5)
Affect lability	1 (0.4)	0 (0.0)	1 (0.3)
Affective disorder	1 (0.4)	0 (0.0)	1 (0.3)
Agitation	1 (0.4)	0 (0.0)	1 (0.3)
Amnesia	1 (0.4)	0 (0.0)	1 (0.3)
Anxiety disorder	1 (0.4)	0 (0.0)	1 (0.3)
Attention deficit/hyperactivity disorder	1 (0.4)	0 (0.0)	1 (0.3)
Cognitive disorder	1 (0.4)	1 (1.0)	2 (0.5)
Depressed mood	1 (0.4)	0 (0.0)	1 (0.3)
Depressive symptom	1 (0.4)	0 (0.0)	1 (0.3)
Disturbance in attention	1 (0.4)	0 (0.0)	1 (0.3)
Hallucination	1 (0.4)	0 (0.0)	1 (0.3)
Mental impairment	1 (0.4)	0 (0.0)	1 (0.3)
Mood altered	1 (0.4)	0 (0.0)	1 (0.3)
Mood swings	1 (0.4)	0 (0.0)	1 (0.3)
Panic disorder	1 (0.4)	0 (0.0)	1 (0.3)
Schizophrenia	1 (0.4)	0 (0.0)	1 (0.3)
Stress	1 (0.4)	0 (0.0)	1 (0.3)
Suicide attempt	1 (0.4)	0 (0.0)	1 (0.3)
Apathy	0 (0.0)	1 (1.0)	1 (0.3)
Feeling of despair	0 (0.0)	1 (1.0)	1 (0.3)
Hallucination, auditory	0 (0.0)	1 (1.0)	1 (0.3)
Sleep disturbance	23 (8.5)	2 (2.0)	25 (6.7)
Insomnia	17 (6.3)	2 (2.0)	19 (5.1)
Sleep disorder	3 (1.1)	0 (0.0)	3 (0.8)
Abnormal dreams	2 (0.7)	0 (0.0)	2 (0.5)
Sleep deficit	1 (0.4)	0 (0.0)	1 (0.3)

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event.

Table 207. Pooled Neuropsychiatric AEs, All Cause, All Grade, Safety Population, Phase 2b Trial

Grouped Query Preferred Term	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Neuropsychiatric events	6 (6.1)	11 (10.9)	5 (9.8)
Depression	3 (3.0)	3 (3.0)	2 (3.9)
Anxiety	2 (2.0)	3 (3.0)	2 (3.9)
Acute stress disorder	1 (1.0)	0 (0.0)	0 (0.0)
Panic disorder	1 (1.0)	0 (0.0)	0 (0.0)
Stress	1 (1.0)	0 (0.0)	1 (2.0)
Amnesia	0 (0.0)	2 (2.0)	0 (0.0)
Anxiety disorder	0 (0.0)	0 (0.0)	1 (2.0)
Bipolar disorder	0 (0.0)	1 (1.0)	0 (0.0)
Completed suicide	0 (0.0)	1 (1.0)	0 (0.0)
Memory impairment	0 (0.0)	2 (2.0)	0 (0.0)
Post-traumatic stress disorder	0 (0.0)	0 (0.0)	1 (2.0)
Suicide attempt	0 (0.0)	1 (1.0)	0 (0.0)
Sleep disturbance	6 (6.1)	11 (10.9)	3 (5.9)
Insomnia	5 (5.1)	8 (7.9)	2 (3.9)
Abnormal dreams	1 (1.0)	0 (0.0)	0 (0.0)
Hypersomnia	0 (0.0)	2 (2.0)	0 (0.0)
Nightmare	0 (0.0)	1 (1.0)	1 (2.0)

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment arm; n, number of subjects with at least one event.

17.2.7. Additional Organ System Based Review

17.2.7.1. Renal Events

Renal toxicity was not identified as a safety concern during early clinical development and no new safety signal was identified in this review. Renal insufficiency is not uncommon in subjects with advanced HIV disease, either due to HIV nephropathy or comorbid illness, including vascular disease.

An overview of renal safety events in the BRIGHTE trial is summarized in Table 208. There were 10 SAEs: five subjects had acute kidney injury (none considered FTR related, one led to FTR discontinuation), 2 had renal failure (FTR was interrupted in both cases), and 1 each had renal impairment (considered FTR related and FTR was interrupted) and glomerulonephritis. One additional nonserious case of renal impairment was also considered related to FTR.

Renal events were much less common in the Phase 2b trial, despite the fact that all subjects were receiving TDF. There was one SAE of acute kidney injury that was considered drug-related, and treatment was discontinued (Table 209).

Table 208. Renal Disorders and Nephropathies HLGT, All Cause, All Grade, Safety Population, BRIGHTE Trial

Adverse Event by PT	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Acute kidney injury	6 (2.2)	4 (4.0)	10 (2.7)
Renal failure	0 (0.0)	3 (3.0)	3 (0.8)
Renal impairment	3 (1.1)	0 (0.0)	3 (0.8)
Chronic kidney disease	0 (0.0)	1 (1.0)	2 (0.5)
Glomerulonephritis	1 (0.4)	0 (0.0)	1 (0.3)
Nephropathy	1 (0.4)	0 (0.0)	1 (0.3)
Renal cyst	1 (0.4)	0 (0.0)	1 (0.3)
Renal tubular dysfunction	1 (0.4)	0 (0.0)	1 (0.3)

Source: adae.xpt; Software: Jreview
Abbreviations: HLGT, high level grouped term; N, number of subjects in treatment group; n, number of subjects with at least one event; PT, preferred term.

Table 209. HLGT Renal Disorders and Nephropathies, All Cause All Grade. Safety Population, Phase 2b Trial

Adverse Event by PT	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Nephropathy	1 (1.0)	1 (1.0)	1 (2.0)
Acute kidney injury	1 (1.0)	0 (0.0)	0 (0.0)
Renal cyst	0 (0.0)	1 (1.0)	0 (0.0)

Source: adae.xpt; Software: Jreview
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; HLGT, high level grouped term; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; PT, preferred term.

Grade 3 and 4 abnormalities in creatinine and creatinine clearance are presented together in Table 210. Following the trend observed in clinical renal events, high grade elevations in creatinine were more common in the BRIGHTE trial compared to the Phase 2b trial. Abnormalities in the FTR population overall were similar to the ATV/r group of the Phase 2b trial.

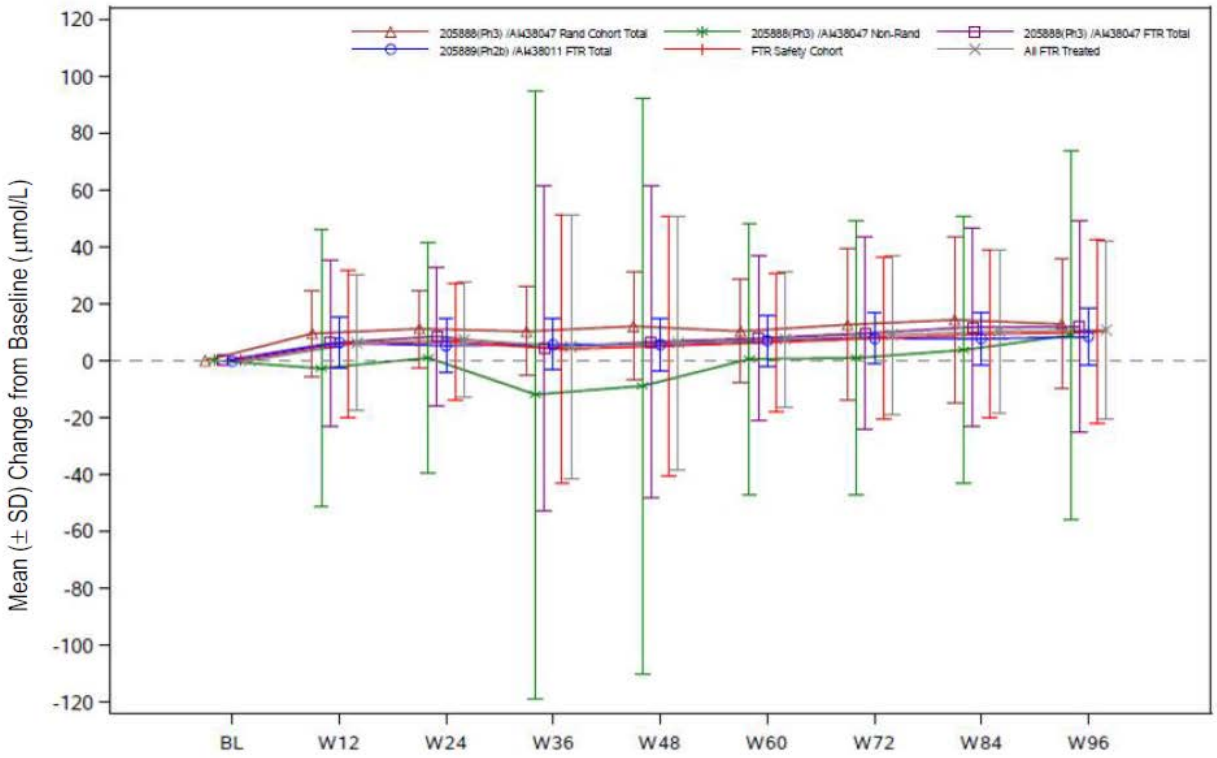
Table 210. Grade 3 and 4 Renal Laboratory Abnormalities, Safety Population, BRIGHTE Trial and Phase 2b Trial

	BRIGHTE Trial		Phase 2b Trial		
Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Creatinine (µmol/L)					
Grade 3	41 (15)	19 (19)	12 (12)	5 (5)	4 (8)
Grade 4	11 (4)	4 (4)	0 (0)	2 (2)	2 (4)
Estimated creatinine clearance (Cockcroft-Gault) (mL/min)					
Grade 3	62 (23)	25 (25)	21 (21)	20 (20)	9 (18)
Grade 4	13 (5)	5 (5)	0 (0)	1 (1)	2 (4)

Source: adlb.xpt; Software: Python
Abbreviations: ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality.

Change in serum creatinine over time is shown graphically in the Applicant's analysis shown in Figure 19. In the Randomized Cohort, a modest increase is observed from baseline to Week 12 which is then stable through Week 96. A smaller magnitude of change is noted for the Non-randomized Cohort, but with high variability. In the Phase 2b trial, a small increase in creatinine is observed early, which is often seen in TDF trials. Creatinine is stable thereafter through Week 96.

Figure 19. Change in Mean (SD) Serum Creatinine, Safety Population, BRIGHTE Trial and Phase 2b Trial



Source: Figure 8, Summary of Clinical Safety
Abbreviations: BL, baseline; FTR, fostemsavir; SD, standard deviation.

Medical Officer's Assessment: *A modest decline in renal function is observed but causality is confounded. In the BRIGHTE trial, underlying disease is the major confounder, whereas TDF exposure is the main confounder in the Phase 2b trial. Overall, few patients had to stop FTR treatment due to declines in renal function or other renal events. Labeling will include graded increases in serum creatinine but no warnings are needed.*

17.2.7.2. Cardiac Events

A broader assessment of cardiac AEs was conducted to supplement the evaluation for arrhythmia. Cardiac events were much more frequent in the BRIGHTE trial compared to the Phase 2b trial. Given the mean age of the patient population and the proclivity for cardiovascular disease in HTE patients, this trend was not unexpected. All PTs in the Cardiac SOC are presented in Table 211 and Table 212. These tables include PTs pooled by the clinical reviewer, as noted in the footnotes.

In the BRIGHTE trial, cardiac SAEs were reported as follows: five subjects had myocardial infarction, three subjects had angina, two subjects had coronary artery disease, and one subject each had atrial fibrillation, atrial flutter, cardiovascular disorder, mitral valve incompetence, myocarditis, and pulseless electrical activity. The only SAE considered FTR-related was myocarditis. Other FTR-related events include coronary artery disease, palpitations, and tachycardia, reported in one subject each. The tachycardia event led to FTR discontinuation. In the Phase 2b trial, all cardiac events were grade 1 and none were SAEs. One subject had sinus bradycardia that was considered FTR-related.

Table 211. Cardiac AEs, All Cause, All Grade, Safety Population, BRIGHTE Trial

Averse Event by PT	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Angina	3 (1.1)	4 (4.0)	7 (1.9)
Myocardial infarction	4 (1.5)	1 (1.0)	5 (1.3)
Coronary artery disease	4 (1.5)	2 (2.0)	6 (1.6)
Valve incompetence	2 (0.7)	3 (3.0)	5 (1.3)
Palpitations	1 (0.4)	3 (3.0)	4 (1.0)
Tachycardia	1 (0.4)	3 (3.0)	4 (1.0)
Bundle branch block right	2 (0.7)	1 (1.0)	3 (0.8)
Congestive cardiomyopathy	1 (0.4)	1 (1.0)	2 (0.5)
Supraventricular tachycardia	0 (0.0)	2 (2.0)	2 (0.5)
Atrial fibrillation	1 (0.4)	0 (0.0)	1 (0.3)
Atrial flutter	1 (0.4)	0 (0.0)	1 (0.3)
Cardiac discomfort	1 (0.4)	0 (0.0)	1 (0.3)
Cardiac failure	1 (0.4)	0 (0.0)	1 (0.3)
Cardiomegaly	1 (0.4)	0 (0.0)	1 (0.3)
Cardiovascular disorder	0 (0.0)	1 (1.0)	1 (0.3)
Diastolic dysfunction	1 (0.4)	0 (0.0)	1 (0.3)
Dilatation atrial	0 (0.0)	1 (1.0)	1 (0.3)
Left ventricular hypertrophy	1 (0.4)	0 (0.0)	1 (0.3)
Myocarditis	0 (0.0)	1 (1.0)	1 (0.3)
Pericardial effusion	1 (0.4)	0 (0.0)	1 (0.3)
Pulseless electrical activity	0 (0.0)	1 (1.0)	1 (0.3)
Sinus bradycardia	1 (0.4)	0 (0.0)	1 (0.3)
Tachycardia induced cardiomyopathy	1 (0.4)	0 (0.0)	1 (0.3)
Ventricular extrasystoles	1 (0.4)	0 (0.0)	1 (0.3)

Source: adae.xpt; Software: Jreview
Angina = angina pectoris + angina unstable
Myocardial infarction = myocardial infarction and acute myocardial infarction
Valve incompetence = mitral and tricuspid valve incompetence
Abbreviations: AE, adverse event; N, number of subjects in treatment group; n, number of subjects with at least one event; PT, preferred term.

Table 212. Cardiac AEs, All Cause, All Grade, Safety Population, Phase 2b Trial

Adverse Event by PT	≥1,200 mg FTR N=99 n (%)	≤800 mg FTR N=101 n (%)	ATV/r N=51 n (%)
Sinus bradycardia	1 (1.0)	1 (1.0)	0 (0.0)
Myocardial ischaemia	0 (0.0)	1 (1.0)	0 (0.0)
Atrioventricular block	1 (1.0)	0 (0.0)	0 (0.0)
Bundle branch block right	0 (0.0)	0 (0.0)	1 (2.0)

Source: adae.xpt; Software: Jreview
Abbreviations: AE, adverse event; ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; N, number of subjects in treatment group; n, number of subjects with at least one event; PT, preferred term.

Medical Officer's Assessment: *The events reported did not follow a pattern to suggest a causal relationship with FTR. In the absence of a cardiac signal, labeling will be restricted to the risk for QT prolongation, as previously discussed.*

17.2.7.3. Pancreatic Events

There were no reports of pancreatitis in the Phase 2b or BRIGHTE trial. Graded elevations in lipase occurred in a notable number of subjects in the BRIGHTE trial but were asymptomatic (Table 213). In the Phase 2b trial, graded elevations in lipase occurred at a comparable frequency between the FTR and ATV/r group.

Table 213. Postbaseline Elevations in Pancreatic Enzymes, Safety Population, BRIGHTE Trial

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Amylase (U/L), Sum	70 (26)	33 (33)	103 (28)
Grade 1 (1.1– 1.5 × ULN)	28 (10)	20 (20)	48 (13)
Grade 2 (1.6 – 2.0× ULN)	40 (15)	11 (11)	51 (14)
Grade 3 (2.1 – 5.0× ULN)	2 (1)	1 (1)	3 (1)
Grade 4 (≥5.0× ULN)	0 (0)	1 (1)	1 (0)
Lipase (U/L), Sum	81 (30)	44 (44)	125 (34)
Grade 1 (1.1–<2.0× ULN)	35 (13)	19 (19)	54 (15)
Grade 2 (1.5–<3.0× ULN)	33 (12)	15 (15)	48 (13)
Grade 3 (3.0–<5.0× ULN)	6 (2)	7 (7)	13 (4)
Grade 4 (≥5.0× ULN)	7 (3)	3 (3)	10 (3)

Source: adlb.xpt; Software: Python
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality; ULN, upper limit of normal.

Medical Officer's Assessment: *Labeling will be limited to elevations in serum lipase. There is no signal for pancreatitis at this time.*

17.2.8. Laboratory Abnormalities

The majority of laboratory abnormalities have been discussed in previous sections, either in the context of organ-specific safety issues, or in Section II.7.6.7, which outlines laboratory abnormalities included in labeling. The remainder of the labs are presented here for completeness. These are not included in labeling because they did not meet the frequency deemed clinically meaningful.

Table 214. Chemistry Postbaseline Laboratory Abnormalities, Safety Population, BRIGHTE Trial

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Albumin (g/L), Sum	25 (9)	18 (18)	43 (12)
Grade 1 (3.0 to < LLN)	16 (6)	12 (12)	28 (8)
Grade 2 (0.600 to 0.799)	8 (3)	5 (5)	13 (4)
Grade 3 (0.400 to 0.599)	1 (0)	1 (1)	2 (1)
Bicarbonate (mmol/L), Sum	103 (38)	42 (42)	145 (39)
Grade 1 (16.0 mEq/L to < LLN)	89 (33)	35 (35)	124 (33)
Grade 2 (11.0 to 15.9 mEq/L)	13 (5)	7 (7)	20 (5)
Grade 3 (8.0 to 10.9 mEq/L)	1 (0)	0 (0)	1 (0)
Glucose (mmol/L)/Hypoglycaemia, Sum	24 (9)	12 (12)	36 (10)
Grade 1 (50 to 54 mg/dL)	17 (6)	6 (6)	23 (6)
Grade 2 (40 to <50 mg/dL)	5 (2)	5 (5)	10 (3)
Grade 3 (30 to <40 mg/dL)	1 (0)	1 (1)	2 (1)
Grade 4 (<30 mg/dL)	1 (0)	0 (0)	1 (0)
Potassium (mmol/L)/Hyperkalemia, Sum	16 (6)	5 (5)	21 (6)
Grade 1 (5.6 -6.0 mmol/L)	7 (3)	4 (4)	11 (3)
Grade 2 (6.1 -6.5 mmol/L)	5 (2)	1 (1)	6 (2)
Grade 3 (6.6 -7.0 mmol/L)	3 (1)	0 (0)	3 (1)
Grade 4 (>7.0 mmol/L)	1 (0)	0 (0)	1 (0)
Potassium (mmol/L)/Hypokalemia, Sum	22 (8)	8 (8)	30 (8)
Grade 1 (3.0 – 3.4 mmol/L)	21 (8)	4 (4)	25 (7)
Grade 2 (2.5 – 2.9 mmol/L)	1 (0)	3 (3)	4 (1)
Grade 3 (2.0 – 2.4 mmol/L)	0 (0)	1 (1)	1 (0)
Sodium (mmol/L)/Hypernatremia, Sum	26 (10)	10 (10)	36 (10)
Grade 1 (146 - 150 mmol/L)	23 (8)	8 (8)	31 (8)
Grade 2 (151- 154 mmol/L)	3 (1)	2 (2)	5 (1)
Sodium (mmol/L)/Hyponatremia, Sum	20 (7)	18 (18)	38 (10)
Grade 1 (130-135 mmol/L)	16 (6)	16 (16)	32 (9)
Grade 2 (125-129 mmol/L)	4 (1)	2 (2)	6 (2)

Source: adlb.xpt; Software: Python
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality.

Table 215. Hematology Postbaseline Laboratory Abnormalities, Safety Population, BRIGHTE Trial

Laboratory Parameters	Randomized Cohort N=272 n (%)	Non-randomized Cohort N=99 n (%)	Overall N=371 n (%)
Leukocytes (10^9/L), Sum	19 (7)	12 (12)	31 (8)
Grade 1 (2.000 to 2.499)	9 (3)	3 (3)	12 (3)
Grade 2 (1.500 to 1.999)	6 (2)	3 (3)	9 (2)
Grade 3 (1.000 to 1.499)	1 (0)	3 (3)	4 (1)
Grade 4 (<1.000)	3 (1)	3 (3)	6 (2)
Platelets (10^9/L), Sum	21 (8)	16 (16)	37 (10)
Grade 1 (100 to <124)	10 (4)	8 (8)	18 (5)
Grade 2 (50 to <100)	9 (3)	5 (5)	14 (4)
Grade 3 (25 to <50)	1 (0)	2 (2)	3 (1)
Grade 4 (<25)	1 (0)	1 (1)	2 (1)

Source: adlb.xpt; Software: Python
Abbreviations: N, number of subjects with relevant laboratory data; n, number of subjects with abnormality.

17.3. Thorough QT Study

The Applicant conducted a thorough QT study to assess the effect of multiple oral doses of FTR on the QTc interval in healthy subjects. The study protocol was reviewed by the Interdisciplinary Review Team for Cardiac Safety Studies (IRT) prior to conducting the study and was found to be acceptable. The following text is copied verbatim from the IRT consultation for IND 73916, dated May 1, 2014.

1 SUMMARY
1.1 OVERALL SUMMARY OF FINDINGS
This study was comprised of two-parts. Part I, the sentinel cohort, was designed to evaluate the safety, tolerability and PK of 2400 mg BMS-663068 BID. Part II, the main study, was designed to evaluate the effect of BMS-663068 on the QTc interval in healthy subjects.

Statistically, but possibly not clinically, significant QTc prolongation effects of BMS-663068 (doses of 1200 mg QD and 2400 mg BID) were detected in this thorough QT Part II study. The largest upper bounds of the 2-sided 90% CI for the mean difference between BMS-663068 1200 mg and placebo was below 10 ms. However, the largest upper bound of the 2-sided 90% CI for the mean difference between BMS-663068 2400 mg BID and placebo was 12.9 ms which is higher than the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms as demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, partially-blinded, placebo-controlled, positive-controlled, 4-way crossover Part II study, 60 subjects received BMS-663068 1200 mg QD, BMS-663068 2400 mg BID mg, placebo and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for BMS-663068 (1200 mg QD and 2400 mg BID) and the Largest Lower Bound for Moxifloxacin, Part II (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
BMS-663068 1200 mg QD	5	3.9	(1.0, 6.8)
BMS-663068 2400 mg BID	5	10.0	(7.0, 12.9)
Moxifloxacin 400 mg*	3	9.5	(6.8, 12.3)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 5.8 ms.

The supratherapeutic dose (2400 mg BID) produces mean Cmax values 2.5-fold the mean Cmax for the therapeutic dose (1200 mg QD). Whether or not supratherapeutic dose covers the expected high exposure clinical scenario will not be known until we see the

results of the effect of intrinsic (hepatic and renal impairment) and extrinsic factors (drug-drug interaction studies other than already conducted with ritonavir).

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

The supratherapeutic dose (2400 mg BID) prolongs QT interval by 12.9 ms which is higher than the threshold for regulatory concern as described in ICH E14 guidelines. The extent of QT prolongation at 1200 mg QD is below 10 ms.

A follow-up consultation was obtained from the IRT during the NDA review. The following text is copied verbatim from the IRT consultation, dated March 6, 2020.

The IRT has reviewed the thorough QT study results for fostemsavir (IND-073916, Dt: 05/01/2014 in DARRTS). The highest evaluated dose of fostemsavir (2400 mg twice daily for 7 days) resulted in an exposure ~5-fold of therapeutic concentration and ~2-fold the worst-case therapeutic concentration with a mean QTc prolongation of 10 msec. If there is reasonable assurance that the 2400 mg twice daily dose represents temsavir exposures that are unlikely to be seen in the patient population, then the sponsor's thorough QT study provides reassurance of safety because patients are unlikely to experience a clinically significant QTc effect (see ICH E14 Q&A R3 #7.1). Under this scenario, we do not recommend labeling the product with 'Warnings and Precautions' for QTc prolongation.

We propose the following edits to the label submitted by the Sponsor (SN0001; link). Our changes are highlighted (addition, deletion) below. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At therapeutic doses, <TRADENAME> does not prolong the QT interval to any clinically relevant extent. At 4-times the recommended dose, the mean (upper 90% confidence interval) QTcF increase was 10 msec (13 msec). The observed increase in QTcF was temsavir concentration-dependent.

~~In a randomized, placebo- and active-controlled, double-blind, cross-over thorough QT study, 60 healthy subjects received oral administration of placebo, RUKOBIA 1,200 mg (2 times the recommended dose) once daily, RUKOBIA 2,400 mg (4 times the recommended dose) twice daily, and moxifloxacin 400 mg (active control) in random sequence. RUKOBIA administered at 1,200 mg once daily did not have a clinically meaningful effect on the QTc interval as the maximum mean time-matched (2-sided 90% upper confidence bound) placebo-adjusted QTc change from baseline based on Fridericia's correction method (QTcF) was 4.3 (6.3) milliseconds (below the clinically important threshold of 10 milliseconds). However, RUKOBIA administered at 2,400 mg twice daily for 7 days was associated with a clinically meaningful prolongation of the QTc interval as the maximum mean time-matched (2-sided 90% upper confidence bound) for the placebo-adjusted change from baseline in QTcF interval was 11.2 (13.3) milliseconds. Steady-state administration of RUKOBIA 600 mg twice daily resulted in a mean temsavir Cmax approximately 4.2-fold lower than the temsavir concentration predicted to increase QTcF interval 10 milliseconds [see Warnings and Precautions (5.2)].~~

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

~~5.2 QTc Prolongation with Higher than Recommended Dosages~~

~~A supratherapeutic dose of RUKOBIA (2,400 mg twice daily, which is 4 times the recommended daily dose) has been shown to significantly prolong the QTc interval of the electrocardiogram [see Drug Interactions (7.3), Clinical Pharmacology (12.2)]. RUKOBIA should be used with caution in patients with a history of QTc interval prolongation, when coadministered with a drug with a known risk of Torsade de Pointes or in patients with relevant pre-existing cardiac disease. Elderly patients may be more susceptible to drug-induced QT interval prolongation.~~

Reviewer's comments: Per ICH E14 Q&A 7.1, if there is reasonable assurance that the 2400 mg twice daily dose represents temsavir exposures that are unlikely to be seen in the patient population, then the sponsor's thorough QT study provides reassurance of safety because patients are unlikely to experience a clinically significant QTc effect. Under this scenario, we do not recommend labeling the product with 'Warnings and Precautions' for QTc prolongation.

Review Team Assessment

After review of all available clinical safety data and DDI data, the review team concluded that there is adequate justification to retain the Applicant's proposed labeling. First, several subjects in the BRIGHTE trial reached the protocol-defined criteria for discontinuation. Most of these subjects were able to safely continue treatment with FTR via an expanded access program but did so with additional monitoring. Second, subjects with HTE patients living with MDR HIV infection often take several medications to manage comorbid conditions, as evidenced by the concomitant medications taken by subjects in the BRIGHTE trial. Some of these medications also prolong the QT interval, such as macrolide antibiotics, which are frequently used long-term

for prophylaxis or treatment of mycobacterial infections. It is unknown whether the risk for QT prolongation is additive, and therefore, additional monitoring would be prudent.

In summary, the primary review team has elected to retain the Applicant's proposed information in Sections 5 and 12 of labeling to alert providers about the risk for QT prolongation. This knowledge will allow providers to construct a monitoring plan that is commensurate with the risk for individual patients.

18. Mechanism of Action / Drug Resistance Additional Information and Assessment

18.1. Mechanism of Action

Crystal Structure Modeling

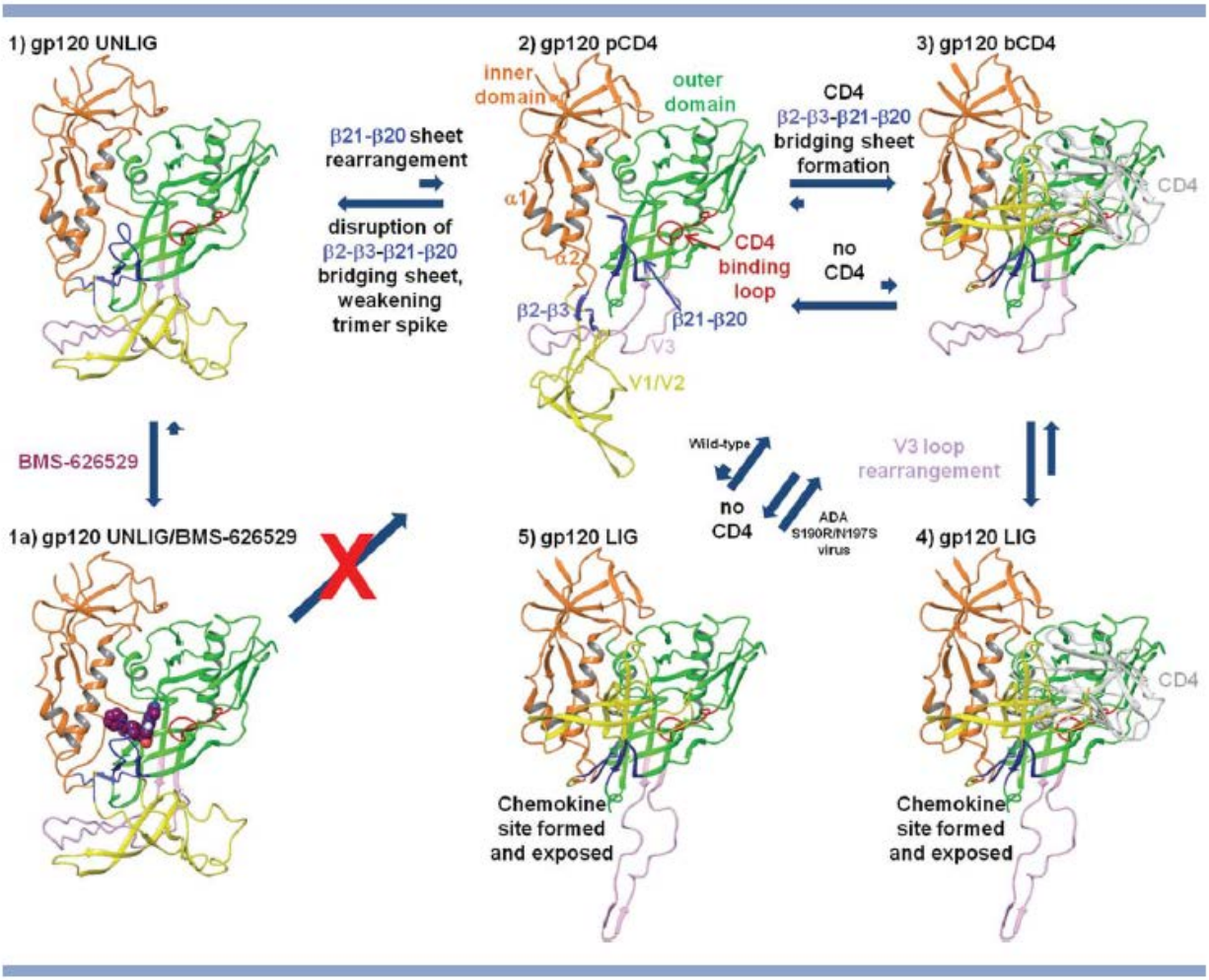
Entry of HIV-1 into host cells occurs via a multistep process that requires interaction of the viral envelope (EN) glycoprotein with two cellular receptors in a sequential manner. The EN glycoprotein is composed of trimers of the gp120 exterior glycoprotein that are noncovalently associated with the gp41 transmembrane glycoprotein; both proteins are formed by post-translational cleavage of the EN glycoprotein gp160. Viral entry is initiated by virus attachment mediated by binding of gp120 with the N- terminus domain 1 of the cellular CD4 receptor. This results in conformational changes to gp120 that assemble and expose a coreceptor binding site. Subsequent binding of the CCR5 or CXCR4 coreceptor results in further conformational changes that culminate in gp41-mediated membrane fusion. Crystal structures of gp120 in both the unliganded "closed" (UNLIG) and CD4/monoclonal antibody-bound (LIG) states show that the gp120 core consists of an inner and an outer domain connected by a four-stranded β-sheet bridging domain (Langley et al. 2015) (Figure 20).

The bridging domain is composed of two strands from the outer domain (β20– β21) and two from the inner domain (β2– β3). In the unliganded state, the bridging sheet strand order is β2– β3- β21– β20, where strands β2–β3 and β21– β20 form antiparallel sheets while β3- β21 is a parallel β-sheet. This bridging sheet arrangement stabilizes the closed state and directs the V1/V2 loops toward the crown of the glycoprotein trimer, where it packs against the V3 loop and buries the coreceptor binding site. However, in the CD4-bound structures, CD4 binds at a highly conserved site, composed of regions from the outer and bridging sheet domains. The interaction of gp120 with CD4 stabilizes changes in the β21– β20 sheet conformation that leads to "opening" of the trimer spike and re-ordering of the bridging sheet (β3– β2- β21– β20). This directs the V1/V2 loops toward CD4 and away from V3 to form and expose the coreceptor binding site.

TMR (BMS-626529), which is the active moiety of FTR, binds within the structurally conserved hydrophobic cavity in the outer domain of gp120, present in the UNLIG Figure 20) conformation of gp120, just underneath the β20– β21 sheet, and adjacent to the CD4 binding loop. Subsequent rearrangement of the β20–β21 sheet into the CD4-binding-competent gp120 pCD4 state is blocked. When docked into the central cavity, TMR was surrounded by amino acid residues that

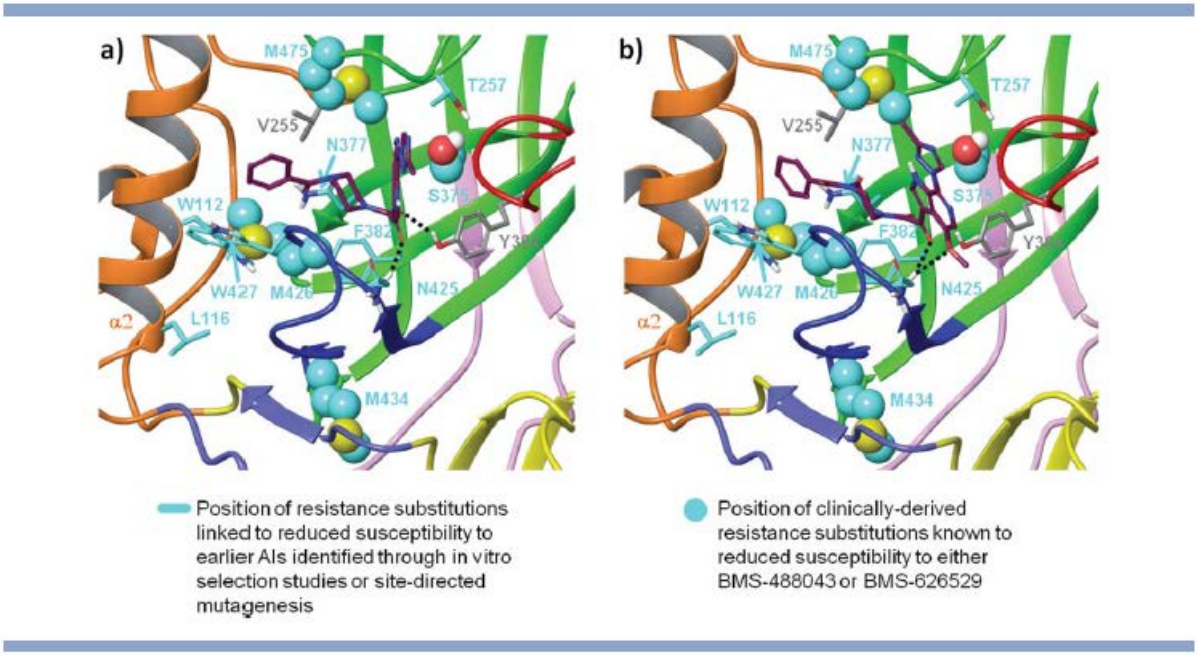
represent the location of clinically- and laboratory-derived substitutions known to confer decreased susceptibility to TMR (Figure 21).

Figure 20. Proposed Stepwise Pathway for HIV-1 gp-120 Attachment



Source: (Langley et al. 2015)
Proposed stepwise pathway for HIV-1 gp-120 attachment, CD4-independent attachment, and inhibition by attachment inhibitors. 1. In the gp120 UNLIG state the bridging sheet is ordered β2– β3- β21– β20 and directs the V1/V2 loops to pack against the V3 loop where they collectively form the quaternary structure of the trimer spike crown. In this state the β21– β20 sheet is misfolded for optimal CD4 binding. Note: the β21– β20 sheet is in equilibrium between nonCD4 and CD4 binding conformations with the nonCD4 binding conformations being the dominant form. 2. In the gp120 pre-CD4 state (pCD4) the β2– β3- β21– β20 bridging sheet is disrupted and the β21– β20 sheet is in equilibrium between nonCD4 and CD4 binding conformations. Based on SAXS data, this is likely to be the predominant form of the gp120 monomer in solution. Note that in the absence of CD4 (1), (2), (3), and (5) are in equilibrium but due to tertiary and quaternary structure involving the bridging sheet and the V1/V2/V3 loops (1) is far more prevalent; however, in the lab-adapted ADA S190R/N197S virus, the population of (2), (3) and (5) are elevated, leading to CD4-independent attachment via (5). 3. In the CD4-bound state (bCD4) CD4 stabilizes the β21– β20 sheet in the CD4 binding conformation and the re-ordered bridging sheet forms (β3– β2- β21– β20) moving the V1/V2 loops near CD4 domains I and II. 4. In the gp120 LIG state the V3 loop has opened to complete the formations and exposure of the chemokine binding site. 1a. Temsavir (BMS-626529) and related AIs are predicted to bind within the structurally conserved region in the outer domain of gp120 UNLIG (1) state. AIs binding within this pocket stabilize the UNLIG state by blocking the β21– β20 sheet from folding into a CD4-binding conformation and occupy the space next to the CD4 binding loop required for CD4:F43 binding, which blocks CD4 binding and the formation of the gp120 pCD4 state and all downstream events. (Langley et al. 2015)

Figure 21. Models of BMS-626529 Docked With HIV-1 gp120



Source: (Langley et al. 2015)
Models of temsavir (BMS-626529) docked with HIV-1 gp120 in a) BMS-626529 Set-1:1 pose; b) Set-2:3 pose. Inner domain (orange), outer domain (green), V1/V2 (yellow), V3 (pink), b3–b2 sheet (light blue), b20–b21 (blue), CD4 binding loop (red), BMS-626529 (maroon). Black dotted lines depict hydrogen bonds.

This model is consistent with direct inhibition of CD4 binding weakly to the nonoptimal CD4 binding site in the gp120 UNLIG state. The model also fits with previous data, which suggested binding of an attachment inhibitor can stabilize a conformation of gp120 that does not recognize CD4 Therefore, the modeling supports that TMR can inhibit both CD4-induced and CD4-independent formation of the liganded “open state” four-stranded bridging sheet and the subsequent formation and exposure of the chemokine receptor binding site. TMR binds to the unliganded (UNLIG) gp120 structure within the structurally conserved outer domain, just underneath the β20–β21 sheet and adjacent to the CD4 binding loop. By binding to this site, TMR inhibits both CD4-induced and -independent formation of the four-stranded bridging sheet and subsequent formation and exposure of the coreceptor binding site.

Inhibition of gp-120 Binding to CD4

TMR (BMS-626529) inhibited the binding of gp120 to soluble CD4 (sCD4) with an IC_{50} value of 14nM in an enzyme-linked immunosorbent assay. The activity of TMR was evaluated against three gp120 variants with substitutions previously shown to confer resistance to a prior gp120 attachment inhibitor (BMS-488043): M426L and M475I, which mapped to the CD4 binding region of gp120, and the M434T substitution, which is located on the β-21 sheet of the bridging sheet area. TMR demonstrated 6- to 40-fold reduced activity against the M434T and M475I variants with IC_{50} values of 90 and 570nM, respectively, and had 305-fold lower activity (IC_{50} value =4300nM) against the M426L variant protein (Table 216).

Table 216. Inhibition of sCD4 Binding to HIV-1 JRFL Envelope gp120 Variants (Report 2017n338498, page 13)

Envelope Protein[a]	$IC_{50} \pm sd$[b] (nM)			
	BMS-626529	BMS-488043	Fold improvement in IC_{50} *vs.* BMS-488043	Fold reduction in potency *vs.* WT, for BMS-626529
WT	14 ± 4	87 ± 37	6	-----
M426L	4,300 ± 2,400	>30,000	>7	305
M434T	90 ± 30	2500 ± 1000	29	6
M475I	570 ± 80	12900 ± 5700	23	40

Source: Lab Notebook 56545
[a] gp120 was expressed from 293T cells, transfected with a plasmid encoding the wild type or variant gp120 domain of the HIV-1 JRFL envelope
[b] sd, standard deviation
Abbreviations: IC_{50}, half maximal inhibitory concentration; WT, wildtype.

Gel filtration was used to examine the competitive binding of [^{3}H] BMS-488043, a previously studied gp120 attachment inhibitor, versus unlabeled TMR to gp120. The IC_{50} value of TMR inhibition was 23nM with an ~7-fold stronger binding affinity than BMS-488043. The binding affinity of TMR for gp120 was assessed using a sedimentation equilibrium technique and showed a K_D value of 3.3nM. The reversibility of TMR binding to gp120 was characterized in the Micro BioSpin gel filtration assay, by monitoring the decrease of gp120-bound [^{3}H] TMR, upon chasing with excess sCD4, as a function of time. The release of the bound [^{3}H] TMR from gp120 was slow, with a half-life calculated to be ~8 hr, which is 16-fold > a parallel experiment using [^{3}H]BMS-488043 where the compound was released with a half-life of 0.5 hr.

TMR binds to the viral EN protein gp120 and prevents HIV-1 EN interaction with its cellular receptor CD4. This mechanism is similar to those characterized for two earlier attachment inhibitors, BMS-378806 and BMS-488043. However, TMR has better activity, higher affinity, and a longer binding half-life than the earlier attachment inhibitors. Substitutions M426L, M475I, M434T, which are located next to the CD4 contact site of gp120 or on the bridging sheet, decreased the binding inhibition of TMR.

Fostemsavir (BMS-663068) is a phosphate prodrug of TMR and contains a methyl-phosphate on the 1-nitrogen of the azaindole moiety. Using two different 4 hr fusion assays rather than the 3- or 5-day antiviral assays, FTR was found to be 50- to 500-fold less active than TMR. The data indicate that FTR itself has only modest antiviral activity, and that hydrolysis to TMR is required for effective fusion inhibition.

Postattachment

Similar to ibaluzimab (IBA), TMR can also act postattachment to CD4 by binding to gp120 and hindering access of CD4-bound gp120 to coreceptors, CCR5 and CXCR4. Results show that

TMR can inhibit CD4-independent viruses, and the proposed mechanism is TMR binding can prevent downstream conformational changes in gp120 required for coreceptor binding. A model by Z. Li et al. (Li et al. 2013) proposes that in CD4-independent virus, gp120 can adopt a conformation that presents the coreceptor binding site in the absence of CD4, while still allowing TMR to bind. This model predicts that TMR blocks both wild-type and CD4-independent gp120 from adopting a CD4-bound conformation and presenting the coreceptor binding site, thus preventing CD4-dependent gp120 from binding CD4 and coreceptor and CD4-independent gp120 from directly binding the coreceptor (Li et al. 2013).

18.2. Antiviral Activity

Subtype B Viruses

The antiviral activity of TMR was assessed against nine M- and T-tropic laboratory strains of subtype B HIV-1. EC_{50} values of TMR ranged from 0.4 to 58nM against eight of nine of the subtype B HIV-1 strains (Table 217). The X4-tropic strain HIV-1 RF was least responsive to TMR with an EC_{50} value >2,000nM. In addition, two other X4-tropic viruses (MN and IIIb) had higher EC_{50} values of 14.8 and 16.2nM and the dual-tropic virus 89.6 had a higher EC_{50} value of 57.6nM. The data show that TMR was 6 to >68-fold more active than its predecessor BMS-488043.

Table 217. Comparison of the Antiviral Activity of Temsavir (BMS-626529) and BMS-488043 Against HIV-1 Laboratory Strains (Report aa2017n338497, page 12)

Virus	Co-receptor	Host	$EC_{50} \pm sd^a$ (nM)	
			BMS-626529	BMS-488043
JRFL	R5	PM1	0.4 ± 0.1	3.0 ± 0.9
SF-162		PM1	0.5 ± 0.2	4.7 ± 0.6
Bal		PM1	1.7 ± 0.5	23.0 ± 0.6
LAI	X4	MT-2	0.7 ± 0.4	4.1 ± 1.8
NL4-3		MT-2	2.2 ± 0.6	17.4 ± 8.5
MN		MT-2	14.8 ± 5.2	>1,000
IIIb		MT-2	16.2 ± 1.7	160 ± 78
RF		MT-2	>2,000	>2,000
89.6	dual	PM1	57.6 ± 11.4	≥871

Source: Lab Notebook 36501
[a] sd, standard deviation
Abbreviations: EC_{50}, half maximal effective concentration.

In addition, the activity of TMR was tested on 19 HIV-1 subtype B clinical isolates, obtained through NIH or from previous Bristol-Myers Squibb (BMS) clinical trials, and included CCR5-, CXCR4- and dual-tropic strains. TMR had activity against 17 of the 19 subtype B strains, with EC_{50} values of ≤50nM (Table 218) and a median EC_{50} value of 2.9nM. The median EC_{50} values were 3.7nM, 40.9nM, and 0.8nM against the R5-tropic viruses, CXCR4-tropic viruses, and dual/mixed viruses, respectively. Although EC_{50} values for TMR display a broad range in antiviral activity across the different tropic strains, the median EC_{50} value against CXCR4-tropic

strains appears higher suggesting a possible tropism effect, which is determined by gp120 (Table 218). Reduced susceptibility was observed against CCR5-tropic strain 92US660 (EC_{50} value of 345nM) and CXCR4-tropic strain 00USBMS026 (EC_{50} value >2,000nM).

The susceptibility of an additional 28 subtype B viruses was assessed to gain a broader understanding of the variability of clinical isolates to TMR. As seen in the above subset, there is significant variability in the EC_{50} values in this subset of subtype B clinical isolates, which ranged from 0.01nM to >2,000nM. Statistical analyses were performed to estimate the values needed to cover the targeted 90th percentile of subtype B viruses. In order to equal or exceed the EC_{50} value for 90% of all subtype B viruses, it is calculated that a 38.34nM concentration would be required. An EC_{50} value of 2.8nM is expected to be ≥ the EC_{50} value of 70% of all subtype B viruses.

Table 218. Antiviral Activity of Temsavir Against Subtype B HIV-1 Clinical Isolates (Report aa2017n338497, page 14)

Virus	Co-receptor	Country	$EC_{50} \pm sd$[a] (nM)
92US715	R5	USA	0.3 ± 0.02
92HT593	dual	Haiti	0.3 ± 0.2
93BR023	ND[b]	Brazil	0.5 ± 0.04
93US143	X4	USA	0.6 ± 0.1
92US140	R5	USA	0.6 ± 0.4
91USBMS003	R5	USA	1.3 ± 0.5
ASM44	dual	USA	1.3 ± 0.3
93BR013	ND	Brazil	2.5 ± 0.3
93US155	R5	USA	2.8 ± 1.3
00USBMS024	ND	USA	**2.9 ± 0.5** [c]
91US005	R5	USA	3.7 ± 1.5
92US056	ND	USA	5.1 ± 1.7
ASM34	R5	USA	6.2 ± 0.8
W0	R5	USA	6.3 ± 1.0
411-1-C	R5	USA	7.3 ± 5.7
92HT599	X4	Haiti	34.5 ± 1.4
JEW	X4	USA	47.3 ± 27.2
92US660	R5	USA	345 ± 73
00USBMS026	X4	USA	> 2,000

Source: Lab notebook 36501
[a] sd: Standard deviation
[b] Not determined
[c] Median EC_{50} value of 2.9 is highlighted in bold
Abbreviations: EC_{50}, half maximal effective concentration.

Non-Subtype B Viruses

A panel of 25 clinical isolates from non-B subtypes (subtypes A, D, E (AE), F, G and Group O) were tested for susceptibility to TMR. Two to four samples of subtypes A, D, E (AE), F, G and group O and 7 subtype C samples were evaluated. TMR had EC_{50} values of <20nM for some of the representative samples of subtypes A, C, D, and F, while having moderate (EC_{50} values of >10nM to <100nM) to poor (EC_{50} values >500 to >2,000nM) antiviral activity against other samples in each of these subtypes (Table 219). TMR showed moderate activity against two subtype G samples and poor activity against the third isolate. TMR had poor activity against all the subtype E (AE) (n=3) and group O (n=2) viruses.

Table 219. Antiviral Activity of Temsavir Against Non-B Subtype HIV-1 Clinical Isolates (Report aa2017n338497, page 16)

Virus	Co-receptor	Subtype	Country	$EC_{50} \pm sd$ [a] (nM)
92RW026	R5	A	Rwanda	4.9 ± 0.8
92UG029	ND [b]	A	Uganda	6.0 ± 1.2
93RW037	R5	A	Rwanda	> 500
93RW018	R5	A	Rwanda	> 2,000
93IN101	R5	C	India	< 0.9
98TZ017	R5	C	Tanzania	4.0 ± 0.8
93MW959	R5	C	Malawi	8.2 ± 1.1
97ZA009	R5	C	South Africa	9.3 ± 2.0
98IN026	R5X4	C	India	38.7 ± 12.0
92ZA012	R5	C	South Africa	81.8 ± 33.2
92BR025	R5	C	Brazil	> 500
93UG053	X4	D	Uganda	< 0.5
94UG105	X4	D	Uganda	1.3 ± 0.4
94UG114	R5	D	Uganda	31.8 ± 16.3
92UG035	R5	D	Uganda	> 2,000
CMU02	ND	E	Thailand	> 2,000
CMU06	ND	E	Thailand	≥ 1,800
CMU10	ND	E	Thailand	> 2,000
93BR029	R5	F	Brazil	11.9 ± 2.8
93BR019	R5	F	Brazil	> 2,000
R132	R5	G	Russia	33.6 ± 6.3
RU570	R5	G	Russia	62.4 ± 6.3
JV1083	R5	G	Nigeria	> 2,000
BCF01	R5	O	Cameroon	3,500
BCF03	R5	O	Cameroon	> 2,000

Source: Lab Notebook 36501
[a] sd: Standard deviation
[b] ND: not determined
Abbreviations: EC_{50}, half maximal effective concentration.

Nine additional subtype A viruses and 10 additional subtype C viruses were examined for activity of TMR. Overall, cell culture activity of TMR against subtype A and C appears to be reduced compared to that observed for subtype B viruses. The EC_{50} values for the subtype C viruses ranged from 0.96 to >2,000nM with 10 isolates having EC_{50} values ≤12nM, 4 isolates with 39 to 165nM EC_{50} values, and 2 isolates with EC_{50} values >2,000nM. The EC_{50} values for subtype A viruses ranged from 0.38 to >2,000nM, with 9 isolates having EC_{50} values ≤16nM and 4 with EC_{50} values >500nM. Further, an additional 2 subtype D viruses and 6 Subtype E (AE) viruses were analyzed, increasing the total number of subtype D and E viruses to 6 and 9, respectively. The subtype D viruses again exhibited a large variability of sensitivity to TMR (<0.46 - >2,000nM), while all the subtype E viruses analyzed were resistant to the TMR. Note, the tropism of these different subtype isolates was not provided.

From the development program for FTR, 1,337 clinical samples from early studies, the Phase 2a, Phase 2b and Phase 3 trials (GSK 206267, GSK 205889 and GSK 205888, respectively) were analyzed for susceptibility to FTR by the PhenoSense Entry Assay (Monogram BioSciences). The subtypes were determined based upon gp160 sequence and subtype B was most prevalent (66%, 881/1,337). There were 156 subtype C isolates, 48 F1 isolates, 43 subtype A isolates, 29 subtype B,F1 isolates, 19 subtype BF isolates, 17 subtype A1 isolates, 5 CRF01_AE isolates and 112 Others (not available, Complex and not recorded). The range in EC_{50} values ranged from 0.018nM to >5,000nM. Of all the isolates tested, 719 (54%) exhibited EC_{50} values below 1nM, 1,071 isolates (80%) had EC_{50} values below 10nM and 1,217/1,337 (91%) exhibited EC_{50} values below 100nM. Variability in FTR susceptibility was observed in all subtypes. For the subtypes with significant numbers of samples, there did not seem to be regional differences (e.g., subtype B isolates from Australia or Europe exhibited a similar range of EC_{50} values).

Subtype B had the highest percentage of isolates with EC_{50} values below 1nM (62%) and 94% of isolates below 100nM with only 6% of isolates with EC_{50} values >100nM (

Table 6). Subtype BF, F1, and B,F1 had higher proportions (21 to 38%) of isolates with EC_{50} values >100nM and all five subtype CRF01_AE isolated (100%) had EC_{50} values >100 nM. Further analysis of the BF1 and F1 isolates in Trial 438047 showed that ENs with high EC_{50} values tended to have known EN polymorphisms, with many having polymorphisms at two of the four known positions (374, 426, 434, 475). The percentage of double polymorphisms in the Los Alamos National Laboratory (LANL) database in these subtypes are relatively low (~6%), while in Trial 438047 that percentage is 11% (6/54 isolates).

The data show a wide range of TMR antiviral activity across subtypes with EC_{50} values ranging from low nM to >2,000 nM against subtypes B, A, C, D, F isolates. TMR did not show activity against subtype E (AE) and group O isolates and only moderately higher nM activity against 2 of 3 subtype G isolates. Even against subtype B isolates, there are some isolates which have very high EC_{50} values. The high variability in antiviral activity of TMR against HIV-1 viruses within and between subtypes likely results from the polymorphic nature of the gp120 target and the presence of EN polymorphisms, which can interfere with BMS626529 binding to EN and inhibit its antiviral activity.

As shown above, TMR did not have antiviral activity against subtype AE (aka E) isolates (five different subtype AE isolates in the Phenosense Entry™ assay or nine subtype E clinical isolates in peripheral blood mononuclear cells [PBMCs]). Thus, the data indicate that subtype AE (or E) viruses are inherently resistant to TMR. The sequences of some subtype AE viruses were examined and showed that there were changes at two positions, S375H and M475I, which are associated with TMR resistance. However, there is no direct evidence that either of these amino acid changes are responsible for the observed resistance to TMR in subtype AE viruses. This subtype is a predominant subtype in Southeast Asia, but it is not found in high frequencies elsewhere throughout the world.

Susceptibility of Longitudinal Samples from Treatment-Naïve Subjects in a Pseudotype Assay

Drs. Douglas Richman and Susan Little (University of California at San Diego) have been following a cohort of naïve patients with HIV-1 for years. This cohort allows an examination of whether the susceptibility of virus within an infected individual changes over time without drug treatment. Banked plasma samples from subjects in this cohort were forwarded to Monogram Biosciences, where they generated pseudotype viruses with the ENs from these subjects and examined them for susceptibility to TMR. Longitudinal samples from 25 patients were generated and data on more than one sample from each subject were obtained for 24 subjects. A wide range of interpatient variability was observed with EC_{50} values ranging from subnanomolar to >20 nM. For each of the patients, most of the longitudinal samples remained in a similar range relatively, although there was intra-patient variability. However, four of these patients lost susceptibility or gained susceptibility to TMR over the longitudinal time frame and the reasons for these changes and the implication regarding clinical response are unclear.

Specificity of Temsavir Antiviral Activity

Several cell culture and biochemical assays were used to characterize the specificity of TMR by assessing its antiviral activity against respiratory syncytia virus, influenza A virus, canine parainfluenza virus, and hepatitis C virus (HCV). TMR was inactive against the three RNA viruses (respiratory syncytia virus, influenza A virus, and canine parainfluenza virus) with EC_{50} values >100 μM and was not inhibitory against HCV in a cell culture replicon system with an EC_{50} value >75 μM.

In biochemical assays, TMR was inactive at 30 μM against three HIV-1 encoded enzymes, integrase, protease and reverse transcriptase. It was also inactive at 25 μM against polymerases from two unrelated RNA viruses (HCV and bovine viral diarrhea virus). In addition, TMR was inactive against HIV-2 strain 287 with an EC_{50} value >2,000 nM.

TMR was evaluated for antiviral activity against HBV and HCV. TMR did not demonstrate inhibition of HBV or HCV viral replication or inhibition of the viability of the HepG2 2.2.15 cells used in the HBV assay or the Huh Luc/Neo cells used in the HCV GT1b replicon assay. The EC_{50} value against HBV and HCV was >10 μM with a selectivity index of 1.0.

Effect of Human Serum on Antiviral Activity

To study the effect of serum on TMR, experiments were performed using normal media (containing 10% fetal bovine serum), or media supplemented with 40% adult human serum. MT-2 cells were infected with HIV-1 LAI or NL4-3, incubated in the presence of serially diluted compounds for 5 days, then assayed for RT activity. The presence of human serum had little effect on the EC_{50} value of TMR, resulting in 2.1- and 1.5-fold increases against HIV-1 LAI and NL4-3, respectively (Table 220). This result is consistent with results showing TMR was 85% bound by human serum protein. As a control, nelfinavir was attenuated by 21- to 25-fold in the cultures containing human serum, due to the >98% binding by human serum protein.

Table 220. Effect of 40% Human Serum on the Anti-HIV Activity of Temsavir (Report 2017n338497, page 19)

Compound	$EC_{50} \pm$ sd (nM)[a]			
	LAI		NL4-3	
	-HS	+HS (fold increase)	-HS	+HS (fold increase)
BMS-626529	0.7 ± 0.4	1.5 ± 0.4 (2.1)	2.2 ± 0.6	3.3 ± 0.9 (1.5)
Nelfinavir	20 ± 10	410 ± 143 (21)	17 ± 9.0	430 ± 152 (25)

Source: Lab Notebook 36501
[a] sd, standard deviation
Abbreviations: EC_{50}, half maximal effective concentration; HS, human serum.

18.3. Cytotoxicity

The cytotoxicity profile of TMR was examined in several cell types from different human tissues. The CC_{50} values >200 µM were observed in MT-2 (T lymphocytes), 293 (Kidney), HEp-2 (larynx), HepG2 (liver), Hela (cervix), HCT116 (colorectal), MCF-7 (breast), and SK-N-MC (neuroepithelium), HOS (bone), H292 (lung), and MDBK (bovine kidney) cells, when measured after three or 6 days in culture (Report aa2017n338497). The CC_{50} values of 105 and 192 µM were obtained in the T cell line PM1 and in PBMCs, respectively, following 6 days in culture (Table 221). These results show that TMR exhibits low to negligible cytotoxicity in cell culture.

The cytotoxicity of BMS-663068 and TMR was evaluated during a 6-day incubation with 9 different human cell lines and PBMCs. An MTS dye-reduction assay was used to quantitate viability. Minimal to no cytotoxic effect was observed with either FTR or TMR, when compounds were present at up to 300 µM. For FTR, a CC_{50} value below 100 µM was seen in only the SH-SY5Y cell line. However, TMR was noncytotoxic when assayed in a parallel experiment. Thus, TMR and FTR appear to have no significant cytotoxic effects in cell culture.

Table 221. Cytotoxicity of Fostemsavir and Temsavir Against Multiple Human Cell Lines

Cell Line	Cell type	BMS-663068 (μM)	BMS-626529 (μM)
PBMC	blood	245	>300
MT-2	T lymphocyte	>300	220
PM1	T lymphocyte	>300	105
KG-1a	Bone myeloblast	200	240
Huh-7	Liver hepatocyte	>300	>75
293T	Kidney epithelial	>300	>300
H1299	Lung carcinoma	>300	>300
SH-SY5Y	Brain neuroblastoma	76	>300
U373	Brain astrocytoglia	>300	nd
HeLa	Cervical adenocarcinoma	>300	>300

Source: Lab Notebook 36501

18.4. Combination Antiviral Activity Studies in Cell Culture

Two-drug combination studies of TMR were performed with commercially-available anti-HIV drugs (non-nucleoside reverse transcriptase inhibitors [NNRTIs]: delavirdine, efavirenz, nevirapine, and rilpivirine; NRTIs: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine and zidovudine; PIs: amprenavir, ATV, DRV, indinavir, lopinavir, nelfinavir, RTV, and saquinavir; and the gp41 fusion inhibitor ENF, and the CCR5 coreceptor antagonist, MVC). Each drug ratio consisted of an array of 3-fold serial dilutions, with the concentrations originally designed to start at 300 or 750 times the EC_{50} value of respective drug. Combination indices were calculated according to Chou and Rideout [Chou TC, Rideout DC, eds. Synergism and Antagonism in Chemotherapy. New York: Academic Press;1991; pp 61-101]. In cell culture studies in HIV-1 (LAI)-infected MT-2 cells analyzed 5-days postinfection, TMR was not antagonistic when used in combination with any of these drugs. Cytotoxicity was assessed using an MTS assay in uninfected cells, exposed to the same drug combinations, and incubated for 6 days. None of the compounds in combination with TMR exhibited antagonism or cytotoxicity, even at the highest concentrations tested.

IBA is a monoclonal antibody against CD4 that has been approved for use in the heavily treatment-experienced patient population. IBA in combination with TMR was assessed in MT-2 cells infected with NL43 virus at a range of drug concentrations near the EC_{50} value of each compound, so that equivalent antiviral activities could be compared. Since the maximum percent inhibition (MPI) for IBA was <80%, the combination indices cannot accurately be computed at higher EC levels (i.e., EC_{75} and EC_{90} levels). The results of the two-drug combination study with IBA show that in cell culture, the effect of coadministration of the two compounds are not antagonistic at all ratios at the EC_{50} level. Cytotoxicity was not observed in any of the mixtures used in the assay. As result of the lower MPI of IBA, the two-drug combination data of the 1:1 EC ratio was analyzed by a second method, the Excess over Highest Single Agent method. The

combination of TMR and IBA was not antagonistic consistent with the results produced above by the combination index software program.

In addition, the anti-HIV-1 activity and cytotoxicity of TMR was evaluated in two-drug combination studies with the integrase strand transfer inhibitor (INSTIs), DTG and RAL. Each two-drug combination was tested three times in MT-4 cells acutely infected with HIV-1_{NL4-3} with broad range of concentrations, and results were interpreted using Prichard and Shipman MacSynergy II three-dimensional model for statistical evaluation of combination assays. No antagonistic interactions or cytotoxicity were observed within the concentration ranges tested between combinations of TMR with DTG or RAL.

Ribavirin, used in the treatment of HCV infection, and two drugs used in the treatment of chronic HBV infection, adefovir dipivoxil and entecavir, were not antagonistic to the antiviral activity of TMR.

18.5. Resistance

Selection and Characterization of Temsavir Resistance Virus

HIV-1 variants of the T-tropic (LAI and NL4-3) and M-tropic (Bal) strains with reduced susceptibility to TMR were selected through cell culture passage in the presence of increasing concentrations of TMR. Following 14 to 49 days in culture, the breakthrough viruses were recovered and assayed for TMR susceptibility. In addition, viral RNA was extracted for sequence determination of the EN regions.

Resistant variants developed in all four independent virus selections, with selected viruses exhibiting a 159-fold increase in EC_{50} value after 31 days of selection using HIV-1_{LAI} and a 100-fold increase in the 14-day selection of HIV-1_{NL4-3} (Table 222). After 49 days, the M-tropic strain HIV-1 Bal exhibited an 18-fold increase in EC_{50} value. Genotypic analysis of the resistant viruses identified amino acid substitutions (L116P/Q, L175P, A204D, V255I, A281V, M426L, M434I and M475I) within gp120. In the HIV-1_{LAI} selected viruses, the M426L substitution was found in association with L116Q or P or with the A204D and A281V substitutions. In the HIV-1_{NL4-3} resistance selection, the M426L and M457I substitutions were observed. The M-tropic virus HIV-1_{Bal} exhibited a slightly different profile, with major substitutions occurring at L175P, V255I, and M434I.

Table 222. Genotypic and Phenotypic Analysis of Temsavir-Selected Viruses (Report 2017n338500, page 14)

Expt.	Days	Final Select Conc. (nM)[a]	EC50, nM (Fold Resistance)	Major gp160 substitutions	Freq.	gp160 domain	Closest CD4 contact point
	HIV-1 LAI						
1	14	4	4.6 (14)	L116Q	2/12	C1	NA[b]
				L116P	1/12	C1	NA
				M426L	8/12	C4	**M426**
				L116P/**M426L**	1/12	C1/C4	NA/**M426L**
2	31	40	48 (159)	**M426L**	4/11	C4	**M426**
				A204D/**M426L**	3/11	C2/C4	NA/**M426**
				A281V/**M426L**	3/11	C2/C4	**A281/M426**
	HIV-1 NL4-3						
1	14	8	53 (100)	**M426L**	3/12	C4	**M426**
				M475I	8/12	C5	**D474**
	HIV-1 Bal						
1	49	24	56 (18)	L175P	1/12	V2	NA
				M434I	2/12	C4	**V430**
				L175P/**V255I**	1/12	V2/C2	NA/**T257**
				L175P/**M434I**	2/12	V2/C4	NA/**V430**
				V255I/M434I	5/12	C2/C4	**T257/V430**

Source: Lab Notebooks 36501, 53369, 55604
[a] Initial EC_{50} values used for selections were 0.5 nM for HIV-1 LAI, 1.0 nM for NL4-3, and 0.75 nM for Bal. These starting concentrations were twice the EC_{50} value for each strain. Final selection concentrations were listed.
[b] NA, not applicable
Abbreviations: Conc., concentration; EC_{50}, half maximal effective concentration.

In general, most substitutions mapped to the conserved regions (C1, C2, C4 & C5) of the gp120 EN, confirming TMR targets the viral EN protein during infection. Resistance substitutions residing in C2 and C4 regions were observed most frequently and were present in all three strains. A substitution from HIV-1 LAI-resistant virus was mapped to C1 (L116Q/P), lies at the terminus to the first α-helix, and could influence V1/V2 loop conformation. The A204D change lies just after ß-sheet 3 and possibly forms a key component of the bridging sheet. The V255I change selected in the HIV-1 Bal background lies deep within the CD4 binding pocket of gp120. One V2 variable region substitution (L175P) was also identified in the HIV-1 Bal-resistant viruses. The frequently selected M426L and M475I substitutions reside at or near CD4 contact points, which the Applicant states support that TMR may bind to gp120 at a site overlapping with the CD4 binding pocket. The results indicated a possible strain dependence on the selection of resistance-conferring substitutions.

The TMR-selected amino acid changes were introduced into the wild-type HIV-1 LAI

EN to produce recombinant viruses. Phenotypic evaluation of HIV-1 LAI recombinant viruses harboring each of the selected five substitutions showed that L116P, A204D, and M426L conferred >340-fold, ≥340-fold, and 81-fold decreased susceptibility to TMR, respectively (Table 223). Recombinant viruses containing A281V showed no change in susceptibility to TMR, and the M475I substitution showed 5-fold reduced susceptibility to TMR.

Table 223. Phenotypes of Recombinant Viruses Containing Temsavir-Selected Substitutions (Report 2017n338500, page 16)

Substitutions	EC_{50} (nM) (Fold Resistance)	Closet CD4 Contact Point
LAI WT	1.5	NA
L116P	>500 (>340)	Not a CD4 contact point
A204D	≥50 (≥340)	Not a CD4 contact point
A281V	0.75 (0.5)	A281
LAI WT	1.2	NA
M426L	98 (81)	M426
M475I	5.8 (4.8)	D474

Source: Lab Notebooks 36501, 53369, 55604
Abbreviations: EC_{50}, half maximal effective concentration; NA, not applicable; WT, wildtype.

The EN gene from subjects involved in Trial 438047 were sequenced at baseline, and the identity of the amino acids at these four key positions were noted. Eight subjects exhibited new polymorphisms in some of these positions, although some were mixtures with known amino acids. Site-directed mutations were made for each polymorphism (S375V, S375Y, M426K, M426V, M434T, M434V, M475L and M475V) in the LAI EN backbone and tested for susceptibility to TMR in a cell-cell fusion assay. The S375Y substitution had an EC_{50} value >20 µM and a fold change of >10,000 (Table 224). The M434T and M475L substitutions exhibited FCs of 15-fold and 17-fold, respectively. The other substitutions produced FCs between 0.5 to 9.5.

Table 224. Susceptibility of Additional Baseline Polymorphisms at Positions 375, 426, 434 and 475 of gp120 to Temsavir (Report 2018n375736, page 5)

	EC_{50} (nM)	FC of EC_{50}/wt EC_{50}
WT	2 ± 0.1	1
S375V	11 ± 0.9	5.5
S375Y	>20000	>10000
M426K	1 ± 0.1	0.5
M426V	6.5 ± 0.3	3.3
M434T	29 ± 2.4	15
M434V	15 ± 1.9	7.5
M475L[a]	34 ± 1.2	17
M475V	19 ± 1.9	9.5

Source: N66632-13, N62748-54, N-62748-62
[a] M475L was not present in any subject at baseline but was included in this analysis since it was identified as a novel gp160 substitution emergent in one subject in the Phase 3 trial as a M475M/L mixture.
Abbreviations: EC_{50}, half maximal effective concentration; FC, fold change; WT, wildtype.

To evaluate the effect of substitutions on EN protein structure, wild type (WT) and resistant $gp120_{JRFL}$ protein variants possessing single substitutions (M426L, M434T, and M475I) were probed in an enzyme-linked immunosorbent assay using a panel of conformation-specific MAbs, which target gp120 at multiple locales (CD4 binding site, CD4-induced epitope, variable loop 3, or others). Unlike their inhibition of TMR susceptibility, these three substitutions only caused modest changes in antibody affinity, suggesting that surface topology of the EN is not greatly affected by amino acid changes leading to TMR resistance.

Temsavir Retains Activity Against CD4-Independent Virus

TMR targets the interaction between gp120 and the host receptor CD4. This mode of action raises the possibility that CD4-independent viruses may be resistant to TMR, or that treatment with FTR may promote the emergence of CD4-independent viruses. CD4-independent laboratory isolates remained sensitive to TMR in CD4 cells, while HIV-1 ENs from viruses resistant to TMR exhibited no evidence of a CD4-independent phenotype. A new model developed by Langley et al. explains that TMR binds gp120 and prevents the gp120 conformation change required for CD4 binding and exposure of the coreceptor binding site (Langley et al. 2015) (D.R. Langley, et al. presented at the 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, USA, 3 to March 6, 2013). In CD4-independent virus, gp120 can adopt a conformation that presents the coreceptor binding site in the absence of CD4, while still allowing TMR to bind. The model predicts that TMR blocks both wild-type and CD4-independent gp120 from adopting a CD4-bound conformation and presenting the coreceptor binding site.

18.6. Cross-Resistance

Assessment of Cross-Resistance Between Temsavir-Resistance Viruses and CD4-Directed Postattachment Inhibitors, CCR5-Coreceptor Antagonists, and gp41 Fusion Inhibitors

TMR, IBA, MVC, and ENF represent different classes of inhibitor inhibiting entry. Resistance to each of these compounds maps to amino acids within gp120 or gp41 so the potential for cross-resistance exists. Four functional EN clones with known TMR-resistant substitutions were examined in a cell-cell fusion assay for susceptibility to IBA, MVC, and ENF (Table 225). The EN clones were derived from baseline samples from subjects in the proof-of-concept study and contain either M426L, M426L/M475I or S375M/M434I. Two EN clones came from a dual-mixed subject with only the M426L substitution, one EN clone was CCR5-tropic, and the fourth was CXCR4-tropic. The four EN clones exhibited susceptibility to IBA and ENF. Against MVC, 3 of 4 EN clones exhibited susceptibility, while the CXCR4-tropic EN clone, as expected, was not inhibited by MVC. Thus, functional EN clones from TMR-resistant clinical samples retain susceptibility to CD4-directed postattachment inhibitor, CCR5-coreceptor antagonist, and gp41 fusion inhibitor classes.

Table 225.Susceptibility of Temsavir-Resistant Clinical Samples to Other Entry Inhibitors (Report 2017n338508, page 18)

Subject (clone)	Tropism	BMS-626529 resistance mutations	BMS-626529	ENF	Ibalizumab	MVC
			Fold-change EC_{50} (mean ± SD)[a]			EC_{50}, nM (mean ± SD)[a]
16 (1)	CCR5	M426L/M475I	2932 ± 404	4.2 ± 2.3	0.6 ± 0.1	7.4 ± 1.3
21 (170)	CCR5	M426L	386 ± 95	13.4 ± 2.8	1.6 ± 0.9	9.2 ± 1.8
21 (169)	CXCR4	M426L	215 ± 76	1.9 ± 0.6	0.5 ± 0.1	>5000
41 (33)	CCR5	S375M/M434I	>19418	1.5 ± 0.3	0.7 ± 0.1	4.0 ± 0.1

Source: ELN: 93256-122
[a] Mean of two independent experiments
Abbreviations: EC_{50}, half maximal effective concentration; ENF, enfuvirtide; MVC, maraviroc; SD, standard deviation.

Temsavir Activity Against Ibalizimab-Resistant Viruses

Conversely, susceptibility of TMR to viruses resistant to other entry inhibitors was also examined. An NL4-3 virus resistant to the anti-CD4 monoclonal antibody IBA was selected through sequential passage in increasing concentrations of antibody. Sequencing of the IBA-resistant virus identified S162N and A605T/A substitutions in the EN. The A162N substitution destroys a potential glycosylation site outside of the V5 region (after V1/V2 but before V3), and this virus is highly resistant to IBA, with an EC_{50} value >995-fold compared to wild-type NL4-3. Additionally, a clinical EN with reduced susceptibility to IBA, termed Ibal-R, was identified with only one potential N-linked glycosylation site (PNGS) in this region. The EC_{50} value of this clone in the cell-cell fusion assay (Ibal-R) is 7-fold higher than that of a sensitive clinical EN (Ibal-S), which contains two N-linked glycosylation sites in the V5 region (3.2 versus 0.45nM, respectively). The Ibal-R exhibits a lower MPI of 80%, which is a characteristic of IBA-resistant ENs. An M426L site-directed mutant of the Ibal-R clone was also made, and these three ENs were analyzed for susceptibility to TMR in a cell-cell fusion assay. Both the Ibal-S and Ibal-R ENs were susceptible to TMR, while the Ibal-RM426L EN exhibited decreased susceptibility to TMR and resistance to IBA (Table 226). The IBA-resistant viruses retained susceptibility to TMR, suggesting a lack of cross-resistance between these agents.

Table 226. Susceptibility of Ibalizumab-Resistant Virus to Temsavir (Report 2017n338508, page 19)

	NL_{4-3} Wild-type	NL_{4-3} (S162N, A605T/A)	Ibal-S (PNGS=2)	Ibal-R	Ibal-R M426L	Ibal-S	Ibal-R	Ibal-R M426L
	EC_{50} nM (mean ± SD)[a]					MPI (mean ± SD)[a]		
BMS-626529	0.12 ± 0.0	0.082 ± 0.081	11.4 ± 2.9	3.9 ± 0.8	455 ± 87	101.7 ± 0.03	101.2 ± 0.0	100.7 ± 0.5
Ibalizumab	1.33 ± 0.1	>995	0.45 ± 0.1	3.2 ± 0.1	5.5 ± 3.2	102.6 ± 0.6	80.0 ± 12.0	83.2 ± 1.8

Source: ELN: 91417-035, ELN: 91417-037, ELN: 94674-014
[a] Mean of two independent experiments
Abbreviations: EC_{50}, half maximal effective concentration; Ibal, ibalizumab; MPI, maximum percent inhibition; PNGS, potential N-linked glycosylation sites; SD, standard deviation.

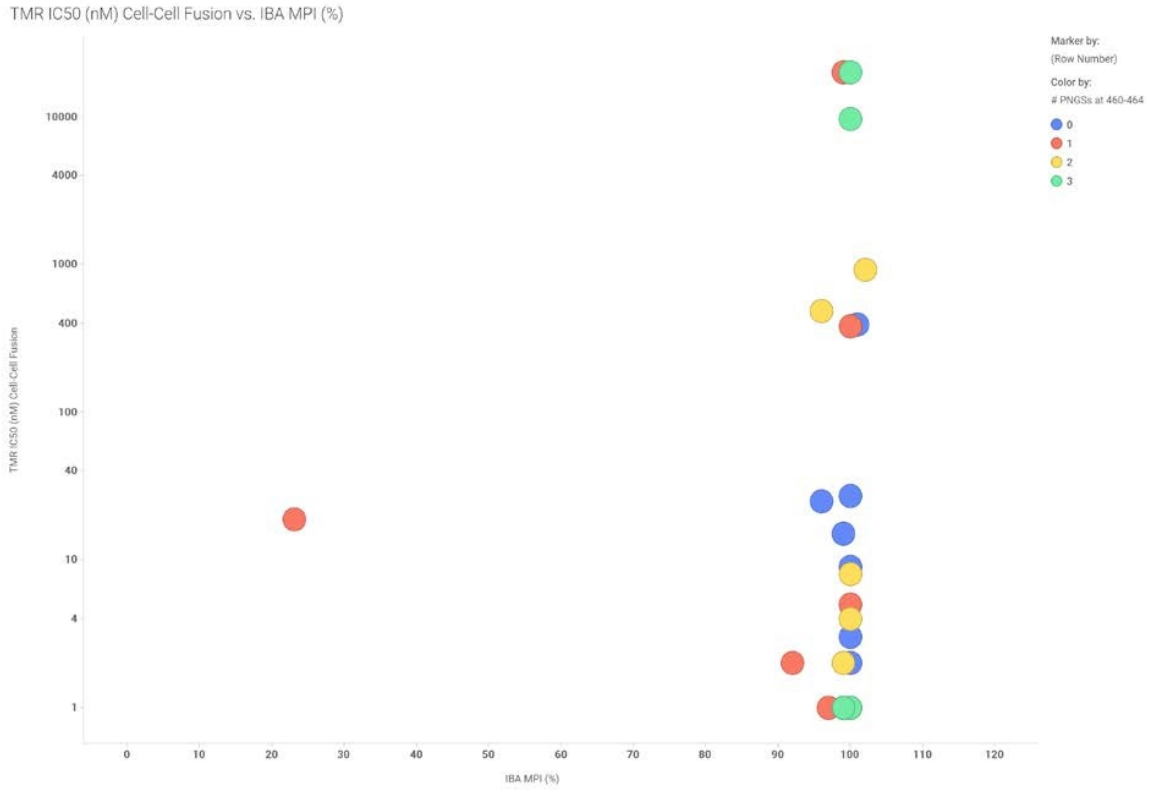
Further Analysis of Ibalizumab Susceptibility in gp160 Proteins With Various Number of PNGS in V5

Both IBA and FTR inhibit virus entry by targeting functions of the HIV-1 EN protein. IBA allows the viral gp160 protein to bind to CD4 and inhibits a downstream step prior to coreceptor engagement. Inhibition is believed to be due to steric interactions with gp120 that prohibit conformational changes required to expose the V3 loop of gp120 that binds to coreceptors CCR5 or CXCR4. This hypothesis is supported by resistance analysis that shows that loss of PNGSs in the V5 region results in decreased susceptibility to IBA, presumably by reducing the prohibitive steric interactions with gp120 and allowing for appropriate conformational changes. In contrast, FTR binds near the CD4 binding site and stabilizes gp120 in a “closed” conformation that is unable to bind to CD4. The amino acids at which substitutions emerge during resistance selection experiments and clinical studies include S375, M426, M434, M475, A204, and L116. All of these positions are located in conserved regions of the EN and the amino acids 375, 426, 434, and 475 surround the binding site of FTR, which is far away in the structure from the highly variable V5 region. In addition, none of these 6 positions in the wild type sequence encode a PNGS, so substitutions that induce reduced FTR susceptibility would probably not affect the PNGS profile of an EN.

Decreased susceptibility to IBA has been shown to be primarily due to the loss of PNGSs in the V5 region of gp120. A short region from amino acids 460 to 464 can encode from 0 to 3 PNGSs, and it’s the loss of sites in this region that have been linked to decreased susceptibility to IBA. To further analyze the susceptibility of BMS and IBA and assess potential cross-resistance, gp160 proteins from 240 baseline samples and 68 postbaseline samples from the Phase 2b FTR Clinical Trial 205889 were analyzed in a cell-cell fusion assay. An additional 28 samples obtained from subjects who were screened in this study who did not meet the entry specifications of the study due to having a TMR EC_{50} value >100nM were also included in the analysis. Given that this region is highly variable, there were many samples that contained ambiguous sequences in or around this region that made it impossible to specifically define the number of PNGSs between amino acids 460 and 464. Those samples were excluded, so only populations with a definitive number of PNGSs were used. From these remaining samples, there were eight subjects with zero PNGSs, two with one PNGS, three with two PNGSs and two with three PNGSs. In

addition, from those that did not meet entry criteria for Study 205889 due to EC_{50} values >100nM, there were two subjects with one or three PNGSs each, while three subjects contained two PNGSs. The data suggest that there is no correlation between TMR susceptibility and the number of PNGSs in V5 of gp160. Envelopes with large differences in susceptibility to TMR were examined (EC_{50} values of 1 to >20,000nM) without a noteworthy change in susceptibility to IBA, regardless of the number of PNGSs in V5 (Figure 22).

Figure 22. Scatter Plot of TMR EC_{50} (nM) in the Cell-Cell Fusion Assay Versus IBA MPI (%) in PhenoSense Entry Assay (Report 2019n421288, page 12)



Source: N66632-29
The number of PNGSs (0, 1, 2 or 3) at Amino Acid Positions 460-464 are indicated by the color scheme indicated in the figure.
Abbreviations: EC_{50}, half maximal effective concentration; IBA, ibalizumab; MPI, maximum percent inhibition; TMR, temsavir.

Additionally, 5 cloned IBA-resistant ENs from different individuals were analyzed in a PhenoSense® Entry Assay for susceptibility to both TMR and IBA (Table 227). All 5 samples exhibited decreased susceptibility to IBA based upon a low MPI (60 to 86%). In addition, the clones with the lowest MPI correlated with higher EC_{50} values to IBA. Three of these clinical samples exhibited susceptibility to TMR, with FCs in EC_{50} values of 0.88, 12 and 13 and also exhibited MPIs of 100% against TMR. The other two clones had EC_{50} values of ~1.6 µM and >5 µM (FCs of 1,458 and > maximum, respectively) and lower MPIs of 74% and 45%, respectively. The nucleotide sequences of these clones were not available.

Table 227. Susceptibility of Temsavir Against Ibalizumab-Resistant Envelopes Derived From Clinical Samples in PhenoSense Entry Assay (Report 2019n421288, page 13)

Sample ID	TMR IC_{50} (μM)	TMR IC_{50}-FC	TMR MPI (%)	IBA IC_{50} (μg/mL)	IBA IC_{50}-FC	IBA MPI (%)
E08_154037_12	>5	>MAX	45	0.749742	31	62
E08_154024_12	0.014782	13	100	0.594808	24	60
E08_134227_16	0.013569	12	100	0.035088	1.45	86
E08_177370_14	1.619040	1458	74	0.211326	8.7	67
DUAL	0.000981	0.88	100	0.054636	2.25	84

Source: 66632-47
Abbreviations: FC, fold change; IBA, ibalizumab; IC_{50}, half maximal inhibitory concentration; MPI, maximum percent inhibition; TMR, temsavir.

In the BRIGHTE Study, 15 subjects were treated with IBA as part of their initial OBT along with FTR, and five of these subjects subsequently failed therapy. Where available, Screening and failure samples were used to determine susceptibility to each drug. A total of 10 samples from 5 cotreated subjects were successfully tested in the PhenoSense® Entry Assay against IBA (one subjects (AI438047.000552) only had a Screening sample amplified). This subject was susceptible to both TMR and IBA at Screening, although there was an M426M/L mixture at Screening that could eventually have affected TMR susceptibility. For the other four subjects, analysis of the protocol-defined virologic failure samples showed that each exhibited reduced susceptibility to both TMR and IBA (Table 228). One of the subjects (AI438047.000153) exhibited reduced susceptibility to TMR at baseline, with an FC of 100 and an M426L polymorphism. However, at baseline, this subject was susceptible to IBA, with an IBA EC_{50} FC of 0.62 and an MPI =99%, indicating that susceptibility to FTR and IBA are not linked. Of the four subjects with sequences at Screening and protocol-defined virologic failure, three (AI438047.000153, AI438047.000336 and AI438047.000559) potentially exhibited fewer PNGSs between amino acids 460 to 464 in the failure sample compared to their Screening sample.

Additional work was performed on these samples. The PDVF samples from three subjects (000336, 000508, 000559) were cloned and site-directed mutagenesis was performed to mutate the known TMR substitutions back to their baseline amino acid (S375, M426 and M475). Analysis of susceptibility of all these clones to both TMR and IBA were performed (Table 229). When all the key TMR amino acids positions (375/426 or 475) were mutated back to baseline substitutions, susceptibility to TMR was greatly increased with TMR EC_{50} values between 1 to 10nM (from values >2 μM for each PDVF clonal EN). These changes in the three EN clones had had no effect on susceptibility to IBA (EC_{50} value changes or in MPI values) (Table 229). As an internal control, there was no change in the susceptibility to RAL with any of the EN clones. This data provides additional evidence that decreased susceptibility to TMR and IBA observed in these subjects who failed on both drugs was not linked.

Table 228. Susceptibility of Temsavir and Ibalizumab in Subjects Who Were Virologic Failures to Both in BRIGHTE Phase 3 Trial (Study 2019n421288, page 14)

Participant ID	Visit	TMR gp120 polymorphisms	TMR IC_{50} (nM)	TMR IC_{50}-FC	IBA IC_{50} (µg/mL)	IBA IC_{50}-FC	IBA MPI (%)	PNGSs at 460-464
AI438047.000153	Screening	M426L	96.28	100.00	0.015029	0.62	99	2
	Unscheduled[a]	M426L	87.34	99.00	0.093108	3.83	72	0-2[c]
AI438047.000336	Screening	S375T	10.89	16.00	0.016563	0.68	100	1-2[c]
	Week 108	S375T M426L	>5000	>3324.51	0.068232	2.81	72	0-2[c]
AI438047.000508	Screening	-	0.47	0.55	0.022852	0.94	93	1
	Week 36	S375H/N M426M/L	>5000	>3651.39	0.069740	2.87	74	1
AI438047.000552	Screening	M426M/L	0.39	0.43	0.017847	0.74	98	1
AI438047.000559	Screening	M426M/T	0.89	0.98	0.016481	0.68	64	1
	Unscheduled[b]	S375N	253.94	223	0.198098	8.16	51	0
	Week 36	S375N M475I	>5000	>2500	1.486080	61.00	62	0

Source: 66632-47
Note: bold text designated PDVF timepoint
[a] Approximately Week 13
[b] Approximately Week 6
[c] Mixture observed
Abbreviations: FC, fold change; IBA, ibalizumab; IC_{50}, half maximal inhibitory concentration; MPI, maximum percent inhibition; PNGS, potential N-linked glycosylation sites; TMR, temsavir.

Table 229. Antiviral Activity Against Site-Directed Temsavir Reversion Mutants (Source: Response From Sponsor to FDA Request)

	Temsavir EC_{50} (nM)	Raltegravir EC_{50} (nM)	Ibalizumab EC_{50} (nM)	Ibalizumab MPI (%)
AI438047000336 Wk 108	>2000	5.41 ± 0.78	2.39 ± 1.14	71 ± 1.7
AI438047000336 Wk 108 T375S,L426M *	10.72 ± 2.07	4.75 ± 0.83	2.66 ± 0.53	69 ± 2.5
AI438047.000508 Wk 36	>2000	4.57 ± 0.93	1.56 ± 0.16	87 ± 2.0
AI438047.000508 Wk 36 N375S,L426M*	1.16 ± 0.57	5.54 ± 1.03	1.47 ± 0.12	64 ± 18.6
AI438047.000559 Wk 36	>2000	4.75 ± 1.01	>800	38 ± 15.9
AI438047.000559 Wk 36 I475M*	5.61 ± 2.01	6.16 ± 2.36	>800	25 ± 0.9

Source: eLN 11532, 11535-7, 11286
* Clones where known TMR substitutions are reverted to wild type sequence
Abbreviations: EC_{50}, half maximal effective concentration; MPI, maximum percent inhibition.

Susceptibility of Temsavir Against MVC-Resistant Viruses

Cross-resistance of TMR with MVC-resistant viruses was examined. Previously, it has been shown that TMR exhibits antiviral activity against some CXCR4-tropic viruses, but not against other CXCR4-tropic viruses. Thus, while CXCR4-tropic viruses, which inherently exhibit resistance to MVC, are not innately cross-resistant to TMR, it appears like TMR has reduced

antiviral activity against some CXCR4-tropic viruses. For CCR5-tropic MVC-resistant ENs, 2 viruses of this phenotype were examined using the PhenoSense Entry™ Assay. Both exhibited a low MPI against MVC, indicating MVC resistance, but one (MVC res 3) was sensitive to TMR, and the other (MVC res 2) was resistant, with a fold change >5,000. This suggests that resistance to MVC in a CCR5-tropic EN does not necessarily encode resistance to TMR. A series of CCR5-tropic EN clones obtained from two subjects treated with either MVC or the investigational CCR5 antagonist aplaviroc were evaluated in a cell-cell fusion assay for susceptibility to both TMR and MVC. In the one subject treated with MVC, four sequential EN clones (S1, S2, R3, R4) were tested. Sensitivity to both MVC and TMR were observed using the S1 and S2 ENs, while resistance to both compounds was observed in the later ENs. The data indicate that some ENs do exhibit cross-resistance to both TMR and MVC, but not all resistance to MVC confers cross-resistance to TMR.

Enfuvirtide-Resistant Viruses

Finally, a series of six clinical ENs resistant to ENF were examined for susceptibility to TMR in the PhenoSense Entry™ Assay. All six ENs exhibited susceptibility to TMR with FC ranging from 0.49 to 2.9. In addition, a series of single amino acid changes in the gp41 region of NL4-3, that are known to result in resistance to ENF, were made by site-directed mutagenesis and all viruses were susceptible to TMR. The data indicate that there is no cross-resistance between ENF and TMR.

Temsavir Activity Against INSTI-, NNRTI-, NRTI-, and PI-Resistant Recombinant Viruses

A series of recombinant viruses containing site-specific resistance substitutions of INSTI, NNRTI, NRTI, and PI drug classes, or genes from clinical isolates with known resistance substitutions, were examined for susceptibility to TMR. Site-specific recombinant viruses with INSTI resistance substitutions Y143R, N155H, or G140S/ Q148H with resistance to RAL of 9- to 494-fold had no change in susceptibility to TMR (Report 2017n338509, page 13). Site-specific recombinant viruses containing NNRTI resistance substitutions, K103N and Y181C, and a rilpivirine-resistant clinical isolate (M41L, D67N, T69D, L741, A98G, K101E, Y181C, G190A, L210W, T215Y) showed decreased susceptibility to rilpivirine, but both viruses were susceptible to TMR with an FC <1-fold (Report 2017n338509, page 12). Viruses resistant to NRTIs with resistance substitutions K65R, L74V, M184V, or TAMs (M41L/D67N/K70R/L210W/T215Y/ K219Q or D67N/K70R/T215F/K219Q) were susceptible to TMR with changes in EC_{50} values of <2-fold (Report 2017n338509, page 11). Finally, a set of provirus clones containing protease genes from clinical isolates resistant to ATV or both ATV and DRV were both susceptible to TMR (Report 2017n338509, page 13). In summary, the INSTI-, NNRTI-, NRTI-, or PI-resistant viruses exhibited wild type susceptibility to TMR, with no evidence of any cross-resistance.

Although the resistance profile of TMR is not fully defined, there are amino acid substitutions involved with binding to gp120 that have been shown to decrease the TMR susceptibility of viruses and have been selected in TMR-resistance selection experiments. NL-Rluc viruses containing either an S375M, M426L or a double M426L/M475I substitutions showed decreased

susceptibility to TMR of 318-fold, 208-fold, and >50,000-fold, respectively. These three TMR-resistant viruses were susceptible (within 3-fold) to the CD4-directed postattachment inhibitor IBA, the gp41 fusion inhibitor ENF, the INSTI RAL, NNRTIs (efavirenz, rilpivirine), NRTIs (abacavir, tenofovir), and PIs (ATV, DRV) (Table 230).

Table 230. Activity of Different Classes of Antiretrovirals Against Viruses With Substitutions That Decrease Temsavir Susceptibility (Report 2018n371420, page 4)

Inhibitor Class		wt	S375M		M426L		M426L/M475I	
	Compound	EC_{50} (nM)	EC_{50} (nM)	FC (vs wt)	EC_{50} (nM)	FC (vs wt)	EC_{50} (nM)	FC (vs wt)
Entry	temsavir	0.2 ± 0.03	63.5 ± 27.8	317.5	41.5 ± 14.5	207.5	>10000	>50000
	Ibalizumab	0.2 ± 0.1	0.3 ± 0.2	1.5	0.2 ± 0.1	1	0.1 ± 0.03	0.5
	enfuvirtide	15.9 ± 7.3	39.6 ± 9.9	2.5	7.2 ± 3.1	0.5	13.7 ± 5.7	0.9
NRTI	tenofovir	0.9 ± 0.4	0.3 ± 0.01	0.3	0.4 ± 0.2	0.4	0.5 ± 0.1	0.6
	abacavir	74.6 ± 66.2	86.2 ± 10.3	1.2	60.1 ± 27.9	0.8	63.2 ± 36.8	0.8
NNRTI	rilpivirine	0.3 ± 0.01	0.2 ± 0.1	0.7	0.1 ± 0.03	0.3	0.1 ± 0.02	0.3
	efavirenz	0.2 ± 0.1	0.1 ± 0.1	0.5	0.1 ± 0.03	0.5	0.2 ± 0.1	1
PI	darunavir	2.2 ± 1.2	2.9 ± 1.4	1.3	1 ± 0.2	0.5	2.4 ± 1.3	1.1
	atazanavir	0.8 ± 0.2	0.3 ± 0.2	0.4	0.7 ± 0.4	0.9	0.5 ± 0.4	0.6
INI	raltegravir	1.1 ± 0.1	1.9 ± 1.2	1.7	0.9 ± 0.4	0.8	1.8 ± 0.3	1.6

Source: N66632-7
Abbreviations: EC_{50}, half maximal effective concentration; FC, fold change; INI, integrase strand inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; wt, wildtype.

Susceptibility of NNRTI, NRTI and PI-Resistant Viruses to Temsavir in a Phenotyping Assay

Monogram Biosciences has developed a Phenosense assay for HIV-1 ENs that allows for evaluation of entry class inhibitors in a controlled assay system. Using cloned EN genes, pseudotyped viruses are generated with a luciferase-based proviral vector, which allows for the evaluation of the sensitivity of the ENs to various classes of entry inhibitors. A cohort of 50 pseudotyped viruses from subjects who had failed NNRTI, NRTI, or PI regimens was analyzed for their susceptibility to TMR. MVC was used as a control in these studies. The wide range of susceptibilities observed with TMR against clinical isolates is also present in this cohort (range 0.052nM to 72.6nM). The absolute EC_{50} values are lower than that observed for the clinical isolates, which is probably a function of the use of a pseudotype assay with a luciferase readout compared to a whole virus assay with a p24 endpoint for clinical isolates. The data show many NNRTI, NRTI and MDR isolates are sensitive to TMR, so there is likely no cross resistance between other drug classes with TMR.

19. Clinical Virologic Resistance Supplementary Materials

19.1. Association Between EN Genotype and Susceptibility in Subjects Enrolled in the 8-Day Monotherapy Study of TEM

In an 8-day monotherapy study of treatment-naïve and treatment-experienced HIV-1-infected subjects (all with subtype B infection), prodrug BMS-663068 was administered QD or BID with or without RTV, resulting in maximum median decrease in HIV-1 RNA from baseline ranging from 1.21 to 1.73 log_{10} copies/mL. Reduced response to TMR was associated with EC_{50} values of >100nM to TMR using the PhenoSense® Entry assay (Monogram Biosciences, San Francisco, CA). Baseline population genotypes and phenotypes from all subjects in the 8-day monotherapy study were evaluated for amino acid substitutions that could account for the lack of response or phenotypic resistance observed for some subjects. Substitutions at amino acid positions 116, 204, 375, 426, 434, and 475 were shown to confer lack of susceptibility to TMR in cell culture (Table 231).

Table 231. EN Substitutions in Subjects with Changes at Key Sites and Susceptibility to Temsavir (Report 2017n338507, page 13)

Subject ID	PhenoSense[a] Entry Baseline IC_{50} (nM)	HXB2 Position	116	204	375	426	434	475
		B Consensus	L	A	S	M	M	M
		AI Selected substitution	P	D/V	I/N	L	I	I
Subjects with EC_{50}>100nm								
48	>10,000				T	L		
5	5291.6					L		
41	1356.9				M		I	
16	2817.5					L		I
54	386					L	I	
1	300					L		
70	271					L		
21	16.35					L		
Subjects with EC_{50}<100nm								
12	11.5				H	R		
48	>10,000				T	L		

Source: ELN 90739-100
[a] All subjects with IC_{50} 100nM are listed; only subjects with IC_{50}<100 Nm and changes at the listed sites are included
Abbreviations: IC_{50}, half minimal inhibitory concentration; EN, envelope; FC, fold change.

Envelopes with the substitutions at positions 375, 426, 434, and/or 475 generally yielded higher baseline EC_{50} values in the PhenoSense® Entry assay than ENs from the study that did not contain any of these changes. M426L was present in the gp120 gene of six of seven subjects with EC_{50} value >100nM at baseline. The seventh subject had both S375M and M434I. Six of these seven subjects were nonresponders in the BMS-663068 monotherapy study, with only Subject 5 with the substitution M426L and EC_{50} value of ~5,300nM responding to treatment. In contrast, 2 of 39 subjects had these baseline substitutions but had EC_{50} values ≤100nM) at baseline; Subject

21 had the M426L substitution and an EC_{50} value of ~16nM, while Subject 12 had an S375H substitution and exhibited an EC_{50} value of ~11nM.

A single functional EN clone from each subject was selected for further analysis. Each clone was selected because it exhibited a large decrease in susceptibility to TMR, with FCs ranging from 143 to >20,000. These functional EN clones were then back-mutated to the subtype B consensus sequence at the identified amino acids, and the change in susceptibility to TMR was determined in a cell-cell fusion assay. In all the cases, ENs that only contained the back substitutions resulted in improved susceptibility (Table 232), and demonstrated that M426L is a major determinant of reduced susceptibility in these ENs, and substitutions M434I, S375T, and M475I also contributed to decreased susceptibility of the EN to TMR.

Table 232. Changes in Temsavir Susceptibility Before and After Back Mutation in EN Clones from Subjects With Temsavir EC_{50} Values >100nM at Baseline in Cell-Cell Fusion Assay (Report 2017n338507, page 15)

	Cell Fusion Assay FC-EC_{50}			
		Sequence Following Back Mutation (Change Compared with Original Clone)		
Subject	**Original Clone**			
1				
Substitution	L426[a]			M426
FC-EC_{50}	466			9
5				
Substitution	L426[a]			M426
FC-EC_{50}	1225			3
70				
Substitution	L426[a]			M426
FC-EC_{50}	143			2
16				
Substitution	L426[a]/I475[a]	L426[a]/M475	M426/I475[a]	M426/M475
FC-EC_{50}	3043	44	9	1
41				
Substitution	M375[a]/I434[a]	M375[a]/M434	S375/I434[a]	S375/M434
FC-EC_{50}	19, 429	1508	59	12
48				
Substitution	T375[a]/L426[a]	T375[a]/M426	S375/L426[a]	S375/M426
FC-EC_{50}	>20,000	436	>20,000	47
54				
Substitution	L426[a]/I434[a]	L426[a]/M434	M426/I434[a]	M426/M434
FC-EC_{50}	>20,000	2405	14	3

Source: ELN 90739-005, -008, -009, -019, -041, -042
[a] Indicate changes from the consensus sequence;
Abbreviations: EC_{50}, half maximal effective concentration; EN, envelope; FC, fold change.

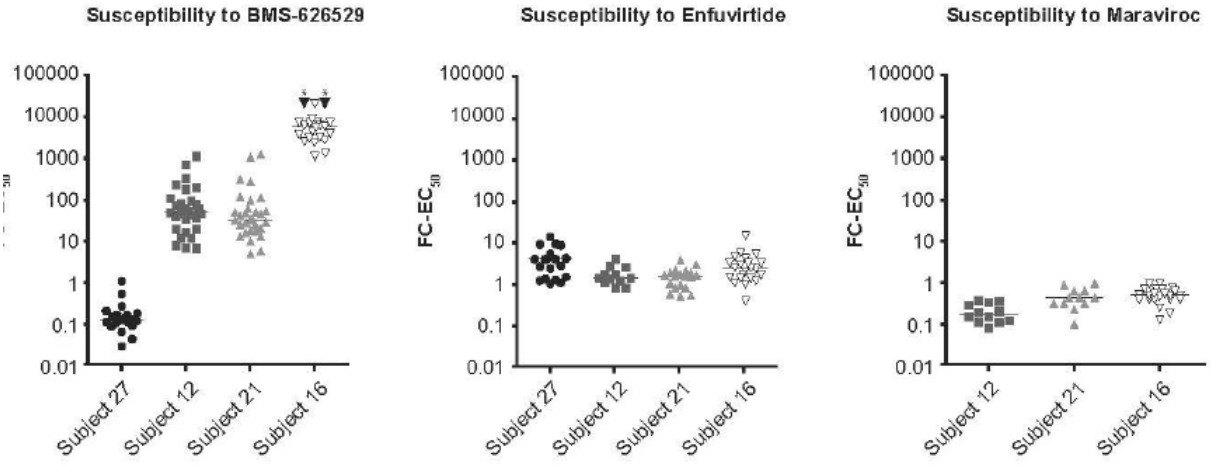
Overall, the presence of the EN resistance substitutions at baseline correlated, with some exceptions, with susceptibility of baseline samples and subsequent response to treatment.

The presence of M426L in gp160 was associated with nonresponse (defined as <1 log_{10} copies/mL maximal decline in HIV-1 RNA) but did not preclude a response in two subjects with M426L in gp120 at baseline.

19.2. Intrasubject Variability in Temsavir Susceptibility

Multiple functional clones from four individuals from the 8-day monotherapy trial with varied baseline TMR EC_{50} values were examined, and each exhibited a broad spectrum of susceptibility to TMR, with FCs in TMR EC_{50} values ranging between 2 to 3 log_{10}. Twelve functional clones from the responder Subject 12 (each clone contained the S375H substitution) exhibited FCs of 7 to 1,138 (Figure 23). Subject 21 was also a responder containing the M426L substitution and 30 functional clones from this subject showed FCs that varied widely between 5 and 1,232. Subject 27 was a responder with a very low baseline EC_{50} value of 0.018nM in the PhenoSense® Entry assay; 19 functional clones from Subject 25 exhibited a wide range in EC50 values, 0.03 to 1.1. Finally, Subject 16 was a nonresponder with both M426L and M475I substitutions and all 22 clones had high EC50 values with FCs ranging from 1,151 to >22,288. The variability in TMR susceptibility was substantially less than the variability observed in the same clones for the entry inhibitors MVC and ENF (Figure 23). Thus, viral ENs not only exhibit a wide range of susceptibility to TMR throughout the population, but also within an infected individual there is a 2 to 3 log_{10} variation in susceptibility within different cloned ENs. Since the signature substitutions in these individuals were present in all examined clones, this suggests that susceptibility to TMR of EN clones containing signature substitutions is context dependent.

Figure 23. Intrasubject Variability of Susceptibility of Envelope Clones to Temsavir, Enfuvirtide, and Maraviroc



	FC-EC_{50}, range			
	Subject 27	Subject 12	Subject 21	Subject 16
BMS-626529	0.03–1.08	7–1138	5–1232	1151–>22288
Enfuvirtide	1.02–13.45	0.75–3.87	0.47–3.68	0.38–5.48
Maraviroc		0.08–0.34	0.1–0.9	0.13–0.89

Source: Report 2017n338507, page 18
Abbreviations: EC_{50}, half maximal effective concentration; FC, fold change.

19.3. Prevalence of EN Polymorphic Sites

The Applicant performed analyses to determine the natural prevalence of the 6 amino acid positions (L116, A204, S375, M426, M434, M475) in gp160 that have been shown to decrease susceptibility to TMR within the population with HIV-1. The LANL database, with the 2018 update containing sequence published through the end of 2017, was used to screen for polymorphisms present at any of the 6 amino acid positions in gp160 in the population and within specific subtypes. A total of 5,454 full-length HIV-1 EN sequences from 189 different subtypes/groups were available with 6 subtypes making up 78% of the database: subtype B viruses, 36% (1,937 isolates); subtype C, 25% (1377 isolates); CRF01_AE, 9% (481 isolates); subtype A1, 4% (220 isolates); CRF02_AG, 2% (133 isolates); and subtype D, 2% (116 isolates).

A summary of the overall prevalence as well as the prevalence in Subtype B is shown in Table 233. The 116 and 204 positions are highly conserved as 99.5% and 97.5% of the sequences are L116L and A204A, respectively. At position 375, S375S is most prevalent making up 76% of the isolates, with S375H present in 11% and S375T in 9% of the isolates. The vast majority of the S375H containing isolates derive from subtype CRF01_AE (476 of 481 isolates) and group O (26 of 27 isolates). At position 475, M475M-containing viruses make up 90.5% of the database, with 482 (8.8%) of isolates containing M475I. However, the majority of the M475I isolates originate from 4 subtypes: CRF01_AE (371/481 total isolates), subtype 01B (21/44), subtype 01BC (7/17), and subtype 107 (7/14). At position 434, M434M-containing viruses make up 87.8% (4,788 isolates) of the database, with M434I the next most prevalent, with 10.2% (556 isolates). The distribution of M434I within the different subtypes is broad and the prevalence in subtype B is 4.8% (93 isolates). At position 426, M426M-containing viruses were the most prevalent, constituting 83% (4,533 of 5,454 isolates) of the database. M426R was next most prevalent, making up 8.8% (482 of 5454 isolates); however, a M426R change in the LAI EN did not affect the susceptibility to TMR. M426L, a polymorphism known to affect susceptibility to TMR, was next in prevalence, with 291/5,454 isolates (5.3%) containing this change. M426L also exhibited a broad distribution among the different subtypes/groups.

Subtype B

In subtype B isolates (n=1,937), there were no observed L116P- or A204D-containing isolates. The M434T and M434V polymorphisms, which have observed FCs of 15-fold and 7.5-fold, respectively, make up <1% of total isolates (Table 233). The M475I, M475L, and M475V polymorphisms, which confer 11-, 17-, and 9.5-FCs, respectively, are present in ~1.5% of the isolates. M426 and S375 have lower consensus frequencies (67.8% and 75.1%, respectively) than the other 4 sites in subtype B. However, the only polymorphism at the M426 site that produces a noteworthy FC in the LAI EN is M426L, with a 98-FC, and it is present in 7.8% of the subtype B isolates. In the FTR clinical trials, a single M426P polymorphism was observed in a subtype B virus at baseline and induces a 6.1-FC in the LAI gp160 context, but this polymorphism is not present in subtype B viruses in the LANL database. Also, an M426V polymorphism was observed in two subjects: 1 subtype B subject possessed an M425I/V mixture, while a second subtype AG subject contained M426V and M434I. M426V is found at a 0.3% prevalence (17 of 5,454 isolates) within the entire LANL database and produces a 3.3-FC in the LAI gp160 gene.

Polymorphisms S375I, S375M, and S375H, which confer 17- to 48-fold decreased susceptibility to TMR make up 3.4% of the isolates. There were two additional polymorphisms observed as mixtures in baseline samples in the Phase 3 FTR trial that were not found in subtype B viruses in the LANL database. S375V was observed in a subtype C subject, while an S375S/Y mixture was observed in a subject infected with a BF1 isolate. When S375V and S375Y were examined in the context of the LAI gp160, these polymorphisms produced a 5.5- and >10,000-FC in susceptibility, respectively.

Table 233. Summary of Natural Prevalence at Amino Acid Sites L116, A204, S375, M426, M434, M475 in LANL HIV Database

Amino Acid Site	% of Isolates	Predominant Subtypes	Prevalence in Subtype B	Fold Change In EC_{50} value
L116L	99.5%		99.6%	1
A204A	97.5%		97.4%	1
S375S	75.5%		75.1%	1X
S375H	10.7%	CRF01_AE, group O, subtype 01B, subtype 01BC, subtype 107	0.5%	48X
S375T	8.9%		16.9%	1X
S375I	1.3%		1.9%	17X
S375M	1.2%		1%	47X
M426M	83.1%	Subtype B and C	67.8%	1
M426R	8.8%		22%	0.86
M426L	5.3%	Broad	7.8%	98
M426V	0.3%		<0.1%	3.3
M434M	87.8%		94%	1
M434I	10.2%	A1, A1D, A1CD A1C, CRF01_AG	4.8%	2
M434T	0.6%		0.8%	15
M434V	0.4%		0.1%	7.5
M475M	90.5%		98.2%	1
M475I	8.8%	CRF01_AE, subtype 01B, subtype 01BC, subtype 107	1.3%	11
M475L	0.1%		0.1%	17
M475V	0.1%		0.1%	9.5

Source: FDA derived from Report 2018n388686
Abbreviations: EC_{50}, half maximal effective concentration.

Double Polymorphisms

Additionally, the prevalence of isolates containing key polymorphisms at any two of the four targeted amino acids S375, M426, M434, and M475 was assessed (Report 2018n391589). The prevalence of two key polymorphisms within the same gp160 gene is generally low. An exception is S375H and M475I, which is found in 7.6% of the LANL population. This is due to the high prevalence of the double polymorphism in subtype CRF01_AE isolates, where 369 isolates (6.8% of the LANL database population) contain this genotype. Excluding the S375H, M475I , S375T, and M434I double polymorphs, the total prevalence of all the other double polymorphs add up to 2.94%. Each double polymorphism was analyzed for susceptibility to TMR in a cell-cell fusion assay. Generally, double polymorphisms resulted in higher fold changes in EC_{50} values towards TMR, especially in ENs containing either S375H/M or M426L

plus one other polymorphism. Many of these combinations exhibited a >100-fold change up to >20,000-fold change in susceptibility to TMR.

Subtype AE

Envelope sequences of 754 CRF01_AE viruses from the LANL database were compared with the subtype B consensus sequence at positions potentially associated with resistance to TMR. At EN positions 116, 204, 426, and 434, subtype B and CRF01_AE had identical consensus residues, whereas consensus residues differed between the two subtypes at positions 375 and 475. Of 754 CRF01_AE EN sequences examined, 751 (99.6%) contained S375H and 580 (76.9%) contained M475I. Of the available sequences of CRF01_AE clinical isolates previously shown to have reduced susceptibility to TMR, 7/8 possessed 375H, while 4/4 isolates also contained 475I (complete sequences were not available for all eight viruses). Site-directed mutagenesis and reverse genetic clones analyzed in cell-cell fusion assays show that both 375H and 475I contribute to the inherent resistance of CRF01_AE strains.

19.4. Effect of Screening EN RAPs on Response

Table 234. Log_{10} Decline at Day 8 by Screening EN RAPs: Randomized Cohort

EN RAP	N	Mean log_{10} Decline in VL: BL to Day 8	Median log_{10} Decline in VL: BL to Day 8	N	Mean log_{10} Decline in VL: BL to Day 8 As-Treated[a]	Median log_{10} Decline in VL: BL to Day 8 As-Treated[a]
Overall	198	0.87	0.91	151	0.93	1.05
No EN RAPs	84	0.94	0.92	63	1.05	1.08
Any change at S375, M426, M434, and M475	114	0.82	0.87	88	0.85	1.03
Predefined EN RAPs: S375H/I/M/N/T, M426L, M434I, and M475I	87	0.74	0.67	66	0.76	0.7
M426L	22	0.57	0.37	19	0.48	0.19
S375H or M	6	0.38	0.16	5	0.46	0.32
M475V or I	2	0	0	1	0	0
M434I	9	0.86	1.04	5	0.89	0.66
S375M, M426L, M434I, and M475I/V	86	0.74	0.66	27	0.53	0.14
S375M, M426L, and M475I/V				24	0.46	0.17
S375M, M426L, M475I/V and A281E/F/H				25	0.44	0.14
With any RAPs L116, A204, V255, or A281	72	0.78	0.79	57	0.83	0.85
Without RAPs L116, A204, V255, or A281	118	0.92	1.05	87	1.00	1.11

Source: Clinical Virology Reviewer's analysis
Note: An S375T or N does not appear to affect response even in present of M426L
Predefined EN RAPs: S375H/I/M/N/T, M426L/P, M434I/K, and M475I
[a] Removed subjects who were <400 copies/mL at Screening or >0.4 log_{10} decline Screening to Baseline.
Abbreviations: BL, baseline; EN, envelope; RAP, resistance-associate polymorphism; VL, viral load.

Table 235. Outcome of Randomized FTR Cohort (Response >0.5 Decline Day 8) by Presence of Screening EN RAPs

EN RAP	Response Rate at Day 8 (>0.5 decline) N=198	Response Rate at Day 8 (>0.5 decline) As-Treated Analysis[a] N=151
Overall	132/198 (67%)	107/151 (71%)
No EN RAPs	61/84 (73%)	51/63 (81%)
Any change at S375, M426, M434, and M475	71/114 (62%)	56/88 (64%)
Predefined EN RAPs: S375H/I/M/N/T, M426L/P, M434I/K, and M475I	50/87 (42%)	37/67 (55%)
M426L, S375M, M475V	11/27 (41%)	8/24 (33%)
S375M, M426L, M434I, and M475V	16/36 (44%)	10/28 (36%)
M475I or V	0/2	0/1
M434I, V or T	8/14 (57%)	6/11 (55%)
M434I or I/V	5/9 (56%)	3/6 (50%)
M434T	3/5 (60%)	3/5 (60%)
M426R, L, K, I/V	45/70 (64%)	36/54 (67%)
M426R	31/43 (72%)	25/30 (83%)
M426L	10/22 (45%)	7/19 (37%)
M426K	3/4 (75%)	3/4 (75%)
M426I/V	1/1	1/1
S375T, N, M, I or Y	39/63 (62%)	32/49 (65%)
S375T	25/35 (71%)	21/27 (78%)
S375N	12/20 (60%)	11/17 (65%)
S375M	0/4 (0%)	1/5 (20%)
S375H	0/1 (0%)	-
S375I	2/2	2/3 (67%)
S375S/Y	0/1 (0%)	0/1
Two RAPs	21/33 (64%)	18/25 (72%)
Three RAPs: S375T/M426R/M434M/T	0/1 (0%)	0/1 (0%)
	N=190	**N=144**
With any change at L116, A204, V255, or A281	46/72 (64%)	37/57 (65%)
Without change at L116, A204, V255, or A281	82/118 (69%)	66/87 (76%)
L116K	1/1	1/1
A204T/S	6/8 (75%)	5/6 (83%)
V255I/A/M	6/9 (67%)	6/8 (75%)
A281T/V/S/Q/E/F	25/45 (56%)	27/45 (60%)
A281T	14/23 (61%)	16/25 (64%)
A281V	8/15 (53%)	9/15 (60%)
A281S	1/2	1/2
A281Q	1/1	1/1
A281E/F/H	0/3	0/2

Source: Clinical Virology Reviewer's analysis
[a] Removed subjects who had <400 copies/mL at Screening or >0.4 $\log_{10}$ decline Screening to Baseline
Abbreviations: EN, envelope; FTR, fostemsavir; RAP, resistance-associate polymorphism.

The presence of polymorphisms S375M, M426L, and M475V at Screening showed lower declines in HIV-1 RNA at Day 8 with median $\log_{10}$ declines of 0.32, 0.19, and 0, respectively. Subjects with M426L at Screening are listed in Table 236 and subjects with S375M or M475V resistance-associated polymorphisms (RAPs) at Screening are listed in Table 237 with data on outcome at Day 8, HIV-1 RNA decline at Day 8, fold change in FTR susceptibility at Screening, other EN RAPS present at Screening and predose concentrations on Day 8.

Table 236. Subjects With M426L in As-Treated Dataset of RAND FTR Subset

PID	Day 8 Success Y/N	Day 8 Decline in HIV-1 RNA	FTR Fold Change at Screening	Other EN RAP at Screening	Predose Concentration on Day 8 (ng/mL)
AI438047.000034	N	0	2	A218T	300
AI438047.000082	N	0.19	42		370
AI438047.000089	N	0	1,009	A218T	135
AI438047.000099	N	0	22		418
AI438047.000113	N	0.14	38		285
AI438047.000116	N	0.41	294		374
AI438047.000201	Y	1.2	723	S375N	1,060
AI438047.000247	Y	1.29	3,963	S375S/N/T	2,320
AI438047.000252	Y	1.2	104	A218T	1,180
AI438047.000300	N	0	390		532
AI438047.000393	Y	1.92	5,809	S375T	166
AI438047.000394	N	0.009	6,391	A281T, S375S/Y	948
AI438047.000417	Y	0.64	50		2,710
AI438047.000513	Y	0.67	2		792
AI438047.000539	N	0.03	6,651		-
AI438047.000602	Y	1.1	2,064	S375S/T	38
AI438047.000611	N	0	234	A281T	142
AI438047.000630	N	0.02	2,605	A281T	884
AI438047.000655	N	0.32	4,968	A281F/H, S375I/M	636

Source: Clinical Virology Reviewer's analysis
Abbreviations: EN, envelope; FTR, fostemsavir; PID, patient identifier; RAP, resistance-associate polymorphism.

Table 237. Subjects With S375H or M and/or M475V or I in As-Treated Dataset of RAND FTR Subset

PID	RAP	Day 8 Success Y/N	Day 8 Decline in HIV-1 RNA	FTR Fold Change at Screening	Other EN RAP at Screening	Predose Concentration on Day 8 (ng/mL)
AI438047.000027	M475M/V	N	0	0.25	A281V	80
AI438047.000040	S375S/M				A281A/V	161
AI438047.000078	S375M/T, M426R	Y	1.53	2.54	V255V/I, A281A/T	1,550
AI438047.000561	S375M	N	0	716		1,960
AI438047.000638	S375M	N	0.44	5,159.92		227
AI438047.000655	S375I/M, M426L	N	0.32	4,968	A281F/H	636

Source: Clinical Virology Reviewer's analysis
Abbreviations: EN, envelope; FTR, fostemsavir; PID, patient identifier; RAP, resistance-associate polymorphism.

19.5. Virologic Failure Listings

Table 238 lists the subjects in the randomized FTR group who were virologic failures at Day 8 (<0.5 $\log_{10}$ decrease in HIV-1 RNA) and indicates whether they were a virologic failure post Day 8. The Screening FTR FC in susceptibility is shown for each of these subjects along with emergent resistant-associated substitutions (RASs) and FTR fold change in susceptibility at post Day 8 virologic failure.

Table 238. Emergent EN RASs at Virologic Failure in Day 8 Virologic Failures in BRIGHTE Trial: Randomized FTR (n=65)

PID	Day 8 Decline In HIV-1 RNA	Screening EN RAP	VF post Day 8? Y/N; TIMEPT of Virologic Failure	EN RASs at Virologic Failure	Screening FTR FC	FTR FC at Virologic Failure
4	0	M434M/I/V	NO		2.38	
8	0		Y; WK16	M434M/L	0.18	0.25
27	0	M475M/V	Y; WK 48	S375S/N, M434I, M475V	0.25	**1142**
34	0	M426M/L	NO		2.08	
35[a]	0	S375T, M434I	NO		29	
40	0	S375S/M	Y; WK 132		1.26	**586**
50	0.39	S375T	Y; WK12	NO POST BL	0.5	
67	0.16	NONE	NO		0.13	
82	0.19	M426L	NO		42	
89	0	M426L	NO		1,009	
90[a]	0.18	M426R	Y; WK60	M426R	0.12	0.2
99	0	M426L	Y; WK36	M426L	22	88
100	0	S375T, M426R	N		1.11	
103[a]	0		N		0.25	
104	0	S375T	Y; WK36	S375S/M/T, M426M/L, M434M/I	1.44	5670
113	0.14	M426L	Y; WK36	M426L	38	26
116	0.41	M426L	N		294	
125	0.28		N		0.9	
184	0.44		N		0.28	
208	0.35		N		0.49	
209	0.07	S375N	N		72	
212	0.17		Y; WK24	S375N	3.52	1318
229[a]	0	S375T, M426R	N		0.2	
243[a]	0.32		N		1.47	
244[a]	0.45		N		0.17	
265[a]	0		N		0.13	
268[a]	0	M426R	N		0.18	
300	0	M426L	N		390	
312	0.32		N		2.66	
323	0	S375T, M434M/T	N		3.45	
358	0	S375H, M475I	N		4747.44	
371[a]	0.28	S375S/N	N		11	
386	0		N		2.67	
394[a]	0.009	S375S/Y, M426L	N		6390.67	
415	0		N		0.31	
423[a]	0	S375S/Y, M426M/R	Y; WK8	S375S/Y, M426M/R	0.39	NR
428	0	S375N, M426K	N		415	
430	0.12	S375S/N	Y; WK36	S375S/N, M426L	1.08	2339

PID	Day 8 Decline In HIV-1 RNA	Screening EN RAP	VF post Day 8? Y/N; TIMEPT of Virologic Failure	EN RASs at Virologic Failure	Screening FTR FC	FTR FC at Virologic Failure
432[a]	0		Y; WK108		2.64	1.9
460	0	M434I	N		928	
483	0.43		N		17	
498	0		N			
527[a]	0.41		Y; WK48		0.32	0.19
539	0.03	M426L	Y; WK24	M426L	6,651.28	4,271
545[a]	0.37		N		1.55	
549[a]	0.33	S375T, M426T	N		1.23	
561	0	S375M	Y; WK36	S375M	716	988
586	0		Y; WK24		0.21	0.27
607	0	M434M/I	N		2.13	
611[a]	0	M426L	N		234	
612[a]	0.31	S375N, M426R	N		13	
620	0	S375N	N		0.72	
630	0.02	M426L	N		2605	
638	0.44	S375M	N		5,159.92	
654[a]	0.02	M426R	N		0.06	
655[a]	0.32	S375I/M, M426L	N		4,967.86	
668[a]	0.41		N			
673[a]	0	S375T	N		25	
684	0.29	S375T, M426R, M434M/R	Y; WK36	S375T/N, M426R, M434M/T/I, M475M/I	2.58	21
694[a]	0	S375S/N	N		0.53	
709	0.21	M426R	N		0.36	
755[a]	0		Y; WK24		0.73	0.7
760	0.07	S375T, M426R	N		0.75	
774	0.42		N		0.93	
783	0.33	M426R	N		0.11	

Source: Clinical Virology Reviewer's analysis
[a] Subjects who were not eligible (<400 copies/mL at Screening and/or Baseline; OSS ≤2)
Abbreviations: BL, baseline; EN, envelope; FC, fold change; FTR, fostemsavir; NR, not reported; PID, patient identifier; RAP, resistance-associate polymorphism; RAS, resistant-associate substitution; VF, virologic failure; WK, week.

Virologic failures from Phase 3 trial 438047 are shown in each group: Randomized FTR (n=51) (Table 239), randomized placebo (n=18) (Table 240), and nonrandomized FTR group (n=50) (Table 241).

Table 239. Virologic Failures in BRIGHTE Trial: Randomized FTR Group (n=51)

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
008									
	Screen	117,382	0		0.18				DTG 1.1 TPV 1.4
DTG TPV/R	WK16	216,174		**M434M/L,** V200V/T, T240K/N, E269E/G, V275A/S, S291I/T, T373K/M	0.25				DTG 1.57 TPV 1.32
027									
	Screen	761,24	0	M475M/V	0.25				ENF 2.3 ETR 0.41 DTG 1.8
DTG ETR ENF	WK48	889		**M434I, M475V**, D113E, T236M, M474N	**1,142**		**M50I**		**ENF 46** **ETR >139** **DTG 11**
040									
	Screen	152,432	0	S375S/M	1.26	**L100I, K103N, Y181I**	G140S, Q148H, M154L		ENF 1.2 DTG 9.6 RPV 0.1 **TDF 2.4**
DTG ENF RPV TDF	WK 132	4,605		NO POST BL	**586**		**L74L/M, T97T/A,** G140S, Q148H, M154L		**ENF 202** **DTG 18** **RPV >64** **TDF 5.9**
050									
	Screen	1,295	0.39	S375T	0.5				DTG 2 **FTC >65** MVC R5 TDF 0.6
DTG FTC MVC TDF	WK 12	4,554		NO POST BL	NR				DTG 3 **FTC >60** TDF 0.5

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
052									
	Screen	38,289	1.7	S375T, L86M	0.84			V82T	DTG 1.2 **DRV 61**
DRV/R DTG	WK36	250		S375T, V 68I, L86I, D113**D/E,** N280N/S, Q442P	0.92			I54V, V82A	DTG 1.6 DRV 9.5
076									
	Screen	23,318	1.25	M426I/V, N80N/S, T202K, S446S/L, L452I/M	2.5				DTG NR DRV/R NR TDF NR ATV NR ENF 1.8
DRV DTG/R TDF ATV ENF	WK16	2,092		**M426I**, N80S, T202E, M446L, L452I	**263**		T97A, E138D, G140S, Q148H		**DTG 19** **DRV/R 48** TDF 1.8 **ATV 7.7** ENF 1.1
080									
	Screen	42,582	2.7		0.62				
DTG MVC AZT	WK60	48,733		NO POST BL	NR	NO POST BL	NO POST BL	NO POST BL	NO POST BL
086									
	Screen	22,348	1.1	S440Q, S446T	0.72		T97A, E138T, G140S, Q148H		**DTG 17** **DRV/R 21** FTC 1.2 TDF 0.71
DTG DRV/R FTC TDF	WK24	78,877		**S375N, M426L, V255V/I,** E293E/G, S440K/Q, S446I/T, N448N/S	**5,472**				**DTG >205** **DRV/R 38** FTC 0.91 TDF 0.63

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
090									
	Screen	205,030	0.18	M426R, D62D/N, V87V/A, K130D/N, E268E/K, T283N/V, S446I/V, G471A/I	0.12				DTG 1.9 DRV/R 0.25 ETR 0.58
DTG DRV/R ETR	WK60	154,074		M426R, Y61H, D62N/S, V87A/G, N94N/D, K97K/R, K130D/E, I225I/L, E268K, T283V, N293E/V, V372V/A, S440N S446I/L, G471I	0.2				DTG 1.5 DRV/R 0.61 ETR 0.59
099									
	Screen	557,636	0	M426L, K130K/N/S, T202T/V, T278T/S, D279D/N, I423I/V, S440E/R	**22**				DTG 1.1 DRV/C 0.81
DTG DRV/C	WK36	4,816		M426L, K130S, T202V, T278S, D279N, I423V, S440E, K502K/R	**88**				DTG 1.3 DRV/C 0.18
101									
	Screen	50,925	0.82	K130H/N, S291P/T E293E/K, T373M/R K429E/Q, R444R/N	0.58	M41L, D67N V75I, E138A M184V			**FTC >82** TDF 1.2 RPV 0.39
FTC TDF RPV	Week 12	3,729		**S375S/N, M426L,** E47E/D, D113E, K130N, S291T, E292K, T373M, K429E, R444N	**3,430**	K101K/Q, K103K/R, G190G/E K219N			**FTC >100** TDF 1.35 **RPV >85**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
104									
	Screen	642,233	0	S375T, T63A, T283V	1.4	D67S, K70R, L74V, M184V, T215F, K219E			ENF 2 **TDF 2**
ENF TDF	Week 36	432,760		**S375S/M/T, M426M/L, M434M/I,** T63A/S, **D113D/E**, **L175Y**, T202T/K, Y217Y/F, E268E/K, T283I/V, K421K/R, I423I/F, M424I/V, M443I/L, L452L/M, D476R/K	**5,670**				**ENF 48** **TDF 3.5**
113									
	Screen	1,007	0.14	M426L	**38**	D67D/N, K70K/R, T215A/I/V, K219K/E	T97T/A, K143Y/C, E157E/Q		DTG 1.3 FTC 1.2 TDF 0.84
DTG FTC TDF	Week 36	737 suppressed at WK72		M426L, V84V/I, L226L/I, **D474D/N**, L494L/V	**26**		E157E/Q		DTG 0.85 FTC 0.78 TDF 0.85
152									
	Screen	69,020	1.31	S375T, M434I, N230N/D, T240K/R, S446S/A	2.5		E138A, G140S, Q148H, G193E		ENF 0.98 DTG 7.1
DTG ENF	Week 24	12,984		**S375T, M426L,** I225I/M, N230D, T240R, S446A	**595**		L74L/M, T97T/A		**ENF 1048** **DTG 85**
154									
	Screen	119,226	1.05		0.14	L74I, E138E/G, M184V, T210W, T215Y			DTG 1.01 **FTC 72** ETR 0.13 **TDF 3.14** **AZT 171**
DTG FTC ETR/C TDF AZT	Week 48	91,772		N94N/D, N229N/K	0.1				DTG 1.2 **FTC 78** ETR 0.15 **TDF 4.34** **AZT 976**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
161									
	Screen	47,369	1.08	S375S/N/Y, M434M/T, E62D/E, A204A/T	**46**	D67N, K70R, T215I, K219Q		V32I, L33F, M36I, I47V, A71V, V82V/I	ATV 1.97 DTG 2.6 FTC 4.3 TDF 1.1
ATV/r DTG FTC TDF	Week 24 and 84	11,857		**S375N,** A48A/T, D62E, A204T	**19**			V32I, L33F, M36I, I47V, A71V, V82V/I, **G73G/S**	ATV 7.8 DTG 2.2 FTC 4.1 TDF 1.04
163									
	Screen	212,346	1.25	D113K	1.7			M46I, I54V, V82A	DRV 0.6 DTG 0.98
DRV/R DTG	Week 36	206,707		K421K/R, D113K	2.7				DRV 0.5 DTG 1.2
189									
F1	Screen	1,177,134	1.5	D99D/N, T232M/R	0.99			V32I/V, M46M/I I47I/V, A71A/T	DTG 1.8 SQV 0.9
DTG SQV/R	Week 24	598,800		**S375N, M426M/L**, D99N, **D113D/E**, T232R, T236T/S	3.3		H51H/Y, T97T/A, S147S/G, V151V/I, N155H, K156K/N		**DTG 5.7** SQV 0.45
190									
	Screen	780,402	0.56	S375N, T232K/R, R419K	1.3				FTC 0.75 TDF 0.7 DTG 1.5 DRV 0.31
FTC TDF DTG DRV/R	Week 16	2,020,635		**S375H/N, M426M/L**, T232R, S256S/T, R419K/N	**142**				FTC 0.78 TDF 0.6 DTG1.5 DRV 0.24

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
195									
	Screen	3,038,951	0.7	S128T, K130S, V208M/T, N229R, T236S, E293Q	0.16	D67N, K70R, M184V, T215T/I, K219E	L74L/M, T97T/A, G140S, Q148H		ENF 0.8 **FTC 75** TDF 0.71 **DTG 59**
DTG FTC TDF ENF	Week 24	1,873,479		**M426L**, T63K, **D113D/E, L175I,** Q114E, S128A/T, K130N, T198S, V200T, V208I, N229K/R, T236L/S, R252R/K, V270I, T278S, T283N, I285L, E293A/V, P369L, K421R, I439I/T	**4,664**				**ENF 38** **FTC 60** TDF 0.64 **DTG 80**
203									
	Screen	218,495	0.78	M434T, K429E	9.27	M41L, L74V, M184V, T215Y		L74M, E92Q, V151I, E157Q G193E	**ABC 6.9** **LAM 124** TDF 0.6 DTG 4.21
ABC LAM TDF DTG MVC	Week 12	25,474		**S375S/N, M426L,** M434M/T, K97K/E, E102E/D, I108I/V, S110S/N, V208V/M, S209S/T, K231K/R, T244S, E268E/R, D279D/N, K282K/D, T290T/K, I423I/F, I424I/V, K429E/Q, L452L/S, **D474D/N**, R476R/K, K502K/R, V505M/T	**6,651**			**L63L/I,** L74M E92Q, V151I E157Q, **S147G** G193E	ABC **5.4** **LAM 74** TDF 0.5 **DTG 29**
212									
	Screen	11,023	0.17		3.5	D67G, K70Q/P/T, M184V, T215D			DTG 0.97 **FTC 84** **TDF 2.2**
DTG FTC TDF	Week 24	578,696		S375N, **D113E**	**1,318**	**L74V, E138K,** D67G, K70Q/P/T, M184V		**V72I, T97A, E138A, G140S, Q148H**	**DTG 42** **FTC 82** **TDF 4.6**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
236									
	Screen	972,447	1.2	S373S/N, A219A/T, T232G/R, E268K, V270V/I/M, V275A/E, S291P/T, H374H/F, K490K/E/R	6.1	L74L/V, M184M/V			MVC R5 TDF 0.92
MVC TDF	Week 16	158,045		**S375N, M426L**, E92T, **L175S,** A219T, I225I/M, T232R, **V255V/I,** E268K/R, V270I, V275A, S291T, H374F, K490R	**591**	**K65R**			**MVC DM** **TDF 2.3**
247									
F1	Screen	450,345	1.3	S375S/N/T, M426L, D474N	**3,963**				DTG 0.93
DTG	Week 96	6,627		No post BL	**3,631**	No post BL	No post BL	No post BL	No post BL
293									
	Screen	17,886	1.1	T232N, E293H, S440R	0.11	D67G, K70R, L74V, M184V, T215V, K219Q		M50L, L74M, E138T, G140S, Q148H	MVC R5 **DTG 47** TDF 0.6 **FTC 119**
DTG FTC TDF MVC	Week 8	125,363		**S375N, M475I,** T232K, V242V/A, T244I, L259F, N280N/D, E293T, I371V, K419K, K421R, I424V, S440N, G459D, K500R	**1,578**				**MVC DM** **DTG 204** TDF 0.57 **FTC 60**
318									
	Screen	84,422	1.0	S375T, N230D/E	5.6	M184V		V32I, L33F, M46L, I54L, A71V, G73S, I84V, L90M	ENF 1.5 **DRV 603** **LAM 85**
DRV/C ENF LAM	Week 36	293,949		S375T, **M426L, M434M/I,** N230E	**3,657**	M184V		V32I, L33F, M46L, I54L, A71V, G73S, I84V, L90M	ENF 1.6 **DRV 517** **LAM 104**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
367									
	Screen	12,554	0.85	E268E/G, T283T/I, E293F/L/S	11	K101Q, M184V, T215Y		M36I, I54V, A71V, V82A, L90M	MVC R5 DRV 1.3 ETR 0.36
DRV/R ETR MVC	Week 48	113,095		R252R/K, E268G, T283I, E293F	8.2	K101H			MVC R5 DRV 0.4 ETR 1.1
389									
	Screen	1,114	2.3	No data	NR	M184M/V			DRV 0.50 DTG 1.23 LAM 1.87
DRV/R DTG LAM	Week 96	737		No post BL	NR			K43K/R	DRV 0.47 DTG 1.25 LAM 0.77
423									
	Screen	433	0	S375S/N, M426M/R	0.39	A98S, E138A			ETR 0.74 RAL 0.85
ETR RAL	Week 8	18,386		No post BL	No post BL	No post BL	No post BL	No post BL	No post BL
430									
	Screen	146,530	0.12	S375S/N, T63S, V84V/I, V85E/K, T283T/I	1.1	D67N, K70R, M184V, T215F/V, K219Q	G140S, Q148H	V32I, L33F, M46I, G48M, F53L, I54M, A71I, G73S, V82A, I84V, L90M	DTG 13 **FTC 82** TDF 1.1 **TPV 13**
DTG FTC TDF TPV/R	Week 36	147,897		**S375N, M426L**, T63A/S, V84I, V85K, T283I, R419R/K	**2,339**	D67N, K70R, **V118V/I,** M184V, T215F/V, K219Q	**T97A, E138E/K**	V32I, L33F, M46I, G48M, F53L, I54M, A71I, G73S, V82A, I84V, L90M	**DTG 156** **FTC 44** **TDF 1.5** **TPV 22**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
432									
	Screen	1,251	0		2.6		M154I, N155N/H	I54M, V77I	DTG 1.2 DRV 0.81
DTG DRV/R	Week 108	13,525		No post BL	1.9		M154I		DTG 0.91 DRV 0.54
452									
	Screen	286,138	1.4	V87V/E, N92N/D, D99D/N, S128T, K130K/N, T240E/K, S243S/T, E268G, A281A/V, T290E, I491I/L, V496I/L, K500K/R	0.41	K65R, L74I, M184V, K219H	T97T/A, E138A/T, G140S, Q148H	V32I, L33F, M46I, I47V, I54M, K55R, G73C, I84V, L90M	DTG 122 DRV 608 FTC 66 TDF 2.4 MVC R5
DTG DRV/R FTC TDF MVC	Week 8	386,759		**S375N, M426L**, V87E, N92D, D99N, I108I/V, V120V/I, S128A, K130E, V208I, S209T, T236T/K, T240H, S243T, E268D, **A281T**, T290V, I371I/V, V372T, T373M, I424V, I439V, R444R/K, **D474D/N,** I491L, V496I, K500R, E509D	**4,979**	K65R, L74I, M184V, K219H	T97T/A, E138A/T, G140S, Q148H	V32I, L33F, M46I, I47V, I54M, K55R, G73C, I84V, L90M	**DTG 123** **DRV 577** **FTC 85** **TDF 2.2** **MVC X4**
468									
	Screen	24,595	1.12	M426R, A204A/T	0.11	V106I, E138A, V179E, L210G, T215C			ETR 0.45 RAL 1.24
ETR RAL	WK 72	6,350		No post BL	NR	V106I, E138A, V179E, L210G, T215CB, **Y181Y/C, H221H/Y**		**L63I, N155N/H**	**ETR 148** **RAL 9.4**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
472									
	Screen	735,298	1.03	S375I/T	7.1	D67D/N, T215F/I/S, K219K/Q	V72I/V, G163E	M36I	DRV 0.83 DTG 1.2 TDF 1 FTC 2.6
DRV/R FTC TDF DTG	WK 72	48,318		NR	NR	No post BL	No post BL	No post BL	DRV 0.5 DTG 1.2 TDF 0.99 FTC 1.1
474									
	Screen	128,032	0.61	M426L, N230N/D, R252R/K, E268E/N, E269E/G, V270I/T, E293E/V, S440K/R, Q442Q/L, K500K/E	**84**				MVC R5 DRV 0.63 DTG 1.11
DRV/R DTG MVC	WK 60	917		**S375S/N**, M426L, V65V/G, P79P/S, **D113D/E**, N230D, R252K, **V255V/A**, E268N, E269G, V270T, E293V, S440K, Q442L, K500E, K510K/R	**295**				MVC R5 DRV 0.66 DTG 1.02
519									
	Screen	23,252	1.32		0.34		V72I	A71V, V77I, I84V, L90M	DRV/R 1.2 DTG 0.99 MVC R5
DRV/R DTG MVC	WK 96	7,206		No post BL	0.32		V72I, F181F/L	A71V, I84V, L90M	DRV/R 1.8 DTG 1.2 MVC R5
527									
	Screen	65,718	0.41	N230D/E/K, I424I/V, G471G/A	0.32		V72I, Y143Y/C, N155N/H	V77I	DRV 0.2 DTG 2.0
DRV/R DTG	WK 48 resuppressed	2,662		**L175T,** N230D, I424V, G471A	0.19		V72I, Y143Y/C, N155N/H	V77I	DRV 0.54 DTG 0.92

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
534									
	Screen	456,191	1.61	K130K/H/N, K227K/Q, E267K/T, K282G, I424I/V, Q442Q/D, R444R/K	0.21	G140S, Q148H	K70Q, Y115F, M184V, K219Q	V32I, L33F, M46I, I47V, I50V, V77I, V82I, L89M	**DRV/R 83** **DTG 14** ENF 1.1 **LAM 121** AZT 0.24
DRV/R DTG ENF LAM AZT	WK 36	4,398		**S375N, M475I,** D99N, K130H, K227Q, E267K, K282R, P369G, I424V, Q442D, R444K	**43** WK 96: **3030**	**T97A,** G140S, Q148H	K70**R, K103N,** Y115F, M184V, H221H/Y	V32I, L33F, M46I, I47V, I50V, V77I, V82I, L89M	**DRV/R 220** **DTG 16** **ENF 89** **LAM 85** AZT 0.51
539									
Other	Screen	128,934	0.03	M426L, D113E, S128V, K429E	**6,651**		V72I, M154M/L, K156N, G193R		MVC R5 DRV 0.58 DTG 0.97 LAM 1.6
DRV/R DTG LAM MVC	WK 24	70,116		M426L, D113E, S128T/V, **L175I/L,** R419R/K, K429E/Q, S440S/A	**4,271**				MVC R5 DRV 0.44 DTG 1.2 LAM 2
550									
	Screen	625,664	1.4	M426R, M434I, S128T, K130H, G471L	6.6	D67N, L74I, M184V, L210W, T215Y K219E/K			MVC R5 TDF 0.88 **FTC 74**
FTC TDF MVC	WK 24	285,966		M426R, M434I, **M475I**, D99D/N, S128I/T, K130K/H/N, V200V/T, I225I/L, D279D/N, G471L/W	**1,684**				**MVC DM** TDF 1.01 **FTC 81**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
555									
	Screen	43,432	1.65		0.44	Y181C, H221H/Y		V32I, L33F, M46I, I47V, I54L	**DRV/R 31** DTG 1.4 ETR 4.2 LAM 1.2
DRV/R DTG ETR LAM	WK8 WK48	354,513 88,405		**S375S/T, M426M/L/R,** E47E/D, T63T/K, V65V/A, N80N/D, Q82Q/K, E102E/D, V208V/T, R252R/K, D279D/N, A281A/V, S291S/P/T, E293N, N295T, N377T, S440K, S446E/V, K485K/R, K490R, K510R	0.5 **36**	E138E/Q, Y181C, H221H/Y	E92E/G, G193G/E	V32I, L33F, M46I, I47V, I54L	**DRV/R 30** DTG 1.3 **ETR 9.3** LAM 1.8
561									
A1	Screen	9,141	0	S375M, Q442I	**716**			L33I, M46I, I47V, F53L, I54L, K55R, I84V, L89I	ABC 1.9 LAM 1.98 **DRV 73**
ABC LAM DRV/R	WK 36	11,014		S375M, T283T/I, T290T/M, Q442I/V	**988**	**L74V, V118V/I, M184V**		L33I, M46I, I47V, F53L, I54L, K55R, I84V, L89I, **I85V**	**ABC 8.1** **LAM 122** **DRV 244**
586									
	Screen	591,495	0	none	0.21		V72I, G163R	A71A/V, L90M	DRV 1.9 DTG 1.5
DRV/R DTG	WK 24	414,296		none	0.27				DRV 1.32 DTG 1.34
602									
	Screen	7,999	1.1	S375S/T, M426L	**2,064**			A71T	DRV 0.7 ETR 0.75
DRV/R ETR	WK 24	1,474 resuppressed		No post BL	NR	**V106V/A** **Y181Y/C**			DRV 0.49 **ETR 3.8**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
608									
	Screen	254,740	1.2	S375S/N, M426R, E269E/D, T290E	0.82	M41L, D67N, V75M, M184V, T215Y, K219Q	E138A, G140S, Q148H	L33F, M46L, G48M, F53L, I54L, K55R, A71T, V82A, I84V	**DTG 7** **LAM 134** TDF 1.4 TPV 1.7
DTG LAM TDF TPV/R	WK8	255,590		S375S/N, M426R, D62D/N, **L175I/V,** V208V/I, E269E/A/D, T290E/K, N295N/K	0.39	**T69T/I, V108V/I/M** M184V, T215Y, K219Q, **L228L/H**	E138A, G140S, Q148H	L33F, M46L, G48M, F53L, I54L, K55R, A71T, V82A, I84V	**DTG 10** LAM NR TDF NR TPV NR
670									
F1	Screen	1,204	1.13	V85L, R419K, R504Q	**56**				DTG 0.99 MVC R5
DTG MVC	WK8	3,304		K46K/R, A48A/T, V85L/P, N88N/K, T232T/A, R419K/N, I439I/T, R444N/T, K502K/R, R504H/Q, R508R/K	**22**				DTG 1.34 **MVC DM**
684									
	Screen	37,772	0.29	S375T, M426R, M434M/R, I109I/K, A204S, R252R/K, A281V, S446I/T/V	2.6	M41L, D67G, K70R, V75M, K101T, E138A, M184V, T215F/Y L228H		V32I, L33F, M46I, I47V, I50V, I54A, K55R, A71V, G73C, L89V, L90M	**DRV 560** DTG 2 ETR 0.37 **TDF 1.6** **FTC 73**
DRV/R DTG ETR TDF FTC	WK36	80,912		**S375N**/T, M426R, M434M/**T/I, M475M/I,** N94N/Y, I109K, A204A/S, R252K, S256S/T, A281V, S364S/P, S446I/V	**21**				**DRV 500** DTG 1.8 ETR 0.5 T**DF 2.5** **FTC 5.1**

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
708									
	Screen	20,533	2.17		**550**		N155N/H, K156N	V32V/I, L33L/F, I47I/V, I54I/M, A71, I84I/V, L90M	ATV/C 1.7 DTG 0.66 FTC 1.6 TDF 1.0 MVC R5
ATV/C DTG FTC TDF MVC	WK96	39,016 resuppressed		No post BL	NR		V72I/V, S147S/G N155N/H, K156N	V32V/I, I47I/V, I54I/M, A71, I84I/V, L90M	ATV/C 2.1 DTG 1.96 FTC 1.2 TDF 1.0 MVC NR
732									
F1	Screen	43,918	0.58		1.7			I54V	DRV 1.7 DTG 0.99
DRV/R DTG	WK24	94,171		No post BL	0.33	No post BL	No post BL	No post BL	DRV 1.6 DTG 0.89
751									
	Screen	1,065	NO DAY 8	S375S/T, D62D/G, V65V/A, V85F, T244T/A, A281A/L, T290I/V, D474D/N,	0.22		G193E	A71A/T, V77V/I	ABC 0.99 LAM 1.9 DRV 0.6 DTG 1.3
ABC LAM DRV/R DTG	WK8	568,408		S375S/T, D62G/K, V65A, V85F/L, T244A, A281A/L/V, T290V, N448N/K, D474N, Q507Q/H	0.17	T215	G193E		ABC 0.87 LAM 1.8 DRV 0.48 DTG 1

PID OBT	Timepoint	Viral Load	Day 8 Decline	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
755									
	Screen	995	0	K130N, N230E, T232K	0.7				MVC R5 DTG 1.8
DTG MVC	WK24	171,578		Q82Q/L, K121K/R, K130E, **L175F/L,** N230D, T232K/Q, F277F/I, **A281A/V,** G459G/D	0.7				**MVC DM** DTG 1.9

Source: Clinical Virology Reviewer's analysis
Bolded equals evidence of emergent genotypic resistance to FTR or optimized background drugs and phenotypic resistance to FTR or optimized background drugs at screen or virologic failure
All subtype B (n=45; 88%) unless indicated otherwise under PID column; 1 A1 subtype, 4 F1 subtypes, 1 other
Abbreviations: ABC, abacavir; ATV/r, ritonavir-boosted atazanavir; BL, baseline; C, cobistat; DM, Dual/mixed tropism; DRV, darunavir; DTG, dolutegravir; EN, envelope; ENF, enfuvirtide; ETR, etravirine; FC, fold change; FTC, emtricitabine; FTR, fostemsavir; INSTI, integrase strand transfer inhibitor; LAM, lamivudine; MVC, maraviroc; NR, not reported; PI, protease inhibitor; PID, patient identifier; OBT, optimized background therapy; R, ritonavir; R5, CCR5-tropism; RAS, resistance associate substitution; RPV, rilpivirine; RT, reverse transcriptase; SQV, saquinavir; TDF, tenofovir disoproxil fumarate; TPV, tipranavir; VF, virologic failure; WK, week; X4, CXCR4-tropism.

Table 240. Virologic Failures in BRIGHTE Trial: Placebo Group (n=18)

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
025								
B	Screen	157,752	S375T	1.95	M41M/L, Y215Y	G140S, Q148H	V77I, L90M	ABC 2 LAM 2.2
DRV/R DTG ABC LAM	WK96	2,870 resuppressed	S375T, **M426M/L, M475M/I**	**1,826**	**M41L, M184V**	G140S, Q148H, **N155N/H**		DRV 0.45 DTG 3.8 **ABC 6** **LAM 88**
033								
B	Screen	92,805		0.48	D67G, K70R, L74I, V75V/L, M184V, T215F, K219E			ENF 1 TDF 0.7 **FTC 52**
ENF FTC TDF	WK72	24,876	**M426L M434M/I, M475M/L, V255I, L175T/V**	**495**	D67G, K70R, L74I, V75V/L, M184V, T215F, K219E			**ENF 24** FTC 80 TDF 0.9

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
056								
B	Screen	569,357	S375T	0.13	D67N, T215L, K219Q		I54V, A71V, V82A	
DRV/R DTG ABC LAM	WK36	6,518	S375T	0.09	D67N, T215L, K219Q		I54V, **K55K/R,** A71V, V82A	DRV 0.98 DTG 1.4 ABC 1.3 LAM 3.7
087								
B	Screen	330	M426R	0.21		T97A, Y143C		MVC R5 **DTG 12**
DTG MVC	WK84	603	M426**L, A281A/D**	769		T97A, Y143C, **E138A, N155H, K156N**		**MVC X4** **DTG 26**
092								
B	Screen	45,214	M426L	407	K70T, T74L/V, Y115F, V179I, M184V, Y188L, H221C/Y		L33F, M46L, I54L, K55R, V82A	ENF 4.5 **DRV 46** **ETR 194** AZT 0.3
DRV/R ETR ENF AZT	WK24	19,785	M426L	564	NO POST BL	NO POST BL	NO POST BL	**ENF 5.7** NO POST BL
144								
B	Screen	-	M426M/K	0.32	K103N		L33V, K43R	DRV 0.28 ETR 0.76 FTC 0.9 TDF 0.78
DRV/R ETR FTC TDF	WK36	3,535 Never suppressed	M426M/K	0.92	K103N		L33V, K43R	DRV 0.3 ETR 0.8 FTC 0.9 TDF 0.77
146								
B	Screen	37,284	M426L	57		G140S, Q148H	L90L/S	DTG 2.5 DRV 0.28
DTG DRV/C	WK72	14,423	No post BL	13				DTG 3.6 DRV 0.5

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
165								
B	Screen	5,822		0.3	M184M/I			MVC R5 DTG 1.2 FTC 4.2 TDF 0.5
DTG FTC TDF MVC	WK16	1,317		0.39	**M184I**	L101L/PF139L		MVC R5 DTG 1.1 **FTC 100** TDF 0.5
295								
F1	Screen	43,500	S375I/M	4,946	D67N, T69D, L74V, Y215Y	Y143R, G193E		DTG 2 TDF 0.66
DTG TDF	WK36	454 resuppressed	S375I/M, **V255V/I**	2,726	D67N, T69D, L74V, Y215Y, V90I/V	Y143R, G193E		DTG 3.9 TDF 1.3
348								
B	Screen	398,388	S375T, M434I	**27**				ATV 0.9 DTG 1.1
ATV/r DTG	WK36	548	No post BL	1.4				ATV 0.8 DTG 1.3
381								
F1	Screen	70,869	M426L, M434V	181			L33F, M46L, K55N, A71V, G73N, T74S, V82A, L89V	ATV 4.9 DTG 1.5
ATV/C DTG	WK60 WK96	33,006	M426L, M434V	288		**M50I/V, L74M, V75T, T97A, S147G, V151I, N155H, K156N**	K43K/R, F53F/L, L90M, L33F, M46L, K55N, A71V, G73N, T74S, V82A, L89V	**ATV 152** **DTG 103**
478								
B	Screen	10,000,001	M426R, A204A/T	0.15	K103K/N	V151V/I		DTG 0.78 ETR 0.75
DTG ETR	WK16	4,805,640 never suppressed	M426R	0.27	K103K/N	V151V/I		DTG 1 ETR 0.99

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
587								
B	Screen	35,866	M426L	5,082	M41L, S68G, L74I, V75T, M184V, T215Y	M154I		EVG 1.4 **FTC 77** TDF 0.9
EVG/C FTC TDF	WK12	1,199	M426L	4,262	M41L, S68G, L74I, V75T, M184V, T215Y	**E92Q**, M154I, **E157E/Q**		**EVG 36** **FTC 57** TDF 0.75
618								
B	Screen	39,091		0.73				DTG 1.8
DTG	WK16	40,770	**S375N, M426M/L, M475I, L175M**	**5,286**		**T97T/A, E138E/K, G140S, Q148H, N155N/H**		**DTG 13**
631								
B	Screen	33,733	S375M	**61**		M50I, V151I, N155H, E157Q	M36I, M46I, I54L A71V, V82T, I84V I85V	DTG 2.9 **DRV 42** MVC R5
DRV/r DTG MVC	WK16	416		No post BL				DTG 2 **DRV 29** MVC NR
759								
B	Screen	30,029	M426R	0.17				MVC R5 DTG 1.3
DTG MVC	WK8	11,947	M426R	0.14				**MVC DM** DTG 1.3
767								
BF1	Screen	108,135	M426L M434M/I	**5,716**	T69N, M184V	L74M, G140C, Q148R, K156N, G163R		DTG 8 **FTC 62** TDF 0.43
DTG FTC TDF	WK16	101,518	**S375S/N**, M426L, M434M/I	**4,031**		**V54I,** L63I, **L74I/M,** V75V/A, V79I, **T97A**, **E138K**, G140C, Q148R K156N		DTG **122** FT**C 74** TDF 0.4

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
796								
B	Screen	40,883		0.57			A71V, V77I	DRV 0.5
DRV/C	WK60	52,396	No post BL	NR	No post BL	No post BL	No post BL	No post BL

Source: Clinical Virology Reviewer's analysis
Bolded equals evidence of emergent genotypic resistance to FTR or optimized background drugs and phenotypic resistance to FTR or optimized background drugs at screen or virologic failure
Abbreviations: ABC, abacavir; ATV/r, ritonavir-boosted atazanavir; BL, baseline; C, cobistat; Dual/Mixed tropism; DRV, darunavir; DTG, dolutegravir; EN, envelope; ENF, enfuvirtide; ETR, etravirine; FC, fold change; FTC, emtricitabine; FTR, fostemsavir; INSTI, integrase strand transfer inhibitor; LAM, lamivudine; MVC, maraviroc; NR, not reported; PI, protease inhibitor; PID, patient identifier; OBT, optimized background therapy; R, ritonavir; R5, CCR5-tropism; RAS, resistance associate substitution; RT, reverse transcriptase; TDF, tenofovir disoproxil fumarate; VF, virologic failure; WK, week; X4, CXCR4-tropism.

Table 241. Virologic Failures in Trial: Nonrandomized Group (n=50)

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
005								
	Screen	37,243	S375T, D113E	0.74	D67N K70R, L210W, T215Y	T97A, G140S, Q148H, M154I	L33F, K43T, M46I, I47V, I54V, K55R, A71T, V77I/V, I84V, L90M	**ENF 48** **DRV 95** **DTG 39** DDI 1.9
DRV/R DTG DDI ENF	WK24	63,595	S375T, **M426L, D113A**	**2,715**			V77I, I85V	**ENF 43** **DRV 160** **DTG 27** DDI 1.8
006								
	Screen	54,730	M426L	**3,204**		E138K, G140S, Q148H, M154L	V32I, L33I, K43T, M46I, F53W, I54V, K55R, A71V, I84V, L89V, L90M	**DRV 61** DTG 5.4
DRV/R DTG	WK24	85,379	M426L, **A281A/T**	**5,670**		**E92E/Q, T97A, E138K/T**	**L33F, I47V, I54L, I85I/V**	**DRV 414** **DTG 66**
012								
	Screen	131,933		0.3		S153S/C, G163H/N	V32I, L33F, K43T, M46I, I47V, I50V, F53L, I72V, T74P, V77I, V82A, L89M/V	DTG 1.5 TPV/R 4.2
DTG TPV/R	WK24	160,542	**M426M/L**	**129**			L89M	DTG 2.6 TPV/R 6.5

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
015								
	Screen	5,215	D113E	1.4	M41M/L, D67N, M184M/V, L210E/G/W, T215C	G140S, Q148H	V32I, L33F, M46I, I47V, I54M, A71V, V82C, I85V, L89V, L90M	**DTG 12** **SQV 7.3** **FTC 35** TDF 0.85
DTG SQV/R TDF FTC	WK132	616	No post BL	**1,123**	**M41L, L210W, T215Y/C**	**E92Q, E138K**, K159K/R		**DTG 118** **SQV 8.2** FTC 6.7 **TDF 2.2**
018								
	Screen	3,524	M426L, S204A/T	9,398	K65R, K70R	M50M/I, V72I, L74M, T97A, Y143C, S147G, K156N, G163R	V32I, L33F, K43T, M46I, I47V, I54L, K55R, A71V, V77I, V82T, I84V, I85V	**DTG 208** IDV 5.7 **TPV 27** **TDF 7.2**
DTG IDV TPV/R TDF	WK24	7,962	M426L	5,670	K65R, K70R	M50M/I, V72I, L74M, T97A, Y143C, S147G, K156N, G163R	**F53F/L**, V32I, L33F, K43T, M46I, I47V, I54L, K55R, A71V, V77I, V82T, I84V, I85V	**DTG 70** **IDV 16** **TPV 30** **TDF 7.2**
023								
	Screen	32,237	M426L	164	M41L, D67H/N K70R, L74V, K101Q, V179Q, Y181C, M184V G190A, L210L/S, T215F, K219Q, L228H		V32I, L33F, K43T, M46I, W53W, I54L, A71V, G73S, T74P, V82T, I84V, L89V, L90M	**DRV 670** DTG 1.1 ENF 0.31 ETR 3.2 **TDF 2.2**
DRV/R DTG ENF ETR TDF	WK36	2,187	M426L	115	**K104K/E, V179E/Q**		**I54L/V**	**DRV 583** DTG 1.5 ENF 0.3 ETR 2.2 **TDF 1.7**
037								
	Screen		M426L	162	D67N, L74V, L210W, T215Y, K219D	T97A, G140S, Q148H, K156N		**DTG 188** **FTC 54** **TDF 1.5**
DTG FTC TDF	WK36		**S375N,** M426L	**4,635**				**DTG 150** **FTC 100** **TDF 1.5**

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
044								
	Screen	104,713	S375N	1.85	M41L, L74I, M184V, T215Y	L74I/M, T97T/A, G140S, Q148H, K156N	V32I, L33F, M46L, I50V, K55R, A71V, G73V, T74P, V82M, L89S, L90M	**DTG 99** **DRV 559** **LAM 134** **ABC 7**
DRV/C DTG ABC LAM	WK36	56,313	S375N, **M426L**	**5,313**		L74I, T97A, A128A/T	V77V/I	**DTG 116** **DRV 572** **LAM 93** **ABC 6.3**
057								
	Screen	76,668		0.33	T215C, K219E		L33F, M46L, I54L, V82A I84V, L89M	**DRV 71** FTC 2.4 TDF 0.7
DRV/R FTC TDF	WK24	17,004	**S375S/N, M426M/L, M434M/I, V255V/I**	**5,670**				DRV **64** FTC 2.6 TDF 0.83
062								
	Screen	18,987	S375T	2.86	M41L, D67N L74I, M184V, L210W, T215F K219Q	T97A, E138T, G140S, Q148H	V32I, L33F, M46L, I54L, K55R, A71V, G73G/S, T74P, V77I, V82T, I84V, L89V L90M	MVC DM ENF 3 **DTG 32** **TPV 31** **FTC 80** TDF 1.1
DTG TPV/R FTC TDF ENF MVC	WK24	16,255	S375M, **M426L**	**5,670**				MVC DM **ENF 4.9** **DTG 194** **TPV 43** **FTC 57** TDF 0.82
065								
	Screen	325,318	M426R	**17**	A98G, L228H/K/N, Y181F		I54L, A71V, G73S, T74P, I84V, L89V, L90M	ENF 0.97 **DRV 268** ETR 0.41
DRV ETR ENF	WK24	846	M426R	9.84	**L228N**			ENF 0.4 **DRV 370** ETR 0.64

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
066								
	Screen	76,668	S375M	**235**	D67A/T, 69INS, M184V, T215Y	L74I/M, E138T, G140S, Q148H, K156N	V32I, L33F, M46L, K55R, A71I, V77I, V82A, I84V, I85V, L89M, L90M	**DTG 145** **DRV 76** **FTC 80** **TDF 8.5**
DTG DRV/R FTC TDF	WK24	389,580		**1,272**	D67T, T215Y/C	L74I	**I54L, L76V**	**DTG 182** **DRV 110** **FTC 94** **TDF 1.4**
072								
	Screen	20,381	M426L	42	D67N, K70R, M184V, T215F K219Q	E138K, G140S, Q148H, M154L	L33I, M46I, I47V, I50V, V82I, L90M	ATV 4.4 **DTG 67** **FTC 80** **TDF 1.6**
ATV/r DTG FTC TDF	WK24	81,695	**S375N,** M426L	**2,146**			V32I, G73S	**ATV 37** **DTG 298** **FTC 104** TDF 0.7
091								
	Screen	40,236	S375T	8.9	L210W, T215D		L33F, I54V, T74S, V77I/V, V82A	DTG 1.1 DRV 0.8 FTC 2.4 TDF 0.53
DTG DRV/R FTC TDF	WK8	52,829		4.2	**M41M/L, T215D/F/Y**			DTG 1.5 DRV 0.58 FTC 1.97 TDF 0.66
094								
	Screen	79,998		1.8	K101V, V106I, V179I, Y188L	L74L/M, E138E/K, G140S, Q148H	V32I, L33F, M46L, I47V, I50V, I54A, A71L, G73S, V82A/V/L, L89L/V, L90M	**DTG 30** **DRV 88** **ETR 7.3**
DTG DRV/R ETR	WK36	58,201	**M426L**	**4,635**	L100L/I, L189V/I	L74L**/I**/M	**I54A/V, V82L, L89V**	**DTG 52** **DRV 584** **ETR 153**

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
102								
	Screen	2,640		0.64	M41L, D67N, K70R, M184V, K219E	L74I, T97T/A, G140S, Q148H, M154M/I	V32I, L33F, M46L, I47V, G48V, I54M, T74S, V82A, I84V	**DTG 48** **DRV 72** **FTC 82** TDF 1.1
DTG DRV/R FTC TDF	WK16	1,533	**M426L**	**351**		**T97A**		**DTG 135** DRV NR FTC NR TDF NR
106								
	Screen	16,594		0.36	L74V, L210W T215C/Y, K219K/D/N	T97T/A, E138K/T, G140S, Q148H, K156K/N	V32I, L33F, M46I, I47V, F53F/L, I54L, A71V, T74P, V82L, I84V, I85I/V	**DTG 47** **DRV 343** TDF 0.77
DTG DRV/R TDF	WK24	39,643	**S375S/N, M426M/L, M475M/I, A281A/V**	**4,342**	K219**N**	**T97A, E138K, K156N**	**L19L/V, I53L, I85V**	**DTG 237** **DRV 583** TDF 0.91
114								
	Screen	94,233		0.32	D67S, K70R, T215V, K219E		V32I, L33F, M46I, I47V, F53L, I54M, A71V, G73S, L90M	SQV **98** D4T 1.7 **TDF 7.8** **FTC 92**
SQV/R D4T TDF FTC	WK16	324,804	**S375N, M426L**	**748**				**SQV 117** D4T 1.9 **TDF 7.5** **FTC 89**
119								
	Screen	71,946	M426T	1.28	M41L, K65R, L210L/W, T215D	L74I, T97A, G140C, Q148R, K156N	M46I, I47V, I50V, F53L, I54M, A71V, G73C, V82I, L90M	**DTG 413** **DRV 768** **FTC 85** **TDF 3.9**
DTG DRV/R FTC TDF	WK36	11,794	**S375M,** M426T, **M475M/I, D113E/D**	**5,670**	**L210W, T215D/E**			**DTG 158** **DRV 675** **FTC 86** **TDF 3.3**

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
121								
	Screen	9,215		1.8	D67G, T215L	T97A, E138K, G140S, Q148H, K156N	V32I, L33F, I54M, A71V, G73S, V77I, I84V, L89V, L90M	**DTG 168** **DRV 384** FTC 4.2 TDF 0.45
DTG DRV/R FTC TDF	WK24	31,667	**S375S/N, M426L**	**5,472**				**DTG 161** **DRV 598** FTC 2.7 TDF 0.42
141								
	Screen	520,526	M426R, M475I	1,055	M41L, D67N, K70R, M184V, L210W, T215F, K219Q		L33F, M46I, I54V, A71V, G73S, V82T I85V, L90M	MVC R5 **DRV 32** **FTC 82** **TDF 3.9**
DRV/R MVC FTC TDF	WK12	783,220		**5,670**				MVC **DM** DRV 2 **FTC 59** **TDF 3.3**
153								
	Screen	84,663	M426L	100	D67N, K70R, M184V, T215V, K219Q		V32I, L33F, I47V, I50I, K55N, A71V/I, G73G/D/N/S, V82A, L90M	TPV 1.6 **FTC 90** **TDF 1.6**
IBL TPV/R FTC TDF	WK12	392,816		99			**A71V, G73S, V82T**	**TPV 14** **FTC 60** TDF 1.1
168								
	Screen	36,763	S375T	0.14	M41L, D67N, M184V, T215F K219E	E157Q G193E	V32I, L33F, M46I, I54A, K55R, A71V/I, G73S, I84V, L90M	**DTG 13** **DRV 71** **FTC 85** TDF 0.74
DTG DRV/R FTC TDF	WK36	13,369	**S375N/T, M426L, M434M/I**	**2,027**				DTG 4.3 **DRV 438** **FTC 78** TDF 0.78

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
192								
	Screen	64,032		0.18		G140S, Q148H		**ENF 133** DTG 3.5
DTG ENF	WK24	23,351	**M426L, M475I**	**4,342**		**T97T/A, N155N/H**		**ENF 119** **DTG 48**
257								
	Screen	443	S375M	1.9	M41L, M184V, L210F, T215Y K219E, K101P, E138G	T97A, E138K, G140S, Q148H	V32I, L33F, M46I, I47V, I54L, A71V/I, V82A, L90M	**DTG 37** **DRV 30** **ETR 162** **FTC 90** **TDF 1.4**
DTG DRV/R ETR FTC TDF	WK60	1,371	S375M, **M426L**	**2,989**				**DTG 92** **DRV 129** **ETR 167** **FTC 79** TDF 1
260								
	Screen	391,264		0.66	M41L, D67N K70K/R, L74I, M184V, T215F K219Q		V32I, L33M, I54L, A71V, G73S, T74P, I84V, L89V, L90M	DTG 2.2 **DRV 549** **FTC 90** **TDF 2.2**
DTG DRV/R FTC TDF	WK16	150,542	**S375S/N, M426M/I, M475M/I**	**310**	K70R	L74I, T97A, **E138K, S147G, Q148R, V151I, N155H, E157Q**	A71I	**DTG 161** **DRV 508** **FTC 82** **TDF 2.5**
287								
	Screen	35,277		0.78	D67N, K70R, K103N, Y181C, T215L, K219E	E138T, G140S, Q148H	D30N, N88D	DTG 5.5 DRV 1.5 FTC 3 **TDF 2.14** **RPV 32**
DTG DRV/R FTC TDF RPV	WK36	17,297	**S375S/I**	**79**		**T97A/T, G193G/E**	**L89L/M**	DTG 7.8 DRV 0.92 FTC 2.5 **TDF 2.1** **RPV 13**

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
294								
	Screen	10,180		2.5	M184V			**FTC 89**
IBL FTC	WK16	8,457	**S375H, D113D/E**	**5,480**				**FTC 52**
311								
	Screen	87,677	D113D/A	7.6	M41L, D67N, M184I, L210W, T215Y, K219K/R	T97A, E138A, G140S, Y143Y/H, Q148H, K156N	V32I, L33F, M46L, I54A, K55R, A71V, L74P, I84V, L89F, L90M	**DTG 51** **DRV 367** **FTC 66** **TDF 2**
DTG DRV/R FTC TDF	WK36	220,096	**M426L,** D113D/A, S204A/T	**4,669**				**DTG 153** **DRV 405** **FTC 70** **TDF 2.1**
322								
	Screen	23,033	NR	814	D67S, K70G, M184V, K219Q	T97A, Y143C, S147G, N155H, K156N	V32I, L33F, M46L, I54L, K55R, A71V, G73T, L74P, V82T, I84V, L89V, L90M	MVC DM **DTG 62** **DRV 604** **TDF 2.5** **FTC 67**
DTG DRV/R MVC TDF FTC	WK24	22,337	**S375N, D113D/E**	**5,286**				**MVC X4** **DTG 78** **DRV 467** **TDF 2.2** **FTC 90**
327								
	Screen	25,485	NR	NR	D67N, K103N, Y181I, M184V, Y188L, L210W, T215C/F, K219E	T97T/A, E138K, G140S, Q148H K156N	V32I, L33F, F53L, I54L, K55R, A71A/T/V, V771, I84V	**DTG 185** **ATV 112** **ETR 147** **LAM 85**
DTG ATV/r ETR LAM	WK36	77,042	No post BL	No post BL		**T97A**	**A71V**	**DTG 182** **ATV 152** **ETR 148** **LAM 109**
336								
	Screen	23,200	S375T	16				
IBL	WK108	25,119	No post BL	**3,325**				

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
380								
	Screen	81		1.2	M184V, K101P, E138R, V179L, L228R	G140S, Q148H		**DRV 629** **ETR 144** **LAM 119**
DRV/R ETR LAM	WK24	2,793	**S375S/N, M426L, D113D/E, A281A/T**	**4,530**	**E138R/G**	N155H/N		**DRV 419** **ETR 41** **LAM 91**
411								
	Screen	62,061		0.35		T97A, E138A, G140S, Q148H	V32I, L33F, M46I, I47V, F53L, I54L, K55R, A71I, G73S, V82T, I84V	ENF 1.2 **DTG 155** **DRV 479**
DTG DRV/R ENF	WK36	64,722	**M426L, M434I**	**4,490**		K156K/N		**ENF 49** **DTG 141** **DRV 327**
431								
	Screen	417,763	M426M/L	2.1				ENF 0.48
ENF	WK24	892,250	**S375N, M426L**	**4,973**				**ENF 65**
463								
	Screen	30,790	S375H, D113H	6,388	E138Q, M184V, L228R	T97A, E138T, G140S, Q148H, M154I	V32I, L33F, M46I, F53L, I54L, K55R, A71I, G73S, V82L, I84V, L89V, L90M	**DTG 92** **DRV 561** **ETR 150** **FTC 79**
DRV/R DTG ETR FTC	WK36	138,936	S375H, D113H	3,651				**DTG 38** **DRV 369** **ETR 163** **FTC 70**
508								
	Screen	16,717		0.55	D67N, L210W, T215Y, K219R	T97A, G140R, Q148R, K156N	V32I, L33F, M46L, I54L, A71V, G73V, T74P, V82T I84V, L89A, L90M	**DTG 162** **DRV 529** **TDF 1.92**
DTG DRV/R IBL TDF	WK36	2,109	**S375H/N, M426M/L, D116L/V**	**3,651**		NO POST BL		DTG NR **DRV 462** **TDF 3.1**

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
530								
	BL	49,850		0.23	M41L, K70K/T, L210W, T215Y	G140S, Q148H	A71T, I84V, L89V, L90M	DTG 3.9 LPV 4.7 **TDF 3.5** FTC 3.7
DTG LPV/R FTC TDF	WK48	7,530	**S375S/N, M426M/L, M434M/I, D113D/E**	**125**	**K219K/E**	**T97A, E138K**	L19L/V	**DTG 16** LPV 6.6 **TDF 3.7** FTC 3.2
535								
	Screen	30,149		0.68	D67G, K70R, V75T, K219R			**ABC 5.9** **LAM 5.3** **TDF 3.4**
ABC LAM TDF	WK24	78,613	**S375N, D113E**	**5,784**	**M184I**			**ABC 5.9** **LAM 87** TDF 1.2
552								
	Screen		M426M/L	0.43	L74I, M184V, T215F, K219Q	K156N		DTG 1.2 **FTC 74** TDF 1.3
DTG FTC TDF IBL	WK72		No post BL	No post BL				DTG 1.2 **FTC 82** **TDF 1.7**
559								
	Screen	9,013	M426M/T	0.98	D67N, K70G, L74I, M184V, T215F, K219H	T97A, G140S, Q148H	V32I, L33F, M46L, I54V, A71V, G73S, T74P, I84V, L89A, L90M	**DTG 134** **DRV 598** **FTC 74** TDF 0.91
DTG DRV/R IBL FTC TDF	WK8	8,853	**S375N**	**223**				**DTG 172** **DRV 583** **FTC 67** TDF 0.91

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
616								
	Screen	11,126	A204S, A281T	0.5	M41L, D67N, M184V, T215Y K219E	T97A, G140S, Q148H, E157E/Q	V32I, M46I/L, I54V, A71V, T74T/A, V82V/L, I84V, L90M	**DTG 172** **DRV 125** **LAM 109** TDF 1.22
DTG DRV/R LAM TDF	WK48	5,168	No post BL	No post BL		NO POST BL	M46I, I54L, L76V	NR
625								
	Screen	22,293	S375T, M426R	168	M41L, D67N L210W, T215Y	G140S, Q148H, E157E/Q	L33F, M46I, I54L, T74S, L76V, I84V, L89M	DTG 6.3 TPV 0.76 **TDF 1.7**
DTG TPV/R TDF	WK24	469	S375N/T, M426R	14				DTG 7.4 TPV 0.52 **TDF 2.2**
676								
	Screen	2,685,239		0.24			V77IS	DTG 0.9 DRV 0.5 FTC 1.4 TDF 0.7
DTG DRV/C FTC TDF	WK36	1,827	**S375N, A281A/T**	4.5			A71A/T	DTG 0.9 DRV 0.5 FTC 1.4 TDF 1.0
680								
	Screen	2,499,909		0.25	D67N, M184V, K219Q, K103S, E138A		L33F, M46M/I, I50V, A71L, T74P, V82A, L89M, L90M	DTG 1.8 **DRV 108** ETR 0.96 TDF 0.55 **LAM 142**
DTG DRV/R ETR TDF LAM	WK16	3,440	**M426M/L**	**122**	K70K/R			DTG 1.8 **DRV 73** ETR 1.3 TDF 0.58 **LAM 121**

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
682								
	Screen	359,559	S375T	0.84	D67N, L74I, M184V, L210W, T215Y	T97A, E138Q, G140S, Q148H, G193E	V32I, L33F, M46I, I54L, L76V, V82VI, I84I	**DTG 118** **DRV 561** **LAM 106** **TDF 2.2**
DTG DRV/R LAM TDF	WK36	266,583	**S375M, M426M/L, M434M/T, M475M/I**	**4,216**		**E138K/Q**		**DTG 205** **DRV 724** **LAM 79** **TDF 1.7**
726								
	Screen	10,897		0.4			M46L, I50V, K55N, A71V, V82A, L89V, L90M	MVC R5 ATV 3.9
ATV/C MVC	WK24	918,286	**M426M/L**	**17**			V32I/V	MVC R5 **ATV 7.3**
747								
	Screen	264,386	M426R	0.16	D67G, K70R, M184V, K219Q	T97A, G140S, Q148H	V32I, L33F, I54L, A71T, V77L, V82M, I84V	**DTG 89** **DRV 89** **LAM 141** TDF 0.77
DTG DRV/R LAM TDF	WK48	12,564	M426R	0.23				**DTG 22** **DRV 89** **LAM 75** TDF 0.7
763								
	Screen	38,419	M426R	1.69	M41L, L74V, L100I, K103N, M184V, L210W, T215Y	L74L/M, E92E/Q, E138E/D/K/N, Y143H/R, V151V/I, M154M/I, K156K/N, E157E/Q	V32I, L33F, I47V, I54L A71I, L76V, V77I, V82V I84I/V, N88D, L89T, L90L/I/M	DTG 2.13 **DRV 356** **ETR 7.2** **LAM 141** TDF 0.8
DTG DRV/R ETR LAM TDF	WK96	27,308	No post BL	0.8		V151I		DTG 1.8 **DRV 312** **ETR 7.6** **LAM 95** TDF 0.83

PID OBT	Timepoint	Viral Load	EN RASs	FOS FC	RT RASs	INSTI RASs	PI RASs	Phenotype
776								
	Screen	25,540	S375M	**668**	D67N, K70R T215F, K219Q	E92Q, V151I, N155H, E157Q	L33F, G48V, L54V, T74S, V77I, V82S, L89M	DTG 8 **DRV 134** TDF 0.43
DTG DRV/R TDF	WK16	27,703	S375M	**402**		**S147G**		**DTG 122** **DRV 187** TDF 0.4

Source: Clinical Virology Reviewer's analysis
Bolded equals evidence of emergent genotypic resistance to FTR or optimized background drugs and phenotypic resistance to FTR or optimized background drugs at screen or virologic failure
Abbreviations: ABC, abacavir; ATV/r, ritonavir-boosted atazanavir; BL, baseline; C, cobistat; D4T, stavudine; DDI, drug-drug interaction; DM, Dual/Mixed tropism; DRV, darunavir; DTG, dolutegravir; EN, envelope; ENF, enfuvirtide; ETR, etravirine; FC, fold change; FTC, emtricitabine; FTR, fostemsavir; IBL, ibalizumab; IDV, indinavir;INSTI, integrase strand transfer inhibitor; LAM, lamivudine; LPV, lopinavir; MVC, maraviroc; NR, not reported; PI, protease inhibitor; PID, patient identifier; OBT, optimized background therapy; RAS, resistance associate substitutions; R5, CCR5-tropism; R, ritonavir; RPV, rilpivirine; RT, reverse transcriptase; SQV, saquinavir; TDF, tenofovir disoproxil fumarate; TPV, tipranavir; VF, virologic failure; WK, week; X4, CXCR4-tropism.

19.6. Exploratory Analysis of EN Substitutions and FTR Resistance

Response or nonresponse to FTR at Day 8 is not fully explained by the absence or presence, respectively, of substitutions at the four EN sites 375, 426, 434, and/or 475. An exploratory analysis was performed examining the response at Day 8 based on the presence of other EN substitutions. In addition, it was determined if these EN substitutions were present at Screening or emerged in virologic failures and if they conferred phenotypic fold changes in susceptibility to FTR.

Polymorphisms D113E or A, T244S, I or V, T283N, I or V, I285L, F376V, I, L, or C, N377S, V, or I, S446A or V, and V430T, A or I were associated with lower response rates at Day 8 (Table 243). Decreased susceptibility to FTR, indicated by higher EC_{50} fold changes, was seen for polymorphisms D113E/A, N377S/V/I and S446A/V. Some of these substitutions were present at Screening in a high number of virologic failures and several had emergent substitutions at these sites in more than one virologic failure. The D113E/A substitution occurred most frequently in 15 of the virologic failures (from all groups). The V255I/A, V271I, A281T/V/D, and T283N/I/V substitutions emerged in four to seven virologic failures. Substitutions at sites V255, A281, D474 and V430 are of interest based on resistance selection experiments in cell culture and crystal structure analyses. Importantly, almost all these virologic failures with emergent substitutions at these exploratory sites had high median fold change values (although with wide phenotypic variability) and were associated with the presence of other substitutions at sites 375, 426, 434 and/or 475.

EN substitutions at sites L116, L175, A204, and A281 were selected in resistance selection experiments in cell culture. The presence of polymorphisms at these sites at Screening did not reduce response at Day 8 (Table 242). However, substitutions at these sites did emerge along with M426L, S375N, or combinations of S375 plus M426L with or without M475, in a few virologic failures, and they conferred high median fold changes in FTR susceptibility (>2500-fold).

Table 242. EN Substitutions Selected in Resistance Selection Experiments

EN Substitutions	Success at Day 8	# VFs with Presence of Substitution at Screening	# VFs with Emergent Substitution N=118	Phenotypic FTR FC with Emergent Substitution at VF (Median)
L116K/V	1/1		1 (with S375H/N and M426M/L)	3,651
L175P	?	?	?	-
A204T/S	6/8 (75%)	6	1 (with M426L)	4,670
A281T/V/D/G/L	27/40 (68%)	33	6 (2 with M426L; 1 with S375N, 1 with S375S/N+ M426L, 1 with S375S/N+ M426M/L+ M475M/I)	2,556

Source: Clinical Virology Reviewer's analysis
Abbreviations: EN, envelope; FC, fold change; FTR, fostemsavir; VF, virologic failure

Table 243. Exploratory Analysis of EN Substitutions in BRIGHTE Trial

EN Substitution	Success at Day 8	Screening FTR FC of Day 8 VF with Substitution	# VFs with Presence of Substitution at Screening	# VFs with Emergent Substitution N=118	Phenotypic FTR FC with Emergent Substitution at VF Median
D62**N/V/K**[b]	9/24 (38%)	0.32	17	3 (all with RASs)	1,142, 4,634, 0.39
D113E/A[a b]	1/3 (33%)	(n=3: 7.6, 6,388, 6,651)	5	15	3,961
T232K/A[b]	46/64 (72%)		34	3	769
T244**S/I**/V[a b]	5/13 (38%)	0.6	7	2	4,115
V255**I/A**[b]	75% 6/8		3	6	1,658
V271**I**[b]	29/42 (69%)		29	4	4,299
A281**T/V/D**/G/L[b]	68% 27/40		33	6	2,556
T283**N/I/V**[a b]	6/15 (40%)	0.39	38% (13/34)	7	1,857
I285**L**[a b]	1/6 (17%)	0.39	3	1 (with M426L)	4,664
F376V/I/L/C[a]	2/6 (33%)	1.92	6	0	-
N377S/V/**I**[a b]	2/7 (29%)	415	7	1	5,670
S446A/V[a]	3/9 (33%)	21.5	11	0	-
D474**N**[b]	67% 52/78		40	3	4,979
V430**T/**A/I[a b]	0/3	0.53		1	0.09

Source: Clinical Virology Reviewer's analysis
[a] Reduced Day 8 response
[b] Substitutions that emerged in VFs
Bolded = substitutions of interest based on resistance selection experiments and crystal structure analysis
Abbreviations: EN, envelope; FC, fold change; FTR, fostemsavir; RAS, resistance-associated substitution; VF, virologic failure.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The Office of Scientific Investigations conducted clinical site inspections and an inspection of the Applicant (ViiV) to ensure the quality and reliability of the data from the BRIGHTE trial, which were submitted in support of NDA 212950. At the request of the review team, the site inspectors added verification of eligibility criteria and verification of the primary endpoint analysis to their standard battery of assessments.

Three sites were selected for clinical inspections: Site 0118, Site 0174, and Site 0163. A summary of the rationale for site selection and the inspection findings are summarized here.

Site 0118 was selected because of high enrollment (highest enrollment in the study with 36 subjects screened and 19 subjects enrolled) and the absence of recent inspections. Informed consent documents were reviewed for all subjects and found to be adequate. The primary endpoint data (HIV-1 RNA levels at Day 1 and Day 8) and the HIV-1 RNA levels at weeks 24, 48, and 96 (when available) were verified for all enrolled subjects. For enrolled subjects,

eligibility criteria, AEs, and concomitant medications were verified. The inspection revealed no significant deficiencies at site 0118.

Site 0174 was selected because of high U.S. enrollment (14 subjects screened and 10 subjects enrolled) and the lack of prior inspections. The primary endpoint data (HIV-1 RNA levels at Day 1 and Day 8) and the HIV-1 RNA levels at weeks 24, 48, and 96 (when available) were verified for all enrolled subjects. There was no under-reporting of AEs or protocol deviations for any of the subjects at the site.

Site 0163 was selected because of moderate U.S. enrollment, financial disclosure >$25,000 (for a subinvestigator), and a prior inspection history of Voluntary Action Indicated (VAI) for failure to adhere to protocol and inadequate records. The inspection identified regulatory deficiencies in the investigator's conduct of this study and a Form FDA 483 was issued to the investigator at the conclusion of the inspection based on failure to conduct the study according to the investigational plan and failure to appropriately reconsent subjects when necessary. Deficiencies included missed physical exam, study visits missed or out of window, treatment noncompliance, and medication dispensing errors. The investigator acknowledged the deficiencies in a written response to the FDA 483. After careful review of the inspection findings, the Office of Scientific Investigations team concluded that the deficiencies did not affect patient safety or data integrity.

The Applicant was inspected because ViiV Healthcare has not been previously inspected and because the application is an original NDA. The BRIGHTE trial was initiated by Bristol-Myers Squibb (BMS) on February 23, 2015; ViiV Healthcare acquired FTR from BMS and took over the sponsorship of the trial in February of 2016. Since transfer to ViiV, the trial has been conducted with oversight and team members from GlaxoSmithKline (GSK), ViiVHealthcare, and PPD. PPD was responsible for investigators, monitors, and record retention; GSK and ViiV were responsible for safety reporting and event escalation and investigation. In general, the Applicant's conduct, oversight, and management of the BRIGHTE trial since acquisition of FTR (one year after the start of the study) appeared adequate, and no significant deficiencies were identified in the Applicant inspection.

Based on the results of these inspections, the Office of Scientific Investigations team concluded that the BRIGHTE trial was conducted adequately and the study data appear reliable in support of the NDA.

21. Labeling Summary of Considerations and Key Additional Information

Prescribing Information

General:

- Information highlighted below are significant changes made to the Full Prescribing Information form the sponsor proposed label submitted on December 4, 2019.

- HIGHLIGHTS and TABLE OF CONTENTS were revised for consistency with the rest of the Prescribing Information.

4. CONTRAINDICATIONS

Elbasvir/grazoprevir was removed from list of drugs that are contraindicated when coadministered with RUKOBIA and grazoprevir was added to list to clinically significant drug interactions under subsection 7.3, Table 3. Refer to Section II.8.2.2 for additional details.

5. WARNINGS AND PRECAUTIONS

5.3 Elevations in Hepatic Transaminases in Patients with Hepatitis B or C Virus Co-Infection

The following additional detail was added to this warning based on clinical trial data:

Elevations in hepatic transaminases were observed in a greater proportion of subjects with HBV and/or HCV co-infection compared with those with HIV mono-infection. Some of these elevations in transaminases were consistent with hepatitis B reactivation, particularly in the setting where anti-hepatitis therapy was withdrawn *[see Adverse Reactions (6.1)]*. Refer to Section II.7.6.6 for additional details.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Presentation of safety information including common adverse reactions, less common adverse reactions, and laboratory abnormalities from the BRIGHTE trial was modified to highlight safety events from the Randomized Cohort (N=271) as opposed to the applicant's proposal to display pooled safety events from both the Randomized and Non-randomized Cohorts (N=371). Safety information from the Non-randomized Cohort was presented separately as a brief summary. Refer to Section II.7.4 for additional details.

Laboratory Abnormalities

- Additional laboratory parameters, including hemoglobin, LDL cholesterol and neutrophils were added to Table 2.
- Additional detail on changes in ALT and AST in subjects with hepatitis B and/or hepatitis C virus co-infection was added. Refer to Section II.7.6.6 for additional details.

7. DRUG INTERACTIONS

7.3 Established and Other Potentially Significant Drug Interactions

- Grazoprevir and voxilaprevir were included in the table of potentially significant drug interactions with a recommendation to use an alternative HCV regimen, if possible. Refer to Section II.8.2.2 for additional details.
- Clinical recommendations for drug interactions was statins were modified to remove specific limited daily doses of statins. Refer to Section II.8.2.2 for additional details.

12. CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Statement that no exposure-response relationship was observed for FTR was added. Refer to Section II.6.4.3 for additional details.

12.4 Microbiology

Mechanism of Action

Statement was added that TMR can inhibit gp120-dependent post-attachment steps required for viral entry into host cells.

Antiviral Activity in Cell Culture

- Data was added to show antiviral activity against CCR5- and CXCR4-tropic viruses. Refer to Section II.6.4.2 for additional details.
- Data was added for non-subtype B isolates, including a subsection on reduced antiviral activity against subtype AE. Refer to Section 18.2 for additional details.

Effect of human serum proteins subsection was removed.

Resistance in Cell Culture

- Duration of cell culture selection and fold changes in TMR susceptibility of breakthrough viruses were added.
- A statement of where substitutions mapped in envelope was added.
- Additional substitutions and their fold changes in TMR susceptibility were added.
- A statement that TMR-resistant viruses showed no evidence of a CD4-independent phenotype was added. Refer to Section II.7.7.1 for additional details.

New subsections on response at Day 8 by genotype and phenotype were added.

A subsection on response at Day 8 by baseline tropism was proposed to show the reduced response of subjects with CXCR4-tropic virus. However, due to the limited number of CXCR4-isolates (n=9) and presence of EN RAPs/high phenotypic TMR values, which confounds the interpretation, this information was removed. Refer to Section II.7.7.1 for additional details.

Resistance in Clinical Subjects

- This section was changed to show the percentage of subjects who experienced virologic failure in the Randomized Cohort through Week 96.
- Applicant agreed to our definition of virologic failure, and resolution of numbers in Table 10 was reached.
- Applicant agreed to include information on rates of genotypic/phenotypic resistance to OBT.

- Applicant agreed to show virologic failure in the Non-randomized Cohort.
- FTR phenotypic data was removed from Table 10 and summarized in text.
- The following statement was removed, “Thirty-four percent (18/53) of the virologic failures in the FTR randomized arm had <0.5 log decline in HIV-1 RNA at Day 8”.

Cross-resistance

Additional information on the cross-resistance potential with ibalizumab was added.

14. CLINICAL STUDIES

- Efficacy results for Week 48 were deleted from Section 14 because response rates were very similar between Week 24 and Week 48.
- Efficacy results in subjects with DTG- and/or DRV/r-containing OBT were added. Refer to Section II.6.4.4 for additional details.
- A summary of virologic and immunologic outcomes in the Non-randomized Cohort was added to inform providers about response rates in a population with extremely limited treatment options. Refer to Section II.6.3.2 for additional details.

22. Postmarketing Requirements and Commitments

The following postmarketing requirement (PMR) will be issued at the time of approval.

Pediatric Research Equity Act (PREA) PMR 3862-1: Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of fostemsavir in treatment-experienced children living with HIV-1 infection who are less than 18 years of age and weighing at least 40 kg. The safety and antiviral activity of fostemsavir in pediatric subjects must be evaluated for a minimum of 24 weeks.

PMR Milestones

Final Protocol Submission:	11/2020
Study Completion:	06/2023
Final Report Submission:	09/2024

23. Financial Disclosure

Table 244. Covered Clinical Study: BRIGHTE Trial (205888)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 463		
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): 8		
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: 0 Significant payments of other sorts: 8 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: ViiV		
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): 21		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 245. Covered Clinical Study: Phase 2b Trial (205889)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 108		
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): 2		
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: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: ViiV		
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): 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 246. Expert Committee of Allergy-Immunology Subspecialists

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
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): 1		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: ViiV		
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): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

24. References

M-a-85, Revision #15 *Beta Lactam and Other Test Methods for Use Under Appendix N and Section 6 of the Grade A Pasteurized Milk Ordinance* (August 2016)

Grundy, SM, NJ Stone, AL Bailey, C Beam, KK Birtcher, RS Blumenthal, LT Braun, S de Ferranti, J Faiella-Tommasino, DE Forman, R Goldberg, PA Heidenreich, MA Hlatky, DW Jones, D Lloyd-Jones, N Lopez-Pajares, CE Ndumele, CE Orringer, CA Peralta, JJ Saseen, SC Smith, L Sperling, SS Virani, and J Yeboah, 2019, 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, Journal of the American College of Cardiology, 73(24):e285.

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ViiV, 2014, Prescribing Information: Dolutegravir Tablets for Oral Use, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204790s001lbl.pdf.

25. Review Team Acknowledgements

Table 247. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Managers	CAPT Anitra Johnson, DHSc, MSN, RN Nina Mani, PhD, MPH
Nonclinical Reviewer	Kuei-Meng Wu, PhD
Nonclinical Team Leader	Hanan Ghantous, PhD, DABT
Virology Reviewer	Lisa Naeger, PhD
Virology Team Leader	Jules O'Rear, PhD
Office of Clinical Pharmacology Reviewer(s)	Sonia Pahwa, PhD Jihye Ahn, PharmD
Office of Clinical Pharmacology Team Leader(s)	Su-Young Choi, PharmD, PhD Justin Earp, PhD
Clinical Reviewer	Prabha Viswanathan, MD
Clinical Data Scientist	Jun Zhu, MD, PhD Jinzhong Liu, PhD
Clinical Team Leader	Sarita Boyd, PharmD Adam Sherwat, MD
Statistical Reviewer	Fraser Smith, PhD
Statistical Team Leader	Thamban Valappil, PhD
Cross-Disciplinary Team Leader	Sarita Boyd, PharmD
Division Director (OCP)	Kellie Reynolds, PharmD
Division Director (OB)	Dionne Price, PhD
Associate Director of Labeling (DAV)	Stacey Min, PharmD
Deputy Division Director (DAV)	Jeffrey Murray, MD, MPH
Division Director (DAV)	Debra Birnkrant, MD
Office Director (or designated signatory authority)	John Farley, MD

OCP= Office of Clinical Pharmacology

OB= Office of Biostatistics

Table 248. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	
RBPM	LCDR Shamika Brooks, PharmD, MHA, BCPS
Drug Substance	Soumya (Shomo) Mitra, PhD Ali Al Hakim, PhD
Drug Product	Hailin (Sheena) Wang, PhD Stephen Miller, PhD
Process/Facility/Microbiology	Mark Johnson, PhD Pei-I Chu, PhD
Biopharmaceutics	Qi Zhang, PhD Elsbeth Chikhale, PhD
ORA	Nayan Patel, PhD
Comparability Protocol	Sreenivasa Eturi, PhD Lyudmila Soldatova, PhD David Lewis, PhD Hasmukh Patel, PhD
Environmental Analysis	Raanan (Ron) Bloom, PhD
CMC ATL	Stephen Miller, PhD
OPDP	Wendy Lubarsky, PharmD Sam Skariah, PharmD
OSI	Karen Bleich, MD Yang-min (Max) Ning, MD, PhD Kassa Ayalew, MD, MPH
OSE/DMEPA	Valerie Vaughan, PharmD Sevan Kolejian, Pharm D
OSE/DRISK	Till Olickal, PhD, PharmD Naomi Boston, PharmD Cynthia LaCivita, PharmD
DMPP	Susan Redwood, MPH, BSN, RN Sharon Mills, BSN, RN, CCRP LaShawn Griffiths, MSHS-PH, BSN, RN

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
ORA = Office of Regulatory Affairs
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DMPP = Division of Medical Policy Programs
DRISK = Division of Risk Management
[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary.

Table 1. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Jeffrey Murray, MD, MPH	OND/DAV	Sections I, II ☐ Authored ☒ Approved
Deputy Director	**Signature:** Jeffrey S. Murray -S Digitally signed by Jeffrey S. Murray -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300079703, cn=Jeffrey S. Murray -S Date: 2020.06.30 14:45:16 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Stacey Min, PharmD	OND/DAV	Section 21 ☒ Authored ☐ Approved
Associate Director for Labeling	**Signature:** Stacey Min -S Digitally signed by Stacey Min -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacey Min -S, 0.9.2342.19200300.100.1.1=2000365089 Date: 2020.06.30 00:47:13 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Sarita Boyd, PharmD	OND/DAV	☒ Authored Section I ☒ Approved Section II, Section III (15, 16, 17, 20, 21, 22, 23
Cross-Disciplinary Team Lead	**Signature:** Sarita D. Boyd -S Digitally signed by Sarita D. Boyd -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarita D. Boyd -S, 0.9.2342.19200300.100.1.1=0013717673 Date: 2020.06.30 09:42:12 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Adam Sherwat, MD	OND/DAV	Section 7.7.2 ☒ Authored ☐ Approved
Team Leader	**Signature:** Adam I. Sherwat -S Digitally signed by Adam I. Sherwat -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011772218, cn=Adam I. Sherwat -S Date: 2020.06.30 09:51:14 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Prabha Viswanathan, MD	OND/DAV	Sections 2, 3, 4, 6 (6.2, 6.3, 6.4), 7 (7.2 - 7.7), 8 (8.3, 8.4), 10, 11, 12, 15, 16, 17, 20, 22, 23 ☒ Authored ☐ Approved
Reviewer	**Signature:** Prabha Viswanathan -S Digitally signed by Prabha Viswanathan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000508593, cn=Prabha Viswanathan -S Date: 2020.06.30 13:18:35 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Stephen Miller, PhD	OPQ/DNDPI	Section 9 ☒ Authored ☒ Approved
Team Leader	**Signature:** Stephen Miller -S Digitally signed by Stephen Miller -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stephen Miller -S, 0.9.2342.19200300.100.1.1=1300087013 Date: 2020.06.30 18:20:48 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Thamban Valappil, PhD	OB/DBIV	Sections 2, 6.2.3, 6.3.1, 6.3.2, 6.3.3, 6.4.1, 6.4.4, 15.1, 16.1, 16.2, 16.3, 16.4 ☐ Authored ☒ Approved
Team Leader	**Signature:** Thamban I. Valappil -S Digitally signed by Thamban I. Valappil -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151694, cn=Thamban I. Valappil -S Date: 2020.06.30 12:20:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Fraser Smith, PhD	OB/DBIV	Sections 2, 6.2.3, 6.3.1, 6.3.2, 6.3.3, 6.4.1, 6.4.4, 15.1, 16.1, 16.2, 16.3, 16.4 ☒ Authored ☒ Approved
Reviewer	**Signature:** Fraser B. Smith -S Digitally signed by Fraser B. Smith -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300174092, cn=Fraser B. Smith -S Date: 2020.06.30 20:52:26 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Hanan Ghantous, PhD, DABT	OND/DAV/DPTID	Sections 7.1, 8.4, 13.1 ☐ Authored ☒ Approved
Team Leader	**Signature:** Hanan N. Ghantous -S Digitally signed by Hanan N. Ghantous -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300169484, cn=Hanan N. Ghantous -S Date: 2020.06.30 09:53:11 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Kuei-Meng Wu, PhD	OND/DAV/DPTID	Sections 7.1, 8.4, 13.1 ☒ Authored ☐ Approved
Reviewer	**Signature:** Kueimeng Wu -S Digitally signed by Kueimeng Wu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kueimeng Wu -S, 0.9.2342.19200300.100.1.1=1300067876 Date: 2020.06.30 16:23:59 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Virology	Jules O'Rear, PhD	OND/OID/DAV	Sections 2, 5, 5.1, 6.4.1, 6.4.2, 6.4.3, 6.4.4, 7.7.1, 18, 19 ☐ Authored ☒ Approved
Team Leader	**Signature:** Julian J. O'rear -S Digitally signed by Julian J. O'rear -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150659, cn=Julian J. O'rear -S Date: 2020.07.01 08:39:24 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Virology	Lisa Naeger, PhD		Sections 2, 5, 5.1, 6.4.1, 6.4.2, 6.4.3, 6.4.4, 7.7.1, 18, 19 ☒ Authored ☒ Approved
Reviewer	**Signature:** Lisa K. Naeger -S Digitally signed by Lisa K. Naeger -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lisa K. Naeger -S, 0.9.2342.19200300.100.1.1=1300191458 Date: 2020.07.01 10:46:39 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Kellie Reynolds, PharmD	OTS/OCP/DIDP	Enter sections. ☐ Authored ☒ Approved Sections 5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.4
Division Director	**Signature:** Kellie S. Reynolds -S Digitally signed by Kellie S. Reynolds -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093770, cn=Kellie S. Reynolds -S Date: 2020.06.30 15:38:16 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Su-Young Choi, PharmD, PhD	OTS/OCP/DIDP	Enter sections. ☐ Authored ☒ Approved Sections 5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.4
Team Leader	**Signature:** Su-young Choi -S Digitally signed by Su-young Choi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Su-young Choi -S, 0.9.2342.19200300.100.1.1=2000766244 Date: 2020.06.30 23:29:37 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Sonia Pahwa, PhD	OTS/OCP/DIDP	Enter sections. ☒ Authored Sections 5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.4 ☐ Approved
Reviewer	**Signature:** Sonia Pahwa -S Digitally signed by Sonia Pahwa -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sonia Pahwa -S, 0.9.2342.19200300.100.1.1=2002011892 Date: 2020.06.30 12:30:12 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Justin Earp, PhD	OTS/OCP/DPM	Enter sections. ☐ Authored ☒ Approved Sections 5, 6.4.3, 14.3
Team Leader	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2020.07.01 15:19:23 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jihye Ahn, PharmD	OTS/OCP/DPM	Enter sections. ☒ Authored Sections 6.4.3, 14.3 ☐ Approved
Reviewer	**Signature:** Jihye Ahn -S (Affiliate) Digitally signed by Jihye Ahn -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001814798, cn=Jihye Ahn -S (Affiliate) Date: 2020.06.30 13:07:17 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical - Regulatory	CAPT Anitra Johnson, DHSc, MSN, RN	OND/DAV	Section 12 ☒ Authored ☐ Approved
Project Manager On behalf of Anitra Johnson	**Signature:** Nina Mani -S Digitally signed by Nina Mani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nina Mani -S, 0.9.2342.19200300.100.1.1=2001231336 Date: 2020.07.01 15:42:57 -04'00'		

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/s/

NINA MANI
07/02/2020 03:09:14 PM

JOHN J FARLEY
07/02/2020 03:12:36 PM