Module 1.8.2

European Union Risk Management Plan (EU-RMP)for Fostemsavir

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RMP version to be assessed as part of this application	
RMP Version number	3.0
Data lock point for this RMP	24 June 2021
Date of final sign off	05 February 2025

Rationale for submitting an updated RMP

Updated the estimated study completion (last subject last visit) and final CSR milestone dates for the ongoing Phase 3 study 205888.

Summary of significant changes in this RMP:

PART	MODULE	Changes made in EU-RMP version 3.0
Part III	III.2 Additional pharmacovigilance activities	Study 205888 completion and final CSR due dates updated.
Part V	V.3 Summary of risk minimisation measures	Final 205888 CSR due date updated.
Annex 2	Tabulated summary of planned, ongoing and completed pharmacovigilance study programme	Final 205888 CSR due date updated.

Other RMP versions under evaluation Not applicable		
RMP Version number	**Submitted on**	**Procedure number**
Not applicable		
Details of the currently approved RMP		
Version number	**Approved with procedure**	**Date of approval (opinion date)**
2.0	PSUSA/10911/202202	01/09/2022

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AI	Attachment Inhibitor
AIDS	Acquired Immune Deficiency Syndrome
APR	Antiretroviral Pregnancy Registry
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV	Atazanavir
AUC	Area Under the Concentration Curve
BCRP	Breast Cancer Resistance Protein
c/ml	Viral copies per ml
CDC	Centers for Disease Control and Prevention
COBI/c	Cobicistat
CPK	Creatine phosphokinase
CSR	Clinical Study Report
CYP	Cytochrome P450
DHHS	Department of Health and Human Services
DRV	Darunavir
DTG	Dolutegravir
EACS	European AIDS Clinical Society
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report

EU	European Union
FDA	Food and Drug Administration
FTC	Emtricitabine
FTR	Fostemsavir
GI	Gastrointestinal
GSK	GlaxoSmithKline
GTE	Generally Treatment-Experienced
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IC50	Inhibitory Concentration producing 50% inhibition
INN	International Nonproprietary Name
IRIS	Immune reconstitution inflammatory syndrome
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for regulatory activities
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NPP	Named Patient Program
NRTI	Nucleoside reverse transcriptase inhibitor
OATP	Organic Anion Transporter Protein
OI	Opportunistic Infections
PI	Protease inhibitor
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PL	Patient Leaflet

PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RAL	Raltegravir
RTV/r	Ritonavir
RMP	Risk Management Plan
RNA	Ribonucleic acid
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TBDR	Texas Birth Defects Registry
TDF	Tenofovir disoproxil fumarate
TdP	Torsades de Pointes
TMR	Temsavir
ULN	Upper Limit of Normal

Trademark Information

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Prezista
Reyataz
Trogarzo
Tybost

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Fostemsavir
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Antiviral for systemic use, Antivirals for treatment of HIV infections, combinations. ATC Code: J05AX29
Marketing Authorisation Holder/ Applicant	ViiV Healthcare
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Rukobia
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Fostemsavir (FTR) is a methyl phosphate prodrug of temsavir (TMR), a human immunodeficiency virus-1 (HIV-1) attachment inhibitor developed for the treatment of adults with multi-drug resistant HIV-1 infection.
	Summary of mode of action: TMR binds directly to the gp120 subunit within the HIV-1 envelope glycoprotein gp160 complex and prevents interaction between the virus and cellular CD4 receptors, thereby preventing viral entry into host CD4+ immune cells.
Hyperlink to the Product Information	Please refer to product information (Module 1.3.1).
Indication(s) in the EEA	Current: Fostemsavir, in combination with other antiretrovirals, is indicated for the treatment of

	adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose of Fostemsavir is one 600 mg tablet orally twice daily.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Prolonged release film-coated tablets. Beige, film coated, biconvex, oval tablets debossed with 'SV 1V7' on one side and plain on the other side. Each film-coated tablet contains 600 mg of FTR (as FTR tromethamine).
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1 Indication

INCIDENCE

Recent data suggests a decline in HIV annual incidence worldwide. Approximately 1.8 million [uncertainty bounds 1.4-2.4 million] adults and children were newly infected with HIV in 2017, down from approximately 2.2 million [2.0-2.5 million] new HIV infections in 2010 [UNAIDS, 2018a; UNAIDS, 2016]. The sharpest declines in new HIV infections in all ages occurred in sub-Saharan Africa (30%) between 2010 and 2017 [UNAIDS, 2018a]. However, the incidence of HIV infection in the Middle East, North Africa, and Eastern Europe and Central Asia has doubled over the last 20 years, following years of stability [UNAIDS, 2018a]. In 2015, an estimated 190,000 (170,000-200,000) new infections occurred in Eastern Europe and Central Asia. By comparison, the estimated 2015 incidence in Western and Central Europe and North America was 91,000 new infections (95% CI: 89,000-97,000) [UNAIDS, 2016]. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that there were 38,500 new HIV infections in 2015, an 8% decline in annual infections from 2010 (41,800) [CDC, 2018b].

Incidence of becoming heavily treatment-experienced (HTE) among HIV-positive patients has not been described in any setting.

PREVALENCE

Worldwide, at the end of 2017, an estimated 36.9 million (uncertainty bounds: 31.1 million–43.9 million) people were living with HIV infection, comprising an estimated 0.8% of adults aged 15-49 years [CDC, 2018a]. However, the global burden of HIV varies by country and region. In Eastern Europe and Central Asia, a reported 1.4 million people (1.3 million-1.6 million) were living with HIV at the end of 2017, compared to 2.2 million people (1.9 million-2.4 million) living in Western and Central Europe and North America. In the United States, the CDC estimated that 1,122,900 people aged 13 and older were living with HIV in 2015 [CDC, 2018a].

Sub-Saharan Africa remains the most severely HIV-affected region, with nearly 1 in every 20 adults (4.7%) living with HIV, and accounting for 71% of the people living with HIV worldwide [UNAIDS, 2014]. After sub-Saharan Africa, the regions with the highest adult HIV prevalence in 2013 were the Caribbean (1.1%) and Eastern Europe and Central Asia (0.6%) [UNAIDS, 2014].

PREVALENCE OF HEAVILY TREATMENT-EXPERIENCED (HTE) HIV PATIENTS

Estimating the prevalence of HTE patients among the HIV-infected population is challenging due to lack of a standardized definition for HTE, and the inherent heterogeneity of this subset

of patients. All definitions of HTE, however, reflect the inability to form new suppressive regimens as a critical component [Panel on Antiretroviral Guidelines for Adults and Adolescents, 2018; Günthard, 2014; Grupo de Estudio del SIDA (GeSIDA), 2015; European AIDS Clinical Society, 2017]. Although drug resistance is the primary driver limiting effective ART treatment options, underlying comorbidities, contraindications, tolerability issues, toxicity, and dosing concerns further undermine the ability to create viable, suppressive regimens, and should be considered when defining HTE patients. Further complicating the identification of the HTE population, multiclass resistance may be observed in long-term survivors, partial adherers to treatment, patients initially infected with drug-resistant virus, and patients infected through perinatal transmission. Ideally, sizing of the HTE population should account for all factors limiting treatment selection simultaneously. To date, only individual aspects of HTE classification have primarily been described in the literature.

An analysis of the OPERA Cohort, which represents approximately 7% of all US HIV patients in care, identified an HTE prevalence of 5.1%, using a definition based on both treatment history (prior exposure to ≥3 core agent classes) and current treatment with a core agent typically reserved for HTE patients (dolutegravir BID, darunavir BID, etravirine + dolutegravir, INSTI+PI, maraviroc, or enfuvirtide). This definition included patients regardless of reasons for discontinuing prior regimens in order to capture individuals with limited remaining treatment options due to any combination of factors [Hsu, 2018]. A cross-sectional description of these HTE patients found that 68% of those with a viral load assessment in the prior 90 days were stable on their current regimen, as indicated by a suppressed viral load (<50 copies/mL).

MULTICLASS RESISTANCE

Decreasing trends in the prevalence of three-class resistance (NNRTI+PI+NRTI) have been observed in Europe. Studies from France [Assoumou, 2013], Portugal [Vercauteren, 2013], and Sweden [Bontell, 2013] report three-class resistance rates based on nationwide data using a similar definition of class resistance (resistance to all drugs in the class). Triple-class resistance rates vary from 2.6% in 2009 in Sweden, to 0.9% in 2009 in France, to 0.6% for the period 2009-2012 in Portugal. In Sweden, three-class resistance rates have consecutively declined each year, reaching a low of 1.4% in 2011. In Italy, three-class resistance using a less restrictive definition (resistance to at least one drug in each of 3 classes) resulted in resistance rates higher than in other European studies (21% in 2007 and 14% in 2009) [Di Giambenedetto, 2011].

In the US, similar trends for three-class resistance (NRTI+PI+NNRTI) have been observed between 2003 to 2012 (from 25% to 9%), driven by decreased resistance to PIs (43% to 21%) and NRTIs (79% to 57%), while observing a slight increase in NNRTI resistance (68% to 75%) [Paquet, 2014]. A comparable decrease in prevalence of three-class resistance for the 2001-2011 period was shown in a Canadian study, where three-class resistance was 28.4% before 2003 and decreased to 6.9% in 2011 [Charest, 2014].

Declining trends of resistance to the protease and reverse transcriptase drug classes most likely reflect HIV treatment advancement. The availability of antiretrovirals directed at novel anti-HIV targets, including INSTIs, decrease dependence on the three major classes of antiretroviral

drugs for HIV management. Additionally, newer agents that do not show cross-resistance with the previous generation of drugs, such as darunavir and etravirine, have more recently become available.

Since the introduction of INSTIs, resistance to these drugs has been increasing. In the US, Obermeier et al., [Obermeier, 2014] estimated an increase of four-class resistance (resistance to at least one drug in NRTI, PI, NNRTI and INSTI classes) from 2.4% in 2009 to 4.5% in 2012. Hurt and colleagues [Hurt, 2014] observed that 55% of the patients with four-class resistance (2.3% of treatment-experienced patients between 2009-2012) had intermediate- to high-level resistance to dolutegravir.

A systematic literature review of drug resistance in HIV-1–infected children showed that rates of multiclass resistance (NRTI + NNRTI + PI) in treatment-experienced children ranged from 0% in some African countries (where PIs might not have been available yet) to 19%-33% in Brazil. The rates of multiclass resistance in North America ranged from 0% to 5% and in Europe ranged from 0% to 16% [Rojas-Sanchez, 2014].

SI.1.1 Demographics of the population in the proposed indication and risk factors for the disease:

No epidemiological demographic data is available for HTE HIV-infected adults with multidrug resistance. In the Phase 3 clinical study conducted with ibalizumab in HTE subjects, the patients enrolled had a median age of 53 years (range 23-65 years), were predominantly male (85%) and White (55%) and had been diagnosed with HIV for a mean of 20 years (median 23, range 2-30 years) [Emu, 2018]. These characteristics are similar to those of subjects enrolled in the FTR Phase 3 study where the median age was 49 years (range 17-73 years), 78% were male, 70% were White, 71% had been treated for HIV infection for 16 years or more, and 86% had a history of AIDS (205888 (AI438047)] 96 Week CSR [Clinical study report]).

Risk factors for the disease

Risk factors for the disease in HTE patients are similar to those in other HIV-infected patients. Only specific fluids, such as blood, semen, vaginal secretions, and breast milk, from an HIV-infected person can transmit HIV. These specific fluids must come in contact with a mucous membrane or damaged tissue or be directly injected into the blood-stream (from a needle or syringe) for transmission to possibly occur [CDC, 2018c]. Primary risk factors for HIV transmission include unprotected vaginal, anal and oral sex, as well as the transfusion of contaminated blood and the sharing of contaminated needles and/or syringes, particularly between injection drug users. Unprotected sex between men is the primary driver of HIV transmission in North America and Western and Central Europe, and accounts for the higher proportion of men living with HIV compared to women in these regions [World Health Organization, 2011]. In Eastern Europe and Central Asia, injection drug use and paid sex are the primary drivers. As well, continuing evidence suggests that unprotected paid sex and sex between men are significant driving factors of the epidemic in sub-Saharan Africa [World Health Organization, 2011].

SI.1.2 The main existing treatment options

Constructing antiretroviral regimens for HTE patients is particularly challenging and tends to be highly individualized. Regimen selection is based on treatment history, prior resistance tests, drug intolerances, comorbidities, and patient willingness to take complex regimens with increased pill burden and more complex dosing schedules. The number of fully active antiretroviral drugs is often diminished with successive treatments failures. Therefore, salvage regimens may be quite complex and require multiple antiretroviral drugs with partial residual activities and compromised genetic barriers to resistance to attain virologic suppression (Tang, 2012; Tashima, 2015). Guidelines recommend against discontinuing therapy in patients with few or no remaining therapeutic options, as disease progression is more rapid in the absence of treatment compared with maintaining the patient on a non-suppressive regimen. Patients often continue to receive a stable, yet non-suppressive, regimen with the goal of preventing disease progression until at least two fully effective drug options become available.

The ARV drugs most frequently used for advanced salvage therapy (all administered twice daily) are ritonavir-boosted darunavir, dolutegravir, etravirine, maraviroc and enfuvirtide [Tang, 2012; Rusconi, 2013]. In the US and the EU, ibalizumab (TROGARZO), has recently become available specifically for use in combination with other antiretroviral(s) for the treatment of adults infected with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

The number of people dying from Acquired Immune Deficiency Syndrome (AIDS)-related causes began to decline in the mid-2000s because of scaled-up combination antiretroviral therapy and the steady decline in HIV incidence since the peak in 1997. In 2017, an estimated 940,000 (670,000–1.3 million) people died from AIDS-related causes worldwide, representing a 34% decline in AIDS-related mortality from 2010 [UNAIDS, 2018a]. AIDS mortality peaked in 2004 with 1.9 million [1.4-2.7 million] deaths. Sub-Saharan Africa, particularly eastern and Southern Africa, experienced a 42% decline in AIDS-related deaths between 2010 and 2017. Western and central Africa saw a 24% reduction over the same period [UNAIDS, 2018a]. Western and Central Europe and North America experienced a 36% decline in AIDS-related deaths from 2010 to 2017; in contrast, Eastern Europe and Central Asia saw no reductions in AIDS-related mortality, and the Middle East and North Africa saw an 11% increase [UNAIDS, 2018a]. Between 2010 and 2017, Asia and the Pacific saw declines in AIDS-related deaths of 39%, Latin America 12%, and the Caribbean 23% [UNAIDS, 2018a]. Mortality reductions have been higher among women compared to men, particularly in sub-Saharan Africa, where women have higher treatment coverage than men [UNAIDS, 2018a].

Globally, deaths among children younger than 15 years of age are reported to also be declining. In 2017, an estimated 110,000 (63,000–160,000) children aged 0-14 years had died from AIDS-related causes, representing 61% fewer deaths in this age group than in 2005 when 280,000 [160,000-420,000] children died [UNAIDS, 2018b].

While mortality rates among the HTE patient population have not been estimated, patients with multiclass resistance or multiclass treatment failure have demonstrated increased risk of AIDS-related mortality in multiple studies, even after controlling for CD4 cell counts and viral load. [Palella, 2014; Pursuing Later Treatment Options II, 2012; Deeks, 2009; Grover, 2008]. When CD4 count is considered, it is highly predictive of near-term risk of opportunistic diseases and mortality among HIV patients, particularly those infected with MDR virus [Egger, 2002; Hogg, 2001; Institute of Medicine, 2010]. In a study of 2,488 individuals from North American and European HIV cohorts with three-class virologic failure, current CD4 cell count but not current viral load was associated with short-term risk of death [Lederberger, 2004]. Baseline viral load is a relatively weak predictor of clinical events and death, compared with CD4 cell count, in patients with advanced immunodeficiency [Langford, 2007]. Even in the presence of resistance mutations, antiretroviral therapy resulting in any appreciable degree of viral load suppression can have benefit to the CD4 cell count, reducing disease progression and risk of death [Lederberger, 2004].

SI.1.4 Important co-morbidities

The most common co-morbid conditions in individuals with persistent HIV viremia are those relating to opportunistic infections as a result of suppression of T-cell mediated immunity. Despite marked reductions in mortality due to opportunistic infections with more widespread use of antiretroviral therapy (ART), morbidity and mortality in individuals with HIV continues to be greater than in the general population. These morbidities include cardiovascular disease, many non-AIDS cancers, non-AIDS infections, chronic obstructive pulmonary disease, osteoporosis, type II diabetes, thromboembolic disease, liver disease, renal disease, neurocognitive dysfunction, and frailty. The appropriate management of these co-morbidities has increasingly become an integral part of the overall management of individuals living with HIV.

Opportunistic infections

Opportunistic infections (OI) are a result of suppression of T-cell mediated immunity. Common OIs include fungal (e.g. cryptococcosis, pneumocystis jiroveci pneumonia (PJP)), bacterial (e.g. tuberculosis), viral (e.g. CMV, herpes simplex virus), and parasitic (e.g. toxoplasmosis) infections. In high-income countries, the use of ART and the use of OI prophylactic medications have resulted in dramatic reductions in the incidence of OIs [Cascade Collaboration, 2006]. In low- and middle-income countries, opportunistic infections continue to be a major co-morbidity and cause of death. In South Africa, HIV patients receiving care in clinics in KwaZulu-Natal in 2014, 21.7% were co-infected with tuberculosis [Nlooto, 2017]. In nearly 3,000 HIV patients receiving care in Guangxi Province, China, between 2012 and 2013, 4.8% were co-infected with tuberculosis [Zhang, 2016]. A study of all-cause mortality in 303 HIV patients in Shanghai, China from 2006-2015 found that PJP (26.4%), tuberculosis (18.5%), and recurrent bacterial pneumonia (10.2%) were among the most common AIDS-related causes of death [Ji, 2017].

Hepatitis C Virus (HCV) / Hepatitis B Virus (HBV) co-infection and liver disease

Liver-related death has been reported to be one of the most frequent causes of non-AIDS related mortality in HIV subjects, and has shown to be associated with advanced immunodeficiency, HCV and/or HBV co-infection, and injection drug use [Weber, 2006]. Although variable by the route of transmission, general estimates for HIV/HBV co-infection range between 5 – 15% and estimates for HIV/HCV co-infection range between 25% - 35% [Inoue, 2016; Rockstroh, 2012]. Generally, HIV-positive patients co-infected with viral hepatitis experience a more rapid progression of liver fibrosis, a higher rate of cirrhosis decompensation and an increased risk of hepatocellular carcinoma at lower CD4+ T cell counts [Thio, 2009]. Mortality from liver disease, mainly due to hepatitis virus infections, ranges from 4% [Smith, 2003] to over 14.5% [Weber, 2006] of all deaths in HIV infected populations.

Malignancies

Malignancies continue to be a major cause of morbidity and mortality in HIV-infected persons. HIV-infected individuals have an increased risk of developing cancer – both AIDS-associated malignancies (ADM) and non-AIDS associated malignancies (NADM). ADMs are linked to immune suppression, and include Kaposi sarcoma (KS), cervical cancer, and non-Hodgkin's lymphomas [National Cancer Institute, 2011]. Elevated prevalence of traditional risk factors for cancer, including older age, smoking and viral co-infections play a significant role in the increased risk of malignancies in HIV-infected patients [Silverberg, 2007]. The risk of developing ADM has been well established in published literature to be closely and inversely associated with CD4 cell count, while the incidence of NADM has been shown to increase with declining CD4 count in most but not all studies [Monforte, 2008].

Cardiovascular Disease

Given the aging of the HIV-infected population, cardiovascular disease (CVD), is becoming a more common co-morbidity with time. HIV infection is a significant predictor of CVD, including myocardial infarction (MI) and atherosclerosis, even among patients with viral load suppression [So-Armah, 2014]. Older age may interact with HIV infection to synergistically increase the risk of CVD, though insufficient data are available to support this hypothesis [So-Armah, 2014]. CVD is the cause of death in up to 10% of HIV-infected patients in the United States, Europe and Australia [Data Collection on Adverse Events of Anti HIV Drugs, 2010]. Studies have shown there is an increased risk of coronary artery disease (CAD) and MI in HIV infected versus uninfected subjects [Calza, 2010].

Type 2 Diabetes Mellitus (DM)

The most recent prevalence estimates of DM in the general population in the United States is 9.4% [CDC, 2017]. Studies among HIV-positive individuals estimate prevalence to be between 5-14% [Polsky, 2011; Brown, 2005a; Brown, 2005b; Smit, 2017] in the United States and between 2-9% [Smit, 2017; De Wit, 2008; Calza, 2011;Galli, 2012] in other Western countries. It is believed that use of cART, while being more effective at controlling an individual's viral load, increase the risk of DM. Protease inhibitors, as a class of drugs, have been linked to increased risk of DM, however, most of the risk appears to be linked to the drug indinavir

[Brown, 2005b; Capeau, 2012; Ledergerber, 2007; Brambilla, 2003]. Certain NRTIs, specifically didanosine [De Wit, 2008; Capeau, 2012] stavudine [Brown, 2005b; De Wit, 2008; Capeau, 2012; Brambilla, 2003], lamivudine [Brown, 2005b; Tien, 2007], have been associated with an increased risk of DM, while others, such as tenofovir [Riyaten, 2015] and emtricitabine [Riyaten, 2015], have been associated with a decreased risk of DM. As people are living longer than ever with HIV, understanding the link between HIV and DM is more important than ever.

Musculoskeletal Disorders

Bone Disorders

HIV-infected individuals are more likely to experience low bone mineral density (BMD), and therefore may have a higher risk of fragility fracture compared to uninfected individuals [Womack, 2011]. A meta-analysis reported 67% of HIV-infected individuals exhibited reduced BMD; 15% had osteoporosis [Brown, 2006]. Rates of avascular necrosis in HIV patients were greater than the rates in the general population in several studies [Walker-Bone, 2016]. Risk factors of low BMD are complex, but likely contributors include: viraemia, ART-related factors, consequences of chronic HIV infection like weight loss, high rates of tobacco and alcohol use, low vitamin D levels (60% - 75% in HIV infected cohorts), elevated tumor necrosis factor (TNF), hypogonadism, relative central fat accumulation, and use of glucocorticoids, which can be prescribed to treat complications of HIV or other comorbidities [McComsey, 2010; Walker-Bone, 2016]. In a retrospective cohort study involving 56,660 HIV-infected patients followed for mean of 5.4 patient-years, exposure to TDF and ritonavir boosted protease inhibitors was associated with an increased osteoporotic fracture risk [Bedimo, 2012].

Rhabdomyolysis

Skeletal muscular myopathies are characterized by muscle pain (myalgia), weakness, and edema, and are diagnosed by detecting elevated blood creatinine phosphokinase (CPK) and myoglobin [Authier, 2005]. Severe myopathies include rhabdomyolysis and myositis, which can result in long-term dysfunction or death in severe cases. Rhabdomyolysis is a rare condition with an incidence of about 2 cases per 10,000 person-years in the U.S. [Nichols, 2007]. Rhabdomyolysis risk has been linked to individual drugs and drug interactions, including antiretroviral (ARV) treatment for HIV infection and treatment of hyperlipidemia with hydroxymethylglutaryl-coenzyme A reductase inhibitors (“statins”) [Aboulafia, 2000; Benveniste, 1999; Chariot, 1994; Mastroianni, 2001; Mendila, 1997]. HIV infection and HAART are independent risk factors for the development of rhabdomyolysis, and other risk factors for rhabdomyolysis in HIV-infected patients include co-infection with hepatitis C, medication-related adverse effects, drug-drug interactions and alcohol and illicit drug use [Towner, 2011; Lennox, 2009; Madeddu, 2015].

HIV-Associated Neurocognitive Disorders (HAND)

Neurocognitive deficiencies have been observed in HIV-infected individuals as a result of viral infection in the brain and central nervous system. HAND is often characterised by problems with memory and concentration, loss of motor skills, and behavioural changes. Estimates of

HAND prevalence are fairly consistent in HIV cohorts globally, including high- and low-income contexts, demonstrating the pervasiveness of this co-morbidity. HAND prevalence in the US-based Multicenter AIDS Cohort Study was 33% among 364 men observed in 2007-2008 [Sacktor, 2016].

Pulmonary Disorders

Non-infection pulmonary disorders, including chronic obstructive pulmonary disorder (COPD), pulmonary hypertension, and lung cancer are co-morbidities in HIV patients that are more prevalent than in the general population irrespective of smoking status and ART treatment status [Thao, 2017].

Kidney Disease

Kidney disease is increasingly observed in the general population of adults aged 50 and older in the United States, and HIV-infected populations have higher rates of chronic kidney disease (CKD), acute kidney injury (AKI), and end-stage renal disease (ESRD) than the general population [Nadkarni, 2014]. As in the general population, black race and comorbid diabetes and hypertension are associated with an increased risk of CKD and ESRD among HIV-infected individuals. The prevalence of comorbid renal disease among HIV patients in Birmingham, Alabama, USA, increased with age group, with a prevalence of 2.2% in the 18-29 age group to 23.3% in the 60+ age group [Vance, 2011].

While advanced age contributes to increased risk of kidney disease, the use of concomitant medications among older HIV-infected individuals for chronic diseases or opportunistic infections may also contribute to nephrotoxicity [Nadkarni, 2014]. The use of tenofovir, indinavir, and ritonavir-boosted PI regimens have been associated with a higher risk of CKD in observational studies [Nadkarni, 2014; Serrano-Villar, 2016].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE:

SII.1 QT prolongation

Although no cardiac tachyarrhythmias were reported in the nonclinical safety pharmacology studies, increases in QT were detected in vivo in the telemetered dog study at TMR concentrations ≥ 3.6 µg/mL (≥7.6 µM). In the in vitro hERG assay, the nominal IC50 of TMR was 27 µM (12.8 µg/mL) which is approximately 63x higher than the TMR free Cmax at the recommended human dose (RHD). In the rabbit Purkinje fibre assay, TMR prolonged action potential duration (by 11-12%) at a nominal concentration of 30 µM, with no effect at lower concentrations. There was no significant effect of FTR in either assay (note: plasma concentrations of FTR are generally not detectable). A delay in cardiac repolarization, such as QT interval prolongation, creates an electrophysiological environment that favours the development of cardiac tachyarrhythmias, particularly Torsade de Pointes (TdP), but also other ventricular tachyarrhythmias.

SII.2 Testicular toxicity

Minimal testicular degeneration with changes in sperm motility, morphology, and sperm count were observed in the 6-month rat toxicity study at dose ≥ 100 mg/kg/day (male AUC ≥ 1865 µg.h/mL; >70x RHD AUC). There were no testicular findings in the 6-month rat study at 30 mg/kg/day (AUC 751 µg.h/mL, >25x AUC at the recommended human dose (RHD) of 600 mg twice daily) and no testicular toxicity was noted in the 2-, 4- or 39-week studies in dogs.

Testicular findings were reported in a fertility and early embryonic development study in rats at doses ≥ 100 mg/kg/day (male AUC 1740 µg.h/mL, >60x RHD AUC). The no adverse effect level (NOAEL) for testicular toxicity was 30 mg/kg/day (>25x RHD AUC) and 10 mg/kg/day (7x RHD AUC) in the rat 26-week and fertility studies, respectively. Considering that the testicular findings occurred only at high systemic exposure in rats, were partially reversible, were not associated with effects on fertility and were not observed in the dogs, the potential risk for testicular changes in humans is low.

SII.3 Reproductive and developmental toxicity

Oral administration of fostemsavir to pregnant rats from days 6 to 15 of gestation elicited transient and non-adverse maternal toxicities at doses ≥300 mg/kg/day (AUC >95x RHD AUC) and developmental toxicities at a dose of 1000 mg/kg/day (AUC >180x RHD AUC). Maternal toxicity included non-adverse reductions in food consumption and group mean body weights, thinning hair or alopecia, and red perivaginal substance. Developmental toxicities consisted of fetal malformation (cleft palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw and protruding tongue), as well as reduction in mean fetal body weights.

In the pivotal study in rats, there were no effects on pre- or post-natal development at a dose of 600 mg/kg/day (>100x RHD AUC).

Oral administration of fostemsavir to pregnant rabbits from days 7 to 19 of gestation elicited minimal maternal toxicities at doses of 50 to 100 mg/kg/day including decreased food consumption and decrease in weight gain. At doses ≥250 mg/kg/day (>100x RHD AUC), maternal toxicity included death, abortion and euthanasia in moribund condition due to body weight loss. Developmental toxicities at doses ≥100 mg/kg/day included reduction in male fetal body weights and an increase in post-implantation loss. Since the developmental toxicity observed at 100 mg/kg/day were observed in conjunction with maternal toxicity, FTR was not considered a selective teratogen in rabbits. In a definitive study in rabbits, there were no effects on pre- or post-natal development at a dose of 50 mg/kg/day (>20x RHD AUC).

In a pre- and postnatal development study in rats, lactational exposure at 300 mg/kg/day (corresponding to a plasma exposure multiple of >95x RHD AUC) was associated with reduced neonatal survival from post-natal days 7 to 14.

FTR derived radioactivity (i.e. TMR and/or TMR derived metabolites) has been shown to cross the placenta in timed pregnant rats following a single dose of radiolabelled FTR, resulting in exposure to all evaluated foetal tissues.

Relevance of these findings to human usage is unknown. Use in pregnant and lactating women is discussed further in Part II: Module SVII.1.2.

SII.4 Photodegradant containing a beta-lactam ring

During manufacture of FTR, there is the potential for the formation of trace amounts of a photodegradant (BMT-218946) containing a beta-lactam ring and therefore the potential to initiate a Type I hypersensitivity reaction. The estimated maximum theoretical concentration of BMT-218946 after oral therapy with FTR is approximately 8.7 ng/mL (14 nM).

The systemic sensitizing potential of BMT-218946 and TMR were assessed using in silico and in vitro studies. In the direct peptide reactivity assay, BMT-218946 and TMR caused non-detectable and minimal lysine depletion, respectively. Further, BMT-218946 was less reactive than penicillin G sodium, cefotiam hydrochloride and cinnamic aldehyde, all of which are known sensitizers. Of note, BMT-218946 was also less reactive than the parent active moiety (TMR). This indicates that the BMT-218946 photodegradant is unlikely to react with lysine residues present in proteins.

BMT-218946 was tested in a Radio-Allergo-Sorbent Test (RAST)-inhibition study and the basophil activation test (BAT) with ezetimibe for comparison. The BAT and RAST-Inhibition results indicated that BMT-218946 yields a lack of cross-reactivity to beta-lactam-specific IgE comparable to that of ezetimibe, which contains a non-acylating beta-lactam ring and, unlike beta-lactams, has been reported to rarely produce hypersensitivity reactions.

At the highest concentration of the FTR photodegradant ever observed (30 µg/g in FTR tablets manufactured prior to the implementation of current controls), the estimated serum level of the

photodegradant (approximately 8.7 ng/mL) just reaches the starting dose commonly used in beta-lactam antibiotic desensitization protocols.

In conclusion, cross-reactivity of beta-lactam specific IgE with BMT-218946 is rare, and when it happens it is weak. Thus, not only does BMT-218946 lack evidence of immunogenicity, it is also poorly antigenic in beta-lactam allergic patients. The combination of low antigenicity and very low maximal BMT-218946 serum concentration (>2000-fold lower than the degranulating concentration used in the BAT studies and just reaching the starting dose commonly used in beta-lactam antibiotic desensitization protocols) makes a clinically relevant exposure to BMT-218946 unlikely.

It is possible that drug substance administered in nonclinical animal studies contained trace amounts of BMT-218946 which were not detectable by the analytical method employed. Animals treated with FTR were evaluated for dermal and respiratory events that are consistent with Type I hypersensitivity reaction. There was no evidence of such events across all animal studies including a multiple dose study in dogs of 9 months duration.

Type I immediate hypersensitivity reaction is included in Part II: Module SVII 1.1.

SII.5 Drug interactions

TMR is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP), but not of Organic Anion Transporter Protein (OATP) 1B1 or OATP1B3. Its biotransformation to two circulating major metabolites, BMS-646915 and BMS-930644, is mediated by unidentified esterases (primary route of metabolism) and CYP3A4 enzymes, respectively. TMR exposures may be influenced by modulators of CYP3A4, P-gp and/or BCRP activity.

In vitro, TMR was an inhibitor of OAT1B1 and OAT1B3 (IC50= 32 and 16 µM respectively), and TMR's two metabolites (BMS-646915 and BMS-930644) inhibited BCRP in vitro (IC50=12.4 µM for TMR). Based on a BID dose of 600 mg FTR and guidelines [FDA Draft Guidance, 2017; EMA guideline, 2013], drug interactions may be expected with substrates of BCRP and OATP1B3 (as observed in the rosuvastatin drug interaction study, see Part II: Module SIV.1), and OATP1B1.

SII.6 Impact on efficacy of varying baseline in vitro susceptibility (diversity of virus envelopes, IC50, subtype AE, group O)

Due to the inherent genotypic diversity of HIV-1 gp120, intrinsic phenotypic susceptibility to temsavir is highly variable and susceptibly to TMR has been observed over a broad range, with IC50 values from low picomolar to >5mM.

TMR has been analyzed for its antiviral activity using a number of cell-based systems. These include laboratory strains, clinical isolates in peripheral blood mononuclear cells (PBMCs) or analysis of over 1300 separate envelopes in the PhenoSense Entry Assay performed at Monogram BioSciences.

Susceptibility to TMR of different HIV subtypes isolated throughout the world was studied in vitro using the Phenosense EntryTM assay. Potent activity was observed for the majority of

viruses from each subtype studied (A, B, C, AG, BF, F, F1), suggesting that FTR could be effective in all parts of the world against all subtypes. The exception was subtype AE viruses, where all 5 viruses tested exhibited decreased intrinsic susceptibility to TMR [Document Number 2019N395182]. Cell culture studies also confirmed antiviral activity of TMR against multiple subtypes (A, B, C, D, F) and decreased susceptibility against subtypes CRF01_AE (E) and group O isolates [Document Number 2017N338504].

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Exposure data is provided by population for the pivotal Phase 3 study (205888/AI438047, HTE subjects) and the Phase 2b supportive study (205889/AI438011, generally treatment experienced (GTE) subjects). Exposure data from these two key studies were not pooled as the trial designs are significantly different and each study targets two very different HIV-infected populations. Furthermore, in the Phase 2b study, FTR doses in the early part of the study differed from those in the Phase 3 study.

Exposure data from the Phase 2a proof of concept study, which included 16 treatment-naïve and 34 treatment-experienced subjects, is not included due to the significant differences in the design; in particular, subjects were only treated with FTR (as monotherapy) for a total of 8 days.

Table 2 Data cut-off dates for studies supporting the safety specification included in the initial application

Study Number	Phase	Patient population	Study time point of analysis	Data cut-off date[1]
205889 (AI438011)	2b	GTE	End of study	08-Dec-2017
205888 (AI438047)	3	HTE	Week 240	24-Jun-2021

1. The cut-off date is the date when the data used in the analysis below were extracted.

Table 3 Number of subjects in the pivotal and supporting FTR Phase 2b/3 studies with adult subjects

Study Number	Phase	Patient population	Age range of subjects in FTR treatment groups[1] (n, %)	Number in FTR treatment groups[2,3]	Number on comparator[2]	Total[2]
205889 (AI438011)	2b	GTE	≤18 (0) 19-64yrs (198, 99%) ≥65 years (2, 1%)	200	51	251
205888 (AI438047)	3	HTE	≤18 years (5, 1%) 19-64yrs (354, 95%) ≥65 years (12, 3%)	371	None	371

1. 205889 End of Study (EOS) Table 1.9 Summary of Demographic Characteristics Intent-to-Treat Exposed population (ITT-E, n=251); 205888 96W Table 1.8 Summary of Demographic Characteristics (ITT-E, n=371)
2. 205889 EOS Table 1.7 Summary of Study Populations (205889) – Safety population; 205888: Table 1.6 Summary of Study Populations (ITT-E population, n=371).
3. 205888: N=371 consists of 272 Randomized subjects with 1-2 fully active ARVs available at study start that may be combined with FTR as part of an optimized background therapy, and 99 Non-randomized subjects with 0 fully active and approved ARVs available at study start.

Table 4 Duration of exposure to FTR (all doses[1]) in GTE adults (Study 205889)

Cumulative (person time) GTE patients		
Duration of exposure	**Patients**	**Person years[2]**
<2 weeks	3 (2%)	<0.1
2 to <4 weeks	0	0
4 to <8 weeks	5 (3%)	0.5
8 to <12 weeks	2 (1%)	0.3
12 to <16 weeks	2 (1%)	0.5
16 to <20 weeks	5 (3%)	1.6
20 to <24 weeks	2 (1%)	0.8
24 to <32 weeks	2 (1%)	1.5
32 to <40 weeks	5 (3%)	3.3
40 to <48 weeks	5 (3%)	4.1
48 to <96 weeks	33 (17%)	44.5
96 to <144 weeks	12 (6%)	27.2
144 to <192 weeks	9 (5%)	28.6
192 to <240 weeks	16 (8%)	67.6
>= 240 weeks	98 (49%)	487.1
Total	**200**	**667.7**

Data Source 205889 Post hoc RMP Table 1 ITT-E population.

1. After the Week 48 analysis, subjects originally randomized to 1 of the 4 FTR groups received OL FTR at the continuation dose of 1200 mg once daily plus TDF 300 mg once daily and RAL 400 mg twice per day, while subjects in the reference arm were retained on open-label ATV/r 300/100 mg once daily plus TDF and RAL. A number of subjects remained on their randomized dose of FTR beyond the Week 96 timepoint. Week 96 data reflect a mix of subjects who remained on their randomized dose of FTR vs. those subjects who had switched to the continuation dose of FTR. By Week 110, all subjects randomized to FTR switched to the continuation dose.
2. Sum across subjects of treatment stop date - treatment start date +1 divided by 365.25. Note: When IP Stop Date is missing, duration is calculated up to the date of last visit or the recorded date of withdrawal/completion, whichever is earlier.

Table 5 Duration of exposure to 600 mg BID FTR in HTE adults (Study 205888)

Cumulative (person time) HTE patients		
Duration of exposure	**Patients[2]**	**Person years[1]**
<2 weeks	6 (2%)	0.1
2 to <4 weeks	2 (<1%)	0.1
4 to <8 weeks	5 (1%)	0.5
8 to <12 weeks	2 (<1%)	0.4
12 to <16 weeks	8 (2%)	2.2
16 to <20 weeks	4 (1%)	1.3
20 to <24 weeks	4 (1%)	1.6
24 to <32 weeks	10 (3%)	5.3
32 to <40 weeks	7 (2%)	4.8
40 to <48 weeks	2 (<1%)	1.7
48 to <96 weeks	36 (10%)	47.2
96 to <144 weeks	19 (5%)	42.7
144 to <192 weeks	12 (3%)	38.7
192 to <240 weeks	26 (7)	108.3
240 to <300 weeks	217 (58)	1113.9
>= 300 weeks	10 (3)	59.4
Total	**370**	**1428.28**

Data source 205888 Week 240 Interim AnalysisTable 1.50020 ITT-E population.

1. Sum across subjects of treatment stop date - treatment start date +1 divided by 365.25. Note: When IP Stop Date is missing, duration is calculated up to the date of last visit or the recorded date of withdrawal/completion, whichever is earlier.
2. Total number of subjects exposed to FTR in Study 205888 is 370 as one subject in the Randomized Placebo cohort discontinued from the Study prior to receiving open-label FTR.

Table 6 Exposure to FTR by age group and gender in HTE adults (Study 205888)

Age group (years)	Patients[2]		Person years[1]	
	M	F	M	F
<35	47 (16%)	28 (34%)	175.3	97.4
35 to <49	102 (35%)	28 (35%)	407.4	113.3
50 to 64	129 (45%)	25 (31%)	494.9	98.8
65 to 74	11 (4%)	0	41.2	0
75 to 84	0	0	0	0
≥85	0	0	0	0
Total	**289**	**81**	**1118.7**	**309.5**

Data source: 205888 Week 240 Interim Analysis Table 1.50030. ITT-E population.

1. Sum across subjects of treatment stop date - treatment start date +1 divided by 365.25. Note: When IP Stop Date is missing, duration is calculated up to the date of last visit or the recorded date of withdrawal/completion, whichever is earlier.
2. Total number of subjects exposed to FTR in Study 205888 is 370, as one subject in the Randomized Placebo cohort discontinued from the Study prior to receiving open-label FTR.

Table 7 Exposure to FTR by Dose (Study 205888 and 205889)

Dose of exposure	Patients[3]	Person years[4]
600 mg BID[1]	370 (100%)	1428.3
1200 mg QD[2]	162 (81%)	467.9
Total (600 mg BID or 1200 mg QD)	532	1896.2

1. HTE patients in study 205888. Data source: 205888 Week 240 Interim Analysis Table 1.50020. ITT-E population.
2. GTE patients in Study 205889. Data source: 205889 Post hoc RMP Table 4. ITT-E population. Subjects received FTR at a dose of either 400 mg BID, 800 mg BID, 600 mg QD or 1200 mg QD until all patients reached 48 weeks, at which time all subjects switched to the continuation dose of 1200 mg QD. This exposure data includes all patient time on 1200 mg QD only.
3. Total number of subjects exposed to FTR in Study 205888 is 370, as one subject in the Randomized Placebo cohort discontinued from the Study prior to receiving open-label FTR.
4. Sum across subjects of treatment stop date - treatment start date +1 divided by 365.25. Note: When IP Stop Date is missing, duration is calculated up to the date of last visit or the recorded date of withdrawal/completion, whichever is earlier.

Table 8 Exposure to FTR by ethnic origin

Ethnic origin	GTE (Study 205889)		HTE patients (Study 205888)	
	Patients	Person years	Patients[2]	Person years[3]
Hispanic or Latino	23 (12%)	92.3	107 (29%)	439.9
Not Hispanic or Latino	59 (30%)	186.7	155 (42%)	545.1
Missing[1]	118 (59%)	388.7	108 (29%)	443.2
Total	200	667.7	370	1428.3

Data source: 205889 Post hoc RMP Table 5; 205888 Week 240 Interim Analysis Table 1.50060. ITT-E population

1. Ethnicity was only required to be collected for US subjects. However, ethnicity was recorded for some, but not all non-US subjects.
2. Total number of subjects exposed to FTR in Study 205888 is 370, as one subject in the Randomized Placebo cohort discontinued from the Study prior to receiving open-label FTR.
3. Sum across subjects of treatment stop date - treatment start date +1 divided by 365.25. For 205888: when IP Stop Date is missing, duration is calculated up to the date of last visit or the recorded date of withdrawal/completion, whichever is earlier.

Table 9 Exposure to FTR by racial origin

Race	GTE (Study 205889)		HTE patients (Study 205888)	
	Patients	Person years	Patients[2]	Person years[1]
African American/African Heritage	63 (32%)	188.5	83 (22%)	330.6
American Indian or Alaska Native	2 (1%)	5.4	8 (2%)	38.9
Asian	2 (1%)	5.8	2 (<1%)	10.3
Native Hawaiian or other Pacific Islander	0	0	1 (<1%)	5.2
White	72 (36%)	277.1	258 (70%)	966.5
Other/mixed	61 (31%)	190.8	18 (5%)	76.8
Total	**200**	**667.7**	**370**	**1428.3**

Data source: 205889 Post hoc RMP Table 6; 205888 Week 240 Interim Analysis Table 1.50090 ITT-E population

1. Sum across subjects of treatment stop date - treatment start date +1 divided by 365.25.
2. Total number of subjects exposed to FTR in Study 205888 is 370, as one subject in the Randomized Placebo cohort discontinued from the Study prior to receiving open-label FTR.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Missing information relevant for the approved indication is included in module SVII.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 10 Important exclusion criteria in the pivotal Phase 3 study

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
History of decompensated cirrhosis or active decompensated cirrhosis, or chronic untreated HBV Baseline abnormalities in liver enzymes and/or total bilirubin, specifically: ALT or AST >7x ULN Alkaline phosphatase >5x ULN Bilirubin ≥ 1.5 x ULN (unless subject has Gilbert's disease, and/or is currently on Atazanavir (ATV) and has predominantly unconjugated hyperbilirubinemia).	PK data from subjects with hepatic impairment was not available at the start of the Phase 3 study. To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study.	No	A PK study in subjects with mild, moderate or severe HI showed that no adjustment of FTR dose is required in these patients. Hepatotoxicity is an established adverse effect of ARVs. This can be a direct effect of ARVs but occurs most often in patients with HBV/HCV co-infection. Monitoring of liver chemistries in patients with HBV/HCV coinfection is recommended.
Pregnant or breastfeeding women	The safe use of FTR during pregnancy and breast-feeding was not established during the clinical developmental phase of the product. In general, EU treatment guidelines do not recommend breast feeding during ARV therapy.	Yes	

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Children and adolescents aged <18 years.	An appropriate dose/formulation was not identified for these patients at study initiation.	No	A paediatric plan to provide these patients with a suitable tablet/formulation and dose is in place (EMEA-001687-PIP01-14-M03).
ARV treatment-naïve patients or ARV-treatment experienced patients without documented historical or baseline resistance, intolerability, and/or contraindications to antiretrovirals in at least 3 classes. HIV-infected subjects who were not failing their current ARV regimen and with confirmed plasma HIV-1 RNA ≤400 copies/mL.	FTR was developed for the treatment of heavily treatment experienced HIV-1-infected patients with multidrug resistance.	No	Fostemsavir, in combination with other antiretrovirals, is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.
History of congestive heart failure or congenital prolonged QT interval Confirmed QT value >500ms at screening or day 1 Confirmed QTcF value >470ms for women and >450ms for men at screening or day 1 Confirmed PR interval >260 ms (severe first degree atrioventricular block) at screening or day 1. Confirmed second or third-degree heart block at screening or day 1.	Excluded due to the potential for QT prolongation at supra-therapeutic exposures of FTR as demonstrated in the thorough QT study (TQT) (206275 [AI438016]. A delay in cardiac repolarization, such as QT interval prolongation, creates an electrophysiological environment that favours the development of cardiac tachyarrhythmias, particularly TdP, but also other ventricular tachyarrhythmias.	No	FTR to be used with caution in these patients with relevant cardiac history and/or use of drugs with known risk of QT prolongation and/or TdP.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Current or anticipated treatment with any of the following: amiodarone, dofetilide, disopyramide, ibutilide, procainamide, sotalol, and quinidine.			
Subjects with current or anticipated treatment with any of the following were excluded: rifampin, Hypericum perforatum (St. John's wort), efavirenz, nevirapine, phenytoin, carbemazepine and phenobarbital.	Strong inducers of CYP3A4 are expected to significantly reduce exposure to TMR and therefore should not be co-administrated with FTR.	No	Concomitant use of FTR with strong CYP3A4 inducers is contraindicated. Moderate inducers of CYP3A4 (such as efavirenz, etravirine and nevirapine) are not contraindicated.
Subjects co-administered simvastatin or lovastatin with boosted protease inhibitors were excluded (as per product information for simvastatin and lovastatin).	TMR is an inhibitor of OATP1B1, OATP1B3 and BCRP; drug interactions with substrates of these transporters was predicted [FDA Draft Guidance, 2017; EMA guideline, 2013]. This was confirmed by the results of a drug-drug interaction study with rosuvastatin in which, co-administration of FTR with rosuvastatin increased rosuvastatin peak (Cmax) and total (AUC[INF]) exposures by 78% and 69%, respectively, compared to administration of rosuvastatin alone [206276 (AI438048) CSR].	No	Use the lowest possible starting dose of statins that are substrates of OATP1B1/3 and/or BCRP with careful monitoring for HMG-CoA reductase inhibitor-associated adverse events (SmPC Section 4.4 and 4.5).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

The Phase 3 study in the target population of HTE adults is limited to 371 subjects with a median duration exposure to FTR at Week 240 of 258.6 weeks (range 0.1 to 319.6 weeks) [Data source 205888 Week 240 interim analysis Table 1.50020]. There was no comparator arm in this study; all subjects received FTR with an optimized background therapy (OBT) tailored to each individual subject, and therefore, adverse events could be due to an effect of FTR, or to an effect of the OBT, concomitant medications or underlying disease. However, supportive long-term data for the safety profile of FTR is provided by the Phase 2b study conducted in GTE patients which involved a further 200 FTR treated subjects and 51 subjects on comparator, and in which subjects were exposed to FTR (all doses) for a median duration of 1645.5 days (approximately 4.5 years).

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 11 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities • Patients with hepatic impairment[1]	Child-Pugh score (used to define mild/moderate/severe hepatic impairment) was not calculated on entry to the clinical studies. Patients with severe hepatic impairment were likely to be excluded from the Phase 3 study (see criteria in Part II, SIV.1) and no HTE subjects had a medical history of elevated bilirubin or chronic elevated total bilirubin. In the Phase 3 study 8% (29) of subjects were HCV and/or HBV infected and were exposed to FTR for a total of 93.2 person-years[2].
• Patients with renal impairment[3]	There were no exclusion criteria for subjects with renal impairment. In the Phase 3 study, an estimated 35% (130) patients had renal impairment and these subjects were exposed to FTR for a total of 566.7 person-years.

Type of special population	Exposure
• Patients with cardiovascular impairment[4]	Patients with congestive heart failure or with risk factors for QT prolongation/other ECG changes were excluded from the Phase 3 study (see criteria in SIV.1). In the Phase 3 study, an estimated 34% (126) subjects had risk factors for cardiovascular impairment and were exposed to FTR for a total of 487.3 person-years.
• Patients with a disease severity different from inclusion criteria in clinical trials	Only 15 ART-naïve and 234 GTE HIV-1 infected patients were exposed to FTR as part of the Phase 2 FTR clinical studies, as the proposed indication is for HTE adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen [see Part II: Module SIII].
Population with relevant different ethnic origin	No ethnicities were excluded however, where reported, the majority of subjects were White and non-Latino/Hispanic [Table 8 and Table 9].
Subpopulations carrying relevant genetic polymorphisms.	No information is available on HTE subjects with genetic polymorphisms.
Paediatric population	None. HTE children and adolescents were excluded from the FTR clinical programme. A paediatric plan to provide these patients with a suitable tablet/formulation and dose is in place (EMEA-001687-PIP01-14-M03).
Elderly population	In the Phase 3 study, there were 12 subjects (all male) aged ≥ 65 years, and they were exposed to FTR for a total of 32.6 person-years [Table 6].

1 Includes subjects with a medical history of elevated bilirubin or chronic elevated total bilirubin. Data source: Module 5.3.5.3 Posthoc RMP Table 41.8 ITT-E population.

2 Data source: Week 240 Interim Analysis Table 1.50070 ITT-E population.

3 Includes subjects with a medical history of acute or chronic renal disease/insufficiency/failure, chronic nephropathy, decreased renal function, end stage renal disease, nephrotoxicity due to tenofovir or ATV, rhabdomyolysis with acute renal failure or high creatinine; subjects with a baseline serum creatinine which is grade 3 or grade 4; and/or a post-baseline increase in serum creatinine to grade 3 or grade 4. Data source: Week 240 Interim Analysis Adhoc Table 1.50081 ITT-E population.

4 Includes subjects with a medical history of hypertension/high blood pressure, hypotension, diabetes, hypertriglyceridaemia, hyperlipidemia, dyslipidemia, hypercholesterolemia, medical intervention, myocardial infarction, abnormal ECG, chest pain, coronary artery disease, vein graft, mild cardiac enlargement, deep vein thrombosis, peripheral vascular disease, dilated cardiomyopathy, sinus tachycardia, pulmonary embolism, blocked arteries, tricuspid or mitral regurgitation, dyspnea, left ventricular hypertrophy, embolism, mild mitral insufficiency, atheromatous disease of carotid arteries, myocardiopathy, first degree AV block, heart murmur, angioplasty and stenting, chronic stable angina, left ventricular hypertrophy, rheumatic fever, mild stroke, bilateral carotid stenosis, hypersensitive cardiopathy, peripheral venous insufficiency, cardiomegaly, premature ventricular contractions, supraventricular tachycardia, ischaemic heart disease with cardiac artery bypass grafting, vasospasm, chronic lower extremity oedema, implantable cardioverter defibrillator, and/or bundle block. Data source: Week 240 Interim Analysis Adhoc Table 1.50081 ITT-E population.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The algorithm used to derive post-marketing exposure data is based on patients taking 600 mg of fostemsavir BID.

SV.1.2 Exposure

Based on IQVIA (Intercontinental Medical Statistics) sales volume data, the estimated total cumulative post-approval exposure for fostemsavir is 738 patient years up to September 2021.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

No studies to investigate the potential for abuse or dependency with FTR have been performed and no concerns relating to this risk have been identified from the FTR clinical development programme. In a nonclinical secondary pharmacology evaluation, FTR did not significantly bind to any receptors or ion channels that would be considered relevant to neuropsychological stimulation.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not all adverse drug reactions (ADRs) or safety concerns for FTR are considered important risks for inclusion in the list of safety concerns in the EU RMP. Further information on these and the reason they are not considered important risks for FTR is provided below.

Based on data to date, product characteristics and target population, the following potential issues are not considered to lead to important risks for the product and are therefore not included as safety concerns in the RMP:

- risks resulting from medication errors; risk for transmission of infectious agents; off-label use; class-associated risks; risks associated with the disposal of the used product; risks related to the administration procedure.

In addition, the following safety concerns specific to FTR are not considered to lead to important risks for the product and are therefore not included as safety concerns in the RMP. These are grouped below under the reason for not including the risk.

REASON FOR NOT INCLUDING AN IDENTIFIED OR POTENTIAL RISK IN THE LIST OF SAFETY CONCERNS IN THE RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

For the following ADRs, the majority of these in the Phase 3 study in HTE adults were non-serious and low grade in severity (grade 1 or 2). In addition, the ADRs were typically self-limited with no interruption of study medication (module 2.7.4 Section 2.1.1.5). All the ADRs listed are included in the SmPC (Section 4.8) as considered related to FTR:

- Gastrointestinal (GI) disorders SOC: nausea, diarrhoea, vomiting, abdominal pain, abdominal pain upper, abdominal discomfort, dyspepsia and flatulence.

- General disorders and administration site conditions SOC: fatigue.

- Nervous system disorders SOC: headache, somnolence, dizziness and dysgeusia.

- Psychiatric disorders SOC: insomnia.

- Skin and subcutaneous tissue disorders SOC: rash, rash generalized, rash maculo-papular, rash pruritic, pruritus, pruritis generalized, rash erythematous, rash macular, rash papular and rash vesicular.

- Investigations SOC: Increased liver enzymes (including ALT increased, AST increased, hepatic enzymes increased and increased transaminases), blood creatine phosphokinase increased, blood creatinine increased and electrocardiogram QT prolonged.

- Musculoskeletal and connective tissues disorders SOC: myalgia.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- **Drug interactions with strong CYP3A4 inducers**: When FTR was co-administeredwith rifampin (a strong CYP3A4 inducer) there was approximately 80% reduction in exposure of TMR (206277 (AI438017) CSR). Based on this, co-administration of FTR with strong CYP3A4 inducers is contra-indicated in the FTR SmPC [see also Part II: Module SII].
- **Drug interactions with OATP1B1/1B3 substrates**: When FTR was co-administeredwith rosuvasatin (OAT1B1/1B3 and BCRP substrate) the exposure of rosuvastatin increased [206276 (AI438048) CSR]. Based on this, the FTR SmPC recommends the use of lowest possible starting dose of statins that are substrates of OATP1B1/3 and/or BCRP with careful monitoring for HMG-CoA reductase inhibitor-associated adverse events when co-administered with FTR [see also Part II: Module SII].
- **Immune reconstitution inflammatory syndrome (IRIS):** As described by French [2007], patients with HIV infection who are very immunodeficient before achieving a virologic response to ART (such as HTE patients) may experience various disorders of immune reconstitution. FTR treatment, like other ART, results in a reduction in HIV viral load and subsequent improvement in CD4+ cell count and immune function which, in some patients, can lead to IRIS. In the Phase 3 study, there were 8/371 (2%) reports of IRIS (including one report of Central Nervous System Immune Reconstitution Inflammatory Response) to Week 144 (cut-off date 6-Sep-2019) and 7 of these were considered by the investigator to be related to study treatment. Only 3 (<1%) of the 8 reports met seriousness criteria and of these, two cases were well substantiated by immunological response and time to onset. In the third serious case, where the patient died, there was a lack of immunologic (CD4 count) and virologic response (HIV RNA) to the newly introduced ART. In addition, a definitive microbiological diagnosis was hampered by the poor condition of the subject, including severe thrombocytopenia, and the cause of the underlying infection was indeterminate. The event evolved into sepsis, progressive multi-organ failure, and death. In the remaining cases of IRIS involving FTR treatment in the Phase 3 study, the condition resolved with continued treatment with FTR and OBT. No reports of IRIS were received from Phase 2 studies conducted in treatment-naïve or GTE patients. The SmPC section 4.4 includes a warning regarding the possibility of IRIS and the adverse event is listed as expected in SmPC section 4.8. IRIS will be addressed as a safety concern in upcoming PSURs.

- **Severe Type I Hypersensitivity:** During manufacture of FTR, there is the potential for the formation of trace amounts of a photodegradant (BMT-218946) containing a beta-

lactam ring and therefore the potential to initiate a Type I hypersensitivity reaction. The estimated maximum theoretical concentration of BMT-218946 after oral therapy with FTR is approximately 8.7 ng/mL (14 nM) (see Section Part II, SII.4). There are no confirmed reports of severe Type I hypersensitivity reaction across the FTR clinical programme. Eight reports of hypersensitivity from the Phase 2b /Phase 3 studies, all were Grade 1 or 2 in intensity, all were considered unrelated to treatment with FTR, and 7 were non-serious and required no interruptions of treatment. In the serious case the event (lip swelling) was thought to be related to ACE inhibitor treatment, and FTR was interrupted for only 1 day. The two SAEs, one each in the Named Patient Program (NPP; Grade 3 drug allergy) and Phase 1 study (Grade 2 anaphylactic reaction), occurred 7 days and 6 days after commencing FTR, respectively. The NPP case reported no symptoms related to a possible anaphylactic reaction. The Phase 1 subject, being dosed with FTR + RTV, did report associated shortness of breath, dysphagia and rash; a causal relationship could not be excluded for either study drug, but given the delayed onset this event is unlikely to represent a Type 1 hypersensitivity reaction. Studies have shown that exposure to clinically relevant concentrations of the photodegradant is extremely improbable and that the antigenicity of BMT-218946 is orders of magnitude less than beta-lactam structures in beta-lactam antibiotics.

- The MAH commissioned an Expert Panel of three allergy-immunology subspecialists with expertise in the area of human allergy to beta-lactam antibiotics to develop a White Paper. This summarized the weight of evidence regarding the systemic sensitizing potential (and therefore the possible risk of serious allergic reaction) associated with BMT-218946 as compared to beta-lactam antibiotics (e.g., penicillins, cephalosporins).
- The data showed that the beta-lactam structure within BMT-21846 is not relevant, and it is not present in sufficient amount to elicit a reaction in highly sensitized persons. The experts observed that the maximum BMT-218946 level (8.6 ng/mL) is just at the starting level for desensitization with oral penicillin. Such a dose is extremely unlikely to sensitize or elicit reactions in already sensitized patients. Furthermore, the combination of low antigenicity and very low maximal BMT-218946 serum concentrations achievable (>2000-fold lower than the degranulation concentration used in the BAT studies) makes a clinically relevant exposure to BMT-218946 almost impossible.
- The totality of the data (including completed in silico and in vitro studies, as well as review of available clinical data) indicate that the photodegradant has very low immunogenic potential. Further, the antigenicity of the photodegradant is orders of magnitude less than culprit beta-lactam antibiotics (e.g., benzylpenicillin, amoxicillin) in sensitized patients, and no further testing is required.
- In the Phase 3 study, the photodegradant was maintained at levels below 30 µg/g (equivalent to 36 µg per day at a daily dose of 600 mg FTR BID). Enhanced manufacturing controls have been implemented at the commercial drug substance and drug product sites of manufacture which minimise formation of the photodegradant and ensure that levels are routinely <10 µg/g, which results in exposures of less than 12 µg/day at a dose of 1,200 mg FTR daily.
- The experts concluded that cross-reactivity of beta-lactam specific IgE with BMT-218946 is rare, and when it happens it is weak. Thus, not only does BMT-218946 lack evidence of

immunogenicity, it is also poorly antigenic in beta-lactam allergic patients. Severe Type I Hypersensitivity will be addressed as a safety concern in upcoming PSURs.

- **Severe musculoskeletal events including rhabdomyolysis:** In the Phase 3 study in HTE adults, a single suspected unexpected serious adverse reaction (SUSAR) of rhabdomyolysis accompanied by a grade 4 elevation in blood creatine phosphokinase (CPK) was reported through Week 144. The subject was being treated with FTR and OBT of dolutegravir, darunavir/cobicistat, tenofovir alafenamide/emtricitabine and etravirine. This report was confounded by elevated CPK at screening, concomitant darunavir/cobicistat, etravirine and other medications, advanced HIV disease and an extensive deep tissue massage conducted just before the event. A comprehensive review of musculoskeletal events and CPK elevations across the FTR clinical programme showed that overall rates of these events are low, and no other cases of rhabdomyolysis have been reported across the clinical programme to date. HIV infection and HAART are independent risk factors for the development of rhabdomyolysis, and other risk factors for rhabdomyolysis in HIV-infected patients include co-infection with hepatitis C, medication-related adverse effects, drug-drug interactions and alcohol and illicit drug use [Towner, 2011; Lennox, 2009; Madeddu, 2015].

  In the post-hoc TMR PopPK-safety response model of subjects in Phase 3 Study 205888 and Phase 2b Study 205889, no exposure-safety relationship was evident between PopPK post-hoc exposure metrics (AUC12,ss, Cmax,ss, Ctrough,ss) and CPK levels in an exploratory (graphical) analysis that included data from HIV patients who participated in Phase 2b Study 205889 and Phase 3 Study 205888 (see Sequence 0000, m2.7.2 Section 2.6.2 for details).

  Protease inhibitors, particularly in combination with NRTIs, are reported to induce CPK elevations and/or rhabdomyolysis (PREZISTA EU SmPC) and clinical and observational study data have shown an increased frequency of muscle symptoms and CPK elevations in patients who received raltegravir (RAL) compared to other ARV therapies such as efavirenz [Lennox, 2009; Madeddu, 2015]. Other drugs known to be associated with myalgia include, but are not limited to, statins, certain anti-fungals, macrolide antibiotics, proton pump inhibitors and certain oncology drugs. Overall, given the low rate of serious events and discontinuations as a result of musculoskeletal events in FTR studies, there is no evidence that FTR causes serious musculoskeletal disorders. Increased blood creatine phosphokinase and myalgia are included as ADRs in the SmPC (section 4.8). Severe musculoskeletal events including rhabdomyolysis will be addressed as a safety concern in upcoming PSURs.

  Bilirubin elevations: A total of 42/370 (11%) subjects in the Phase 3 study (to Week 144), and 77/200 (39%) subjects in the completed Phase 2b study have recorded a treatment-emergent Grade 3 or Grade 4 elevation in direct bilirubin (DB) or total bilirubin (TB). A Grade 3 DB elevation is determined by any increase in DB >ULN, even in the absence of other signs or symptoms of hepatic disease, and therefore alone can be of little clinical relevance. There are no criteria for Grade 1 or Grade 2 elevations in DB in the DAIDS toxicity grading used in the studies. No subject recorded Grade 4 DB elevations (> ULN with life-threatening consequences e.g., signs and symptoms of liver failure) in

either study. No subject in the Phase 2b study recorded either a Grade 3 or Grade 4 elevation in TB.

Overall, approximately half (20/42) of the Phase 3 subjects recorded only a single G3/4 bilirubin elevation. In 12 subjects both ALT and AST remained in normal range. Marked elevations in ALT/AST in the absence of underlying disease occurred in a single subject (predominantly AST) at a different timepoint to the Grade 3 DB elevation and this resolved on FTR + OBT. There were no AEs of jaundice reported in the Phase 3 study and a single AE of ocular icterus was reported in a subject receiving ATV.

A total of 27 Phase 3 subjects with a Grade 3 DB elevation had no associated Grade 3-4 TB elevation. In 12 of these 27 subjects TB remained <1.1 x ULN throughout the study (i.e. below a Grade 1 elevation), 8 recorded a Grade 1 TB elevation and 7 a Grade 2 TB elevation. Relevant SAEs/AEs or medical history were reported in 9 out of the 27 subjects; a further 10/27 subjects received ATV as part of their OBT. Given the number of other concomitant medications administered to these subjects any contribution of a single agent or combination of agents, although feasible, is difficult to determine.

A greater proportion of subjects in the Phase 2b study reported a Grade 3 DB elevations than in the Phase 3 study. This difference might reflect the longer follow-up in the Phase 2b subjects, and/or represent a contribution from the background regimen of RAL and TDF administered to all subjects in this study. No subject in the Phase 2b study recorded a Grade 3 or Grade 4 TB elevation, and in the majority of subjects (53 of 77) TB remained <1.1 x ULN throughout the study; 21 subjects recorded a Grade 1 TB elevation; 3 subjects a Grade 2 TB elevation. Overall, approximately half of the 77 subjects recorded only one or two G3 DB elevations. Fewer subjects in this study had a relevant medical history or SAE/AE compared to the Phase 3 study. In 25 of the 77 subjects ALT and AST remained in normal range throughout the study; in a further 7 subjects ALT remained in normal range with AST close to normal range. Associated marked elevations in ALT/AST occurred in only 2 subjects and there were no AEs of jaundice or ocular icterus reported. Elevations in bilirubin will be addressed as a safety concern in upcoming FTR PSURs.

Known/potential risks that do not impact the risk-benefit profile:

- **Potential risk of thrombotic events due to increased levels of oral contraceptives:** A drug-drug interaction study conducted to investigate the effect of FTR on the concentrations of a combined oral contraceptive containing ethinyl estradiol (EE) and norethindrone acetate (NE) in 26 healthy female subjects showed increases in EE concentrations of approximately 40% when combined with FTR. There was no clinically meaningful effect of FTR on concentrations of NE. In the presence of TMR, the Cmax and AUC of EE were increased by 39% and 40%, respectively, with corresponding 90% confidence intervals (CI) of 1.28 to 1.51 and 1.29 to 1.51. (206279 (AI438019) CSR). Research on the safety of oral contraceptives has demonstrated that the relative risk for a thrombotic event is related to EE dose and therefore, the risk could be increased in some patients co-administered FTR and EE. However, while the consequences of thrombotic events can be serious, the estimated risk in the general population is low (~7/10,000 person-years) for patients receiving EE-containing contraceptives and can be maintained at

a low level by use of low dose EE [Manzoli, 2012; Heit, 2016]. No concerns relating to this risk have been identified to date in clinical studies involving FTR. Advice relating to this risk is included in Section 4.4 of the FTR SmPC and details of the study results are in SmPC Section 4.5. Although the potential effects of fostemsavir on EE exposure in the presence of a pharmacoenhancer have not been evaluated, results of drug interaction studies have shown that the concomitant use of pharmacoenhancers (i.e., cobicistat and ritonavir) with darunavir or ATV decreases EE exposures compared to without pharmacoenhancers [Majeed, 2017; PREZISTA USPI; REYATAZ USPI; TYBOST USPI). Results from these drug interaction studies consistently show that the addition of pharmacoenhancers does not further increase EE exposures.

- **Impact on efficacy of varying baseline in vitro susceptibility (diversity of virus envelopes, IC50, subtype AE, group O):** Due to the inherent genotypic diversity of HIV-1 gp120, intrinsic phenotypic susceptibility to temsavir is highly variable and susceptibly to TMR has been observed over a broad range, with IC50 values from low picomolar to >5mM.

  In the Phase 2a study, subjects with a baseline IC50 >100 nM showed a reduced antiviral response in terms of decrease in HIV-1 RNA viral load from baseline in an eight-day study [Nettles, 2012]. Based on these results, a TMR IC50 cut-off of <100nM was applied to inclusion criteria in the Phase 2b study in GTE subjects.

  An exposure-response analysis across both Phase 2a and Phase 2b studies showed a relationship between protein binding adjusted (PBA) IC50-adjusted Ctau and antiviral response after 7 days of FTR monotherapy [Savant Landry, 2015]. However, inclusion criterion mandating baseline TMR IC50 was not applied in Phase 3 given the target HTE population. Results from the Phase 3 study 205888 showed that in the Randomized Cohort, TMR IC50 FC at Baseline did not predict virologic response at Day 8. TMR IC50 fold change (FC) >100-fold was associated with a median change in HIV-1 RNA from Day 1 to Day 8 of <0.5 log10 c/mL but did not preclude a >0.5 log10 c/mL response to FTR functional monotherapy. With the addition of an optimized background regimen, there was no influence of increasing TMR IC50 FC on virologic outcome at Weeks 24, 48 or 96.

- **Testicular Toxicity**: The nonclinical testicular findings described in Part II: Module SII were observed in rat toxicology studies (duration from 2 weeks to 26 weeks) and in the pivotal fertility study in rats. The findings were only observed at FTR exposures in excess of clinical exposures in adults following the RHD (i.e. 60x the adult clinical exposure (AUC) following 600 mg FTR BID). Of note, no similar findings were observed in 2, 4 or 39 week repeat dose toxicology studies in dogs. The testicular degeneration/atrophy of seminiferous epithelium in the rat studies was partially reversible: following the 8-week recovery period in the 26-week toxicity study, slight degeneration/atrophy of the seminiferous epithelium occurred only in 1 male at the high dose. The findings were not associated with effects on fertility. The clinical relevance of the nonclinical findings is unknown. In the 26-week toxicity study, there were no effects in rats at AUC multiple of 29x the adult human exposure. Considering that the testicular findings occurred only at high systemic exposure in rats, were partially reversible, were not associated with effects

on fertility, and were not observed in the dog studies, the potential risk for testicular changes in humans is low [m2.4 Section 4.4.2].

- **Medication residue in stools:** During the Phase 3 study, 5 subjects (in the randomized cohort) reported what appeared to be remnants of FTR tablets in their stools. All subjects had a relevant intercurrent gastro-intestinal illness (expected to increase GI transit time) at the time of their reporting FTR remnants and/or an established history of a chronic gastrointestinal condition (Table 12). A stool sample from one of the affected subjects was analysed by the Sponsor and the presence of FTR was confirmed via non-quantitative analysis. Three of 5 subjects were virologically suppressed (HIV-1 RNA <40 copies/mL) at the time FTR was identified in stool, and a fourth subject had their viral load subsequently become undetectable. These reports were self-limited; resolving in short duration (days) without intervention or interruption of drug. The fifth subject, with severe diarrheal illness related to refractory CMV colitis, had repeated episodes of remnants in their stool and subsequently died of complications of advanced AIDS. This subject had poor virologic response to study therapy. None of the reports of FTR tablet remnants in stool were associated with a loss of virological suppression in subjects who were previously suppressed. There were no reports of tablet remnants in stools in any other FTR clinical studies. Remnants of other extended-release medications such as the extended-release antiretroviral, nevirapine, have been reported in the literature. In a prospective study of more than 250 subjects, there was no compromise in virological outcomes among the 22% of subjects who witnessed nevirapine XR in their stool compared to those who did not, including those who witnessed remnants of the nevirapine XR in their stool on a regular basis [Lee, 2015]. The potential for the occurrence of this risk is considered to be low.

Table 12 Summary of Subjects with Reports of Tablet Remnants in Stools

Subject *	Number of Events	Time to Onset (Study Day)	Duration (Days)	Relevant Medical Current Condition / History and Concurrent Medications
A	6	796	1	Gas, indigestion, nausea, constipation, colitis, diarrhea, vomiting, peptic ulcer disease in medical history.
		800	1	
		864	1	
		878	1	
		905	1	
		912	1	
B	1	432	1	Diarrhea reported at time as complication of ongoing treatment for lymphoma (concurrent SAE)
C	1	115	Not reported	Medical history of chronic diarrhea; report preceded by AE of anal incontinence (study day 52 to 97)

Subject *	Number of Events	Time to Onset (Study Day)	Duration (Days)	Relevant Medical Current Condition / History and Concurrent Medications
D	Unknown	Unknown	Unknown	Medical history of irritable bowel syndrome and gastroesophageal reflux disease. Received treatment for diarrhea (Psyllium, study day -190 to day 64)
E	>1	Unknown	Unknown	Refractory CMV colitis (reported as an SAE) with profuse diarrhea at the time of the event. Medical history of diarrhea.

*This does not refer to study assigned subject IDs

- **Use in geriatric patients:** elderly HTE subjects (aged ≥65 years) were under-represented in the Phase 3 study (12/371, 3%). However, data from Phase 1/2a/2b/3 population PK and PK/PD analyses found no impact of age on TMR PK or exposure-antiviral response. The subjects included in this population PK analysis had a median age of 42 years (range 17 to 73 years) [Document number: 2018N392690_00]. In addition, a subgroup analysis of the primary efficacy endpoint at day 8 in the Phase 3 study showed no difference in response to FTR in subjects aged 50 years or over [205888 (AI438047)] 96 Week CSR].
- **Off label use in children, harm from overdose** and **increased Cmax due to chewing/breaking the ER tablet:** these potential risks have not been included as important risks in the RMP because the clinical outcome that could be associated with these (ventricular tachyarrhythmias as a result of QTc prolongation) is already included as an important potential risk. In all 3 scenarios, the concern relates to the risk of higher exposure to TMR. Clinically meaningful QTc prolongation was observed in the TQT study only at a supra-therapeutic dose.

  A paediatric plan to provide these patients with a suitable tablet/formulation and dose is in place (EMEA-001687-PIP01-14-M03).

  In the post-hoc TMR PopPK-safety response model of subjects in Phase 3 Study 205888 and Phase 2b Study 205889, no exposure-safety relationships were evident between PopPK post-hoc exposure metrics (AUC12,ss, Cmax,ss, Ctrough,ss) and safety endpoints of interest, including QTcF, rash and change from baseline (at each visit through Week 24) in AST, ALT, direct bilirubin, CPK and serum creatinine in an exploratory (graphical) analysis that included data from HIV patients who participated in Phase 2b Study 205889 and Phase 3 Study 205888 (see m2.7.2 Section 2.6.2 for details).

SVII.1.2Risks considered important for inclusion in the list of safety concerns in the RMP

There are no important identified risks with FTR for inclusion in the RMP.

IMPORTANT POTENTIAL RISK 1: VENTRICULAR TACHYARRHYTHMIAS DUE TO QTC PROLONGATION

A supra-therapeutic dose of FTR (2400 mg BID) has been shown to significantly prolong the QTc interval of the electrocardiogram in a TQT study [206275 (AI438016) CSR]. Based on modelling of these data, the threshold for clinically significant QTc prolongation (≥10 ms) is 7,500 ng/mL TMR, which is 4.2x higher than the Cmax associated with the adult dose (600 mg BID) in HTE HIV-1 infected patients enrolled in Phase 3 study. A delay in cardiac repolarization, such as QTc interval prolongation, creates an electrophysiological environment that favours the development of cardiac tachyarrhythmias, particularly torsade de pointes (TdP), but also other ventricular tachyarrhythmias, and therefore, ventricular tachyarrhythmias due to QTc prolongation is considered a potential risk with FTR.

Risk Benefit Impact:

To the data lock for this RMP, no ventricular tachyarrhythmias were observed in patients in the Phase 2 or Phase 3 FTR studies, however such events in response to QTc prolongation are typically rare. The FTR SmPC indicates patients who may be at increased risk of ventricular tachyarrhythmias due to QTc prolongation which include patients with a history of QTc interval prolongation or pre-existing cardiac disease, patients taking concomitant medication with a known risk for QT prolongation or elderly patients. Data to date suggest no significant impact on benefit risk is expected however due to the serious nature of the event and limited experience with FTR, it is considered an important potential risk until further experience with the use of FTR is accumulated.

MISSING INFORMATION 1: USE IN PREGNANT AND LACTATING HTE WOMEN

Pregnant and lactating HTE women were excluded from the Phase 3 study. Subjects who became pregnant during the study were required to discontinue unless the benefit of continuing was considered to outweigh the risks.

Risk-benefit impact:

Although Phase 3 study inclusion criteria required the use of approved highly effective methods of contraception, 4 HTE subjects became pregnant during the Phase 3 study. The outcome was induced abortion in 1 case, and live birth in the remaining 3 cases. In the 3 reports in subjects which resulted in live births (no congenital anomalies), two subjects continued in the study as the benefit was considered to outweigh the possible risks, and one discontinued following exposure to FTR in first trimester only. In addition to these 4 pregnancies in study subjects, there was 1 report of pregnancy in a subject's partner which also resulted in a live birth with no congenital anomalies. In the Phase 2b study, there was one pregnancy with exposure to FTR+ RAL+TDF during the first 10 weeks of pregnancy, which resulted in a normal live birth at 41 weeks. Based on nonclinical study findings [Part II: Module SIII], the SmPC advises that the use of FTR should be avoided during pregnancy.

MISSING INFORMATION 2: LONG TERM SAFETY DATA

With antiretroviral therapies, some toxicities have taken considerable time/years to manifest and limited data are available on long term use of FTR from clinical trials.

Risk-benefit impact:

No safety concerns relating to long term use were identified in the nonclinical studies (including 2-year non-clinical carcinogenicity studies). In the completed Phase 2b study in GTE subjects, which ran for over 5 years, almost half the subjects (98, 49%) were exposed to FTR for ≥240 weeks (4.6 years) with a total of 487.1 person-years exposure (Table 4). The total exposure to FTR in the Phase 2b study (all doses) was 667.7 person-years (Table 4). In the ongoing Phase 3 study in HTE subjects, to the cut-off date for the 144-week analysis, 370 subjects were exposed to FTR for a median duration of 171.36 weeks (range 0.1 to 230.3 weeks) [60 Day Safety Update Report, statistical output Table 1.8802]. As shown in Table 5, 182 subjects in study 205888 (49%) have been exposed to FTR for between 144 and <192 weeks (2.8 to <3.7 years); their total exposure is 608.0 person years; 81 (22%) of subjects have been exposed to FTR for between 192 and <240 weeks with a total exposure of 321.8 person-years. The total exposure to FTR in the Phase 3 study to Week 144 was 1042.1 person-years (Table 5). Longer term safety will be monitored post-authorization through routine and additional pharmacovigilance activities.

SVII.2 New safety concerns and reclassification with a submission ofin updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1Presentation of important identified risks and important potential risks

There are no important identified risks for FTR.

Important potential risk: Ventricular tachyarrhythmias due to QTc prolongation

Potential mechanisms:

A delay in cardiac repolarization, such as QTc interval prolongation, creates an electrophysiological environment that favours the development of cardiac tachyarrhythmias, particularly torsade de pointes (TdP), but also other ventricular tachyarrhythmias. A supra-therapeutic dose of FTR (2,400 mg twice daily) has been shown to significantly prolong the QTc interval of the electrocardiogram (study 206275/AI438016) and therefore, ventricular tachyarrhythmias due to QTc prolongation are considered a potential risk with FTR. Inhibition of the cardiac delayed rectifier potassium current (hERG) is the likely mechanism by which temsavir prolonged QTc interval [Part II: Module SII].

Evidence source(s) and strength of evidence:

The risk of ventricular tachyarrhythmias due to QTc prolongation, which can be life-threatening, is considered an important potential risk based on the finding that a supra-therapeutic dose of FTR prolonged QTc interval in the TQT clinical study in healthy volunteers.

Characterisation of the risk:

Although no concerns relating to this risk have been identified in the clinical studies, ventricular tachyarrhythmias due to QTc prolongation are expected to be relatively rare. Given the seriousness of ventricular tachyarrhythmias, this concern has been included as an important potential risk. Data from the ongoing Phase 3 study will continue to be monitored for any signals relating to this risk.

Clinical ECG findings and relevant AEs are summarized below. AEs relevant to this risk were identified in the clinical programme using the Torsade de Pointe/QT prolongation SMQ (broad).

The only clinically relevant Ventricular Tachyarrhythmias-Related AEs were the reports of QT prolongation

Clinical ECG findings

Mean changes over time in QTc interval were minimal in the Phase 2b and Phase 3 studies. A total of 11 subjects across both studies have recorded either a QTcB/ QTcF of >500 msec, or maximum change in QTcB/QTcF of ≥ 60msec (thresholds of particular concern), including data through Week 240 in the Phase 3 study. In 8/11 subjects, these were isolated events, and in one subject, occurred on two occasions. These nine subjects were asymptomatic, and continued FTR treatment in Phase 2b/3 studies without interruption. In the remaining two cases, one subject, with prolonged QTcB at screening, experienced first-degree atrioventricular block, intraventricular conduction delay (>120 msec) and right bundle branch block during the study (reported as a non-serious AE not considered related to treatment), and the other subject had underlying cardiovascular disease and received amiodarone treatment; both subjects discontinued the study due to meeting protocol discontinuation criteria for QTcF prolongation.

Both Phase 2b and Phase 3 studies had protocol-defined QTcF criteria for study discontinuations (Phase 3 study: confirmed QT >500 msec for all subjects (male or female) or confirmed QTcF >450 msec in male subjects and >470 msec in female subjects; Phase 2b study: confirmed QTcF or QTcB > 500ms for all subjects, male or female). Through Week 240 of the Phase 3 study, 11/371 (2.9%) subjects discontinued due to meeting the protocol defined discontinuation criteria. Two of the 11 subjects that discontinued Phase 3 recorded a QTcF >500 msec.

Ten of the 11 subjects who met QT prolongation protocol stopping criteria in the Phase 3 study were either transitioned to the FTR NPP (Study 207214) or had access to commercial FTR supply. Two NPP patients have subsequently reported a serious cardiac adverse event, both considered unrelated to treatment with FTR:

- The first was a Grade 2 SAE of atrioventricular block complete. The Grade 2 event, requiring hospitalization, occurred in a subject with a history of left bundle branch block and hypertension, and was considered unrelated to FTR.
- The second, a fatal SAE of cardiac arrest occurred in a subject with concurrent cachexia, pneumonia, varicella zoster, epilepsy and progressive multifocal leukoencephalopathy. The cause of death was reported to be disease progression.

In the Phase 2a study (206267), no QTcF or QTcB values of more than 450 msec were observed, and in most subjects, the changes from Baseline were <30 msec. Changes in QTcB or QTcF of 30 to 60 msec were each observed in 4 subjects (8.0%), with no relevant difference in incidence between regimen groups (module 2.7.4 Section 4.1.2).

The majority of subjects in Phase 1 had QTcB and QTcF values ≤ 450 msec throughout the studies.

In the Phase 1 clinical TQT study, the upper bounds of the two-sided 90% confidence intervals (CIs) for ΔΔQTcF exceeded 10 msec with a maximum upper bound of 13.299 ms at 5 hours following a supra-therapeutic dose of 2400 mg twice daily. The geometric mean total Cmax following administration of a supra-therapeutic dose of 2,400 mg twice daily of fostemsavir was 8.9 ug/mL (3.35 µg/mL to 17.7 µg/mL). Administration of a dose of 1,200 mg once daily, did not have a clinically meaningful effect on QTc interval since the upper bounds of the two-sided 90% CIs for ΔΔQTcF did not exceed 10 msec (maximum upper bound = 6.343 ms at 6 hours) [206275 (AI438016) CSR]. A positive relationship was demonstrated between TMR plasma concentrations (Cp) and change in the QTc interval. The relationship between Cp (ng/mL) and the change in baseline corrected QTcF interval between active and placebo (ddQTcF) (msec) was best described by a linear slope-intercept model. Based on simulations from the updated modelling of the TQT clinical data, the threshold for clinically significant QTc prolongation (≥10 ms) is 7,500 ng/mL temsavir, which is 4.2x higher than the maximum concentration associated with FTR 600 mg BID regimen in HTE HIV-1 infected patients enrolled in the Phase 3 study [Clinical Pharmacology Modelling Report, Document number: 2018N392689_00].

Adverse events from the TdP SMQ

Across the Phase 2b and Phase 3 studies, there were a total of 14/570 (3%) subjects with an AE from the TdP SMQ (see Table 13). Most of these (8/14) were electrocardiogram QT prolonged; the remaining events were syncope (4/14) and loss of consciousness (2/14). Two reports were serious:

- A subject, experienced SAEs of loss of consciousness and disorientation (both Grade 3, duration 2 days) on Study Day 147. The events were considered possibly related to treatment with FTR and OBT of DTG, tipranavir, RTV and TDF/FTC). FTR and OBT treatment were continued without interruption. This subject did not have any recorded QTcF intervals >450ms but had an ECG abnormality of sinus bradycardia at Baseline and during the study (Study Day 93) and recorded a QTcF increase of between 30 and 60 msec on one occasion (Data Source: Study 205888 (AI438047)] 96 Week CSR, Listing 329).

- A subject randomized to the 1200 mg once daily FTR dose group, experienced syncope (Grade 3 SAE) and septicemia (Grade 4 SAE) of unknown origin with onset on Study Day 855. The subject died due to septicemia on the same day. The events were considered unrelated to FTR. Myocardial ischemia (Screening) and other non-specific ST/T (Study Day 1) ECG abnormalities were recorded in this subject (Data Source: 205889 (AI438011) End-of-study CSR, Listing 23).

There were no trends in time to onset or duration of the 14 events (Table 13).

Table 13 Integrated data from Phase 2b and 3 studies: AEs from TDP SMQ[1]

TdP SMQ	Phase 2b FTR total (N=200)	Phase 3 total (N=370)	FTR Safety Cohort[2] (N=553)	All FTR (N=570)
Number of subjects with event	2 (1)	12 (3)	13 (2)	14 (2)
Number of events	2	12	13	14
Event characteristics, n (%)				
Serious	1 (50)	1 (8)	2 (15)	2
Drug-related	0	3 (25)	3 (23)	3 (25)
Leading to withdrawal	0	3 (25)	3 (23)	3 (25)
Fatal	0	0	0	0
Number of occurrences, n (%)				
One	2 (100)	12 (100)	13 (100)	14 (100)
Two	0	0	0	0
Three or more	0	0	0	0
Outcome (serious events only), n (%)				
N	1	1	2	2
Recovering/resolving	0	1 (100)	1 (50)	1 (50)
Not recovered/not resolved	1 (100)	0	1 (50)	1 (50)
Maximum grade or intensity, n (%)				
Mild or Grade 1	1 (50)	4 (33)	4 (31)	5 (36)
Moderate or Grade 2	0	5 (42)	5 (38)	5 (36)
Severe or Grade 3	1 (50)	3 (25)	4 (31)	4 (29)
Grade 4	0	0	0	0
Action taken, n (%)				
Dose not changed	1 (50)	9 (75)	9 (69)	10 (71)
Dose interrupted	1 (50)	0	1 (8)	1 (7)
FTR withdrawn	0	3 (25)	3 (23)	3 (21)
Time to onset of first occurrence, n (%)				
<2 weeks	0	1 (8)	1 (8)	1 (7)
2-<4 weeks	0	0	0	0
4-<12 weeks	1 (50)	2 (17)	2 (15)	3 (21)
12-<24 weeks	0	4 (33)	4 (31)	4 (29)
24-<48 weeks	0	1 (8)	1 (8)	1 (7)

TdP SMQ	Phase 2b FTR total (N=200)	Phase 3 total (N=370)	FTR Safety Cohort[2] (N=553)	All FTR (N=570)
48-<72 weeks	0	1 (8)	1 (8)	1 (7)
72-<96 weeks	0	0	0	0
>=96 weeks	1 (50)	3 (25)	4 (31)	4 (29)
Mean	63.1	50.7	56.0	52.5
SD	83.51	59.27	59.97	59.40
Median	63.1	22.0	23.0	22.0
Min	4	0	0	0
Max	122	160	159	160
Duration of first occurrence, n (%)				
<2 weeks	0	4 (33)	4 (31)	4 (29)
2-<4 weeks	0	2 (17)	2 (15)	2 (14)
4-<12 weeks	0	2 (17)	2 (15)	2 (14)
>=12 weeks	0	1 (8)	1 (8)	1 (17)
Ongoing	2 (100)	3 (25)	4 (31)	5 (36)
Mean	N/A	5.1	5.1	5.1
SD	N/A	8.18	8.18	8.18
Median	N/A	2.7	2.7	2.7
Min	N/A	0	0	0
Max	N/A	25	25	25

N/A = not applicable

1. Data integrated from the Phase 2b and Phase 3 studies includes data from subjects in the Phase 3 study through Week 96 data lock.
2. The FTR Safety Cohort includes all Phase 2b/3 subjects who received at least one dose of FTR ≥1200 mg daily; Sequence 0000, Module 2.7.4 Section 2.1.5.3.1.

One additional subject reported a Ventricular Tachyarrhythmias-Related AESI in the ongoing Phase 3 study through Week 144:

- A subject in the Randomized Cohort of Phase 3 Study 205888, experienced a non-serious Grade 1 AE of syncope on Study Day 1177, that resolved on the same day. The event was not considered related to treatment with FTR and OBT, which were continued without interruption. No other associated AEs were reported. This subject had no recorded QTcF intervals >450 msec, change in baseline QTcF >60 msec, or other ECG abnormalities.

In addition, through Week 240 in the ongoing Phase 3 study, there have been 3 further reports of syncope and 1 report of ventricular tachycardia in 3 subjects, all in the Randomized Cohort and a second report of loss of consciousness in a fourth subject:

- A subject experienced non-serious Grade 1 AEs of ventricular tachycardia and syncope (Study days 1431 and 1505 respectively) which occurred in association with an SAE of mesenteric vein thrombosis (Grade 3, Study Day 1431, resolved) and a non-serious AE (Grade 1) of coronary artery disease (Study Day 1431, ongoing); none were considered

drug-related. ECG abnormalities reported during the clinical trial include sinus bradycardia (Study Day 339) and QTcB prolonged (Study Day 1998; QTcB of 455ms, QTcF of 447 ms). FTR and OBT treatment were continued without interruption.

- A subject experienced an SAE of acute myocardial infarction (Grade 3, Study Day 1464), followed by an SAE of cerebrovascular accident (Grade 3, Study Day 1474) and an SAE of syncope (Grade 4, Study Day 1485); none were considered drug-related and following treatment, all resolved during the study. No ECG abnormalities were reported within the clinical trial. FTR and OBT treatment were continued without interruption.

- A subject experienced a non-serious AE (Grade 2, Study Day 1177) of syncope which was not considered drug-related. ECG abnormalities reported during the clinical trial included QTcB and QTcF prolonged (30-60ms, Study Day 260) and short PR interval (Study Day 1010). FTR and OBT treatment were continued without interruption.

- A subject with a medical history of alcohol abuse and previous SAE of loss of consciousness (Grade 3, considered possibly related to treatment with FTR and OBT) on Study Day 147, reported a further episode of loss of consciousness (Grade 2, non-serious, not-related) on Study Day 839. FTR and OBT treatment were continued without interruption.

In the comparator arm of the Phase 2b study (ATV/r), there were two AEs (both non-serious) from the TdP SMQ (single reports of syncope (2%) and loss of consciousness (2%)), and no reports of electrocardiogram QT prolonged (N=51; 205889 (AI438011) End-of-study CSR).

No abnormalities in ECG parameters were reported as an AE in the Phase 2a Study. There was one non-serious AE of syncope in the Phase 2a Study (Grade 1); in a subject with an onset during the treatment phase, which was considered unrelated to study drug by the investigator and which required no treatment. No other AEs from the SMQ Torsades de Pointes/QT prolongation (broad) were reported (module 2.7.4, Section 2.1.5.3.2).

In the Phase 1 studies, a single AE of syncope was reported in the single-dose bioavailability study (Study 206288/AI438054); module 2.7.4, Section 2.1.5.3.3). The event occurred one hour after the first single dose of FTR, lasted 8 minutes, and was reported as non-serious, Grade 2 intensity and not considered related to study treatment. There were no associated ECG findings at time of the event. No action was taken. No events were reported following five subsequent single doses of FTR and the subject did not discontinue from the study.

Risk factors and risk groups:

No additional risk factors have been identified in HTE HIV-infected patients beyond those previously described for the general population [Frommeyer, 2015].

Preventability:

In the clinical use of FTR in HTE HIV-infected subjects, plasma concentrations of TMR could be increased in specific circumstances. However, the results of the thorough QT study showed that the margin between the Cmax at which clinically significant QT prolongation observed

compared to the Cmax in HTE HIV-1 infected patients enrolled in the Phase 3 study is approximately 4.2-fold.

The SmPC section 4.4 describes patients who may be at increased risk of ventricular tachyarrhythmias due to QT prolongation which includes patients with a history of QT interval prolongation or pre-existing cardiac disease, patients taking concomitant medication with a known risk of ventricular tachyarrhythmias or elderly patients.

Impact on the risk-benefit balance of the product:

Based on available data, the risk-benefit balance remains favourable for HTE adults.

Public health impact:

There is no available data to confirm the potential public health impact as no events of cardiac ventricular tachyarrhythmias occurred in the clinical programme. The incidence of QTc prolongation events (adverse events or protocol-defined discontinuations) in the Phase 3 study was low, and typically asymptomatic.

SVII.3.2Presentation of the missing information

Use in pregnant and lactating women

Evidence source:

Findings in the nonclinical reproductive toxicology studies at ≥17x the RHD AUC included fetal malformations in rats and maternal and developmental toxicity in rabbits (see Part II: Module SII). In a pre- and post-natal development study in rats, FTR was not teratogenic and there was no effect on intrauterine mortality at any dose. However, lactational exposure (at an exposure multiple of 131x RHD AUC) was associated with reduced neonatal survival, suggesting that FTR was a selective developmental toxicant during postnatal life. There was no maternal toxicity evident in any phase of the study and the exposure safety multiple for neonatal toxicity at the NOAEL dose was 35x RHD AUC. FTR derived radioactivity (i.e. TMR and/or TMR derived metabolites) has been shown to cross the placenta in pregnant rats, resulting in exposure to all evaluated foetal tissues (module 2.4 Section 4.7].

Although Phase 3 study inclusion criteria required the use of approved highly effective methods of contraception, to 96 weeks in the Phase 3 study, there were 4 reports of pregnancy in study subjects: 3 live births, (2 with exposure during all 3 trimesters, and one with exposure during first trimester only) and 1 induced abortion. The 3 pregnancies which continued to term all resulted in live births with no congenital abnormalities. In one case, intrauterine growth restriction was reported which was considered related to FTR treatment by the investigator; the subject received DTG and DRV/r as OBT and had a history of advanced HIV-1 infection, neurotoxoplasmosis, urinary tract infections, and chronic smoking. Delivery of an infant by caesarean section occurred at an estimated gestational age of 39 weeks, with no congenital abnormalities reported. Apgar scores were 9 and 10 at 1- and 5-minutes, respectively. No period of observation in the neonatal intensive care unit was required. In addition to these 4 pregnancies in study subjects, there was 1 report of pregnancy in a subject's partner which also

resulted in a live birth with no congenital abnormalities. In the Phase 2b study, there was one pregnancy with exposure to FTR+ RAL+TDF during the first 10 weeks of pregnancy, which resulted in a normal live birth at 41 weeks.

FTR is included in the list of antiretrovirals (ARVs) monitored by the Antiretroviral Pregnancy registry (APR). [Antiretroviral Pregnancy Registry, 2018]. Details of the registry can be found in Part III.2.

Population in need of further characterisation

As clinical experience of the use of the FTR during pregnancy is limited it is not possible to define the risk in this patient population. Further information is required to understand the safety profile (e.g. pregnancy outcomes and risk of birth defects) in pregnant women taking FTR.

Safety of FTR in pregnancy will be monitored post-authorization through routine and additional pharmacovigilance activities [Part III].

Long term safety data

Evidence source:

With antiretroviral therapies, some toxicities have taken considerable time/years to manifest.

No safety concerns relating to long term use of FTR were identified in the nonclinical studies (including 2-year non-clinical carcinogenicity studies).

Limited data are available on long term use of FTR from clinical trials. In the ongoing Phase 3 study in HTE subjects, to the cut-off date for the 96-week analysis, 370 subjects were exposed to FTR for a median duration of 772.5 days/ 2.1 years (range 1 to 1,200 days) [205888 (AI438047)] 96 Week CSR]. Through Week 144, the median duration of exposure to FTR in the Phase 3study is 171.36 weeks (range 0.1 to 230.3 weeks) [60 Day Safety Update Report, statistical output Table 1.8802].As shown in Table 5, 182 subjects in study 205888 (49%) have been exposed to FTR for between 144 and <192 weeks (2.8 to <3.7 years); their total exposure is 608.0 person years; 81 (22%) of subjects have been exposed to FTR for between 192 and <240 weeks with a total exposure of 321.8 person-years. Longer term safety will be monitored post-authorization through routine and additional pharmacovigilance activities [Part III].

In the Phase 2b study in GTE adults, which ran for over 5 years, the median time on any dose of FTR was 1645.5 days (approx. 4.5 years; range 1 to 2052 days, module 2.7.4 Section 1.2.3.1) with 57% (114/200) subjects completing between 240-300 weeks (4.5 to 5.7 years) of FTR treatment (module 2.7.4 Section 1.2.3.1).

Population in need of further characterisation

The long term safety of FTR will be monitored through routine pharmacovigilance activities and continued monitoring and characterization of data from the ongoing Phase 3 study.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Ventricular tachyarrhythmias due to QT prolongation
Missing information	Use in pregnant and lactating women Long term safety data

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required.

III.2 Additional pharmacovigilance activities

A summary of the studies that are planned/ongoing for FTR to address specific safety concerns is presented below.

STUDY SHORT NAME AND TITLE: Antiretroviral Pregnancy Registry (APR)

RATIONALE AND STUDY OBJECTIVES: The APR is an international registry that monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. The APR is MAH sponsored study involving the collaborative effort of multiple companies [Antiretroviral Pregnancy Registry, 2020].

Data from the APR will be used to monitor the use of FTR in pregnancy.

STUDY DESIGN: Clinicians register pregnant women with prenatal exposures to any ARV before the outcome of pregnancy is known, report data on exposure throughout pregnancy, and provide birth outcome data. Registration is voluntary and confidential. Defects are reviewed by a teratologist, and all data are reviewed semi-annually by an independent Advisory Committee. Exposure is classified and analysed by the earliest trimester of exposure to each individual ARV medication. Birth defect prevalence (any pregnancy outcome > 20 weeks of gestation with a defect/live births) is compared to both internal and external comparator groups. The external comparators used are two population-based surveillance systems – Metropolitan Atlanta Congenital Defects Program (MACDP) [Correa, 2008; Correa-Villasenor, 2003] by the CDC and the Texas Birth Defects Registry (TBDR) [Texas Birth Defect Surveillance System, 2013]. Internal comparators include exposures to other drugs and exposures in the 2nd or 3rd trimester of pregnancy relative to 1st trimester exposures when organogenesis occurs. Statistical inference is based on exact methods for binomial proportions. APR has 80% power and Type 1 error rate of 5% to detect doubling of risk for overall birth defects. For specific defects, the power varies with the population's frequency of the defect and the size of the exposed group. The overall APR rates of birth defects in all ARV-exposed infants is 2.8% while the background birth defect rate in the CDC reference populations is 2.7% and the TBDR is 4.2% [Antiretroviral Pregnancy Registry, 2020].

STUDY POPULATION: Annually, the Registry enrolls approximately 1300-1700 pregnant women exposed to antiretroviral drugs for the treatment of HIV and HBV infection and prevention of HIV infection. This number includes approximately 1300 or 25% of the 5000

HIV infected women who give birth to live infants annually in the US and approximately 350 pregnant women from other countries [Antiretroviral Pregnancy Registry, 2020].

MILESTONES: A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR will be presented in the FTR PSUR.

STUDY SHORT NAME AND TITLE: A Multi-arm, 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 Multi-drug Resistant HIV-1 (BRIGHTE Study)

RATIONALE AND STUDY OBJECTIVES: This ongoing Phase 3 study is designed assess the efficacy and safety of fostemsavir in heavily treatment-experienced patients. Despite the availability of different classes of antiretroviral agents providing a variety of treatment options, treatment failure continues to occur as a result of ARV drug resistance, drug-associated toxicity and tolerability problems, and poor adherence. Thus, there is an ongoing need for new classes of antiretroviral drugs capable of providing potent, durable antiviral activity against current antiretroviral-resistant viruses. As a novel attachment inhibitor prodrug, fostemsavir may fulfil the unmet medical need of HIV-1 infected adults who are heavily treatment-experienced.

Primary objective: to compare the efficacy of fostemsavir to placebo, when given on a background of a failing regimen.

Secondary objectives include the durability, safety and tolerability of the response to FTR when given with an optimized background regimen, and to assess disease progression and emergence of resistance.

STUDY DESIGN: A Multi-arm, Phase 3, Randomized, Placebo Controlled, Double Blind Clinical Trial.

STUDY POPULATION: Heavily treatment-experienced HIV-1 infected adults enrolled into either the Randomized Cohort, HTE subjects with ≤ 2 remaining fully active ARVs or the Non-randomized Cohort, HTE subjects with no remaining fully active ARV.

MILESTONES:

Final protocol approved: 30 Dec 2014

Study start: 23 Feb 2015

Estimated study completion (last subject last visit): 31 Dec 2025

Estimated final study report: 31 Dec 2026

III.3 Summary Table of additional Pharmacovigilance activities

Table 15 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3- Required additional pharmacovigilance activities				
Antiretroviral Pregnancy Registry Ongoing	Monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort.	Use in pregnant women	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR is presented in the PSUR.	-
A Clinical Trial to Investigate the Efficacy and Safety of Fostemsavir in HTE Subjects Infected with Multi-drug Resistant HIV-1 (BRIGHTE Study) Ongoing	To assess the efficacy and safety of fostemsavir in heavily treatment-experienced patients.	Ventricular tachyarrhythmias due to QT prolongation Long term safety data	Final protocol approved	30 Dec 2014
			Study start	23 Feb 2015
			Study completion	31 Dec 2025
			Final study report	31 Dec 2026

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None proposed.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Based on the available clinical and nonclinical data, routine risk minimisation activities are considered sufficient for management of the risks with FTR.

Table 16 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Ventricular tachyarrhythmias due to QT prolongation	**Routine risk communication:** • SmPC section 4.4, 4.5 and 4.8. • Patient leaflet (PL) section 2 and 4. **Other routine risk minimisation measures beyond the Product Information:** This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV.
Use in pregnant and lactating women	**Routine risk communication:** • SmPC section 4.6. • PL section 2. **Other routine risk minimisation measures beyond the Product Information:** This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV.
Long term safety data	None.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 17 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Ventricular tachyarrhythmias due to QT prolongation	**Routine risk minimisation:** • SmPC section 4.4, 4.5 and 4.8. • PL section 2 and 4. **Other routine risk minimization measures beyond the Product Information:** • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV. **Additional risk minimization measures**: None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activity:** A Clinical Trial to Investigate the Efficacy and Safety of Fostemsavir in HTE Subjects Infected with Multi-drug Resistant HIV-1 (BRIGHTE Study). Final study report due: 31 Dec 2026.
Use in pregnant and lactating women	**Routine risk minimisation measures:** SmPC section 4.6. PL section 2. **Other routine risk minimisation measures beyond the Product Information**: • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV. **Additional risk minimization measures**: None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activity:** Antiretroviral pregnancy registry.
Long term safety data	None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activity:** A Clinical Trial to Investigate the Efficacy and Safety of Fostemsavir in HTE Subjects Infected with Multi-drug Resistant HIV-1 (BRIGHTE Study) Final study report due: 31 Dec 2026

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for fostemsavir

This is a summary of the risk management plan (RMP) for fostemsavir. The RMP details important risks of fostemsavir, how these risks can be minimised, and how more information will be obtained about fostemsavir's risks and uncertainties (missing information).

Fostemsavir's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how fostemsavir should be used.

This summary of the RMP for fostemsavir should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of fostemsavir's RMP.

I. The medicine and what it is used for

Fostemsavir, in combination with other antiretrovirals, is authorised for treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen (see SmPC for the full indication). It contains temsavir as the active substance and it is given by a tablet by mouth.

Further information about the evaluation of fostemsavir’s benefits can be found in fostemsavir’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/rukobia.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of fostemsavir, together with measures to minimise such risks and the proposed studies for learning more about fostemsavir's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of fostemsavir is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of fostemsavir are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of fostemsavir. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Ventricular tachyarrhythmias due to QT prolongation
Missing information	Use in pregnant and lactating women Long term safety data

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important potential risk: Ventricular tachyarrhythmias due to QT prolongation	
Evidence for linking the risk to the medicine	The risk of ventricular tachyarrhythmias due to QT prolongation, which can be life-threatening, is considered an important potential risk based on the finding that a supra-therapeutic dose of FTR prolonged QTc interval in the thorough QT (TQT) clinical study in healthy volunteers. Based on modelling of TQT clinical data, the threshold for clinically significant QTc prolongation (≥10 ms) is 7,500 ng/mL TMR, which is 4.2x higher than the Cmax associated with FTR 600 mg BID regimen in HTE HIV-1 infected patients enrolled in the Phase 3 study. This safety threshold for QT prolongation is

	sufficiently high to cover the Cmax increase due to co-administration of pharmacoenhancers. No significant clinical events relating to this risk have been identified to date in clinical studies involving FTR.
Risk factors and risk groups	No additional risk factors have been identified in HTE HIV infected patients beyond those previously described for the general population [Frommeyer, 2015].
Risk minimisation measures	**Routine risk minimisation:** • SmPC section 4.4, 4.5 and 4.8. • PL section 2 and 4. **Other routine risk minimization measures beyond the Product Information:** • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV. **Additional risk minimization measures**: None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activity:** **Short study name:** A Clinical Trial to Investigate the Efficacy and Safety of Fostemsavir in HTE Subjects Infected with Multi-drug Resistant HIV-1 (BRIGHTE Study). See section II.C of this summary for an overview of the post-authorisation development plan.

Important missing information 1: Use in pregnant and lactating women	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6. PL section 2. **Other routine risk minimisation measures beyond the Product Information**: • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV. **Additional risk minimization measures**: None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activity:** **Short study title:** Antiretroviral Pregnancy Registry (APR)

	See section II.C of this summary for an overview of the post-authorisation development plan.

Important missing information 2: Long term safety data	
Risk minimisation measures	None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activity:** **Short study title:** A Clinical Trial to Investigate the Efficacy and Safety of Fostemsavir in HTE Subjects Infected with Multi-drug Resistant HIV-1 (BRIGHTE Study) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of fostemsavir.

II.C.2 Other studies in post-authorisation development plan

Study Short Name: Antiretroviral Pregnancy Registry (APR).

Purpose of the Study: The APR is an international registry that monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort.

Study Short Name: A Multi-arm, 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 Multi-drug Resistant HIV-1 (BRIGHTE Study).

Purpose of the Study: This ongoing Phase 3 study is designed assess the efficacy and safety of fostemsavir in heavily treatment-experienced patients**.**

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.