Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Fostemsavir trometamol

Proprietary Product Name: Rukobia

Sponsor: ViiV Healthcare Pty Ltd

September 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ARV	Antiretroviral
ASA	Australian specific annex
AST	Aspartate transaminase
AUC	Area under the concentration versus time curve
BCRP	Breast cancer resistance protein
CCR5	C-C chemokine receptor type 5
CI	Confidence interval
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
C_{tau}	Trough plasma concentration at the end of a dosing interval
CXCR4	C-X-C motif chemokine receptor 4
DLP	Data lock point
E-R	Exposure-response
ERAUC	Exposure ratio based on area under the concentration versus time curve
EU	European Union
FDA	Food and Drug Administration (United States of America)
GI	Gastrointestinal

Abbreviation	Meaning
gp120	Glycoprotein 120
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus 1
HIV-2	Human immunodeficiency virus 2
HTE	Heavily treatment experienced
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INSTI	Integrase strand transfer inhibitor
ITT	Intent to treat
ITT-E	Intent to treat - exposed
MDR	Multidrug resistant
MRHD	Maximum recommended human dose
NNRTI	Non-nucleoside reverse transcriptase
NOEL	No observable effect level
NRTI	Nucleoside reverse transcriptase
OAT	Organic anion transporter
OBT	Optimised background therapy
OCT	Organic cation transporters
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PND	Post-natal day
PopPK	Population pharmacokinetic(s)

Abbreviation	Meaning
PSUR	Periodic safety update report
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event
TGA	Therapeutic Goods Administration
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Rukobia
Active ingredient:	Fostemsavir trometamol
Decision:	Approved
Date of decision:	9 July 2021
Date of entry onto ARTG:	14 July 2021
ARTG number:	337863
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	ViiV Healthcare Pty Ltd Level 4, 436 Johnston Street Abbotsford, VIC, 3067
Dose form:	Extended release tablet
Strength:	600 mg fostemsavir (as fostemsavir trometamol)
Container:	Bottle
Pack size:	60
Approved therapeutic use:	*Rukobia is indicated in combination with other antiretroviral agents for the treatment of heavily treatment-experienced adults with multidrug-resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance or safety considerations (see Section 5.1 Pharmacodynamic properties, clinical trials).*
Route of administration:	Oral
Dosage:	Therapy should be initiated by a physician experienced in the management of human immunodeficiency virus (HIV) infection.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Adults

The recommended dosage of fostemsavir is 600 mg orally twice daily.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by ViiV Healthcare Pty Ltd (the sponsor) to register Rukobia (fostemsavir trometamol) 600 mg, extended release tablet for the following proposed indication:

> *Rukobia is indicated in combination with other antiretroviral agents for the treatment of heavily treatment experienced adults with multidrug resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen due to resistance, intolerance or safety considerations (see Section 5.1 Pharmacodynamic Properties, Clinical Trials).*

While there is currently no cure available for HIV (or human immunodeficiency virus) infection, which if left untreated can ultimately lead to the development of AIDS (or acquired immunodeficiency syndrome), the development and introduction of highly effective antiretroviral (ARV) therapy has greatly improved the lives of HIV-infected individuals. Despite the availability of different classes of ARV agents providing a variety of treatment options, treatment failure continues to occur because of ARV drug resistance, drug-associated toxicity, tolerability problems, and poor adherence. Living with active HIV infection has significant health needs by itself.

Human immunodeficiency virus 1 (HIV-1) and human immunodeficiency virus 2 (HIV-2) are two distinct viruses. HIV-1 accounts for around 95% of all infections worldwide. As fostemsavir (Rukobia) discussed in this submission, and its' pharmacologically active metabolite temsavir is not active against HIV-2, the following focuses on subtypes of HIV-1.

Diagnostic tests for HIV-1 infection include assays for HIV-1 ribonucleic acid (RNA), capsid structural protein p24 antigen, and HIV-1 and HIV-2 antibodies. Initial laboratory testing

should include assessment of HIV staging parameters (chiefly, $CD4^+$ T cell count, HIV RNA plasma concentrations) as well as a HIV genotype test for detection of drug resistance.

Currently, there are no reliable figures for prevalence of multidrug resistant (MDR) HIV-1 infection. The sponsor expanded on the concept of 'heavily treatment experienced' (HTE) patients instead. Rates for the HTE population vary by region and country; the estimated prevalence ranges from approximately < 1% to 5.1%.[2,3]

Fostemsavir is a methyl-phosphate prodrug of the active moiety temsavir, which has been developed for the treatment of HIV-1 infected HTE patients with multi-drug resistance. Fostemsavir is a first-in-class drug for the treatment of HIV. It has a new mechanism of action. It binds directly to the glycoprotein 120 (gp120) envelope glycoprotein on the surface of HIV. This prevent initial interaction between HIV and $CD4^+$ T cell surface receptors, preventing entry into and infection of host T cells and other immune cells.

Heavily treatment experienced patients are whose current ARV regimen if failing, have MDR virus and have few remaining therapeutic options. There are 1 to 2 available ARV classes that can be combined as part of a viable regimen, also known as salvage therapy. These ARV classes must lack cross-resistance with other available products which is increasingly difficult. In the United States of America (USA), the ARV drugs most frequently used for advanced salvage therapy are ritonavir-boosted darunavir, dolutegravir, etravirine, maraviroc, and enfuvirtide. In addition, ibalizumab is a recently approved anti-CD4 monoclonal antibody with a targeted indication for use in adults with MDR HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen. Ibalizumab however, is not available in Australia.

While the primary goal of ARV therapy is always to achieve complete virologic control, if suppression is not achievable, which appears the case for the HTE population, additional treatment objectives exist including partial reduction of the viral load, preserving immunologic function, preventing clinical progression of disease, and minimising additional resistance to agents that are potentially important to future treatment options. A new ARV class for this group would provide another option.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in European Union (EU) on the 4 February 2021 and the USA on 2 July 2020. The indications for these approvals are given in Table 1, below.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	10 January 2020	Approved on 4 February 2021	*Rukobia, in combination with other antiretrovirals, is indicated for the treatment of*

[2] Bajema K et al. Prevalence of heavily treatment-experienced persons with HIV in the United States, 2000-2017. Tenth International AIDS Society Conference on HIV Science (IAS 2019), abstract MOPEB246, 2019.
[3] Hsu R, et al. Identifying Heavily Treatment-Experienced Patients in the OPERA Cohort. 22nd International AIDS Conference; July 23–27, 2018; Amsterdam, the Netherlands. Poster THPEB044.

Region	Submission date	Status	Approved indications
			adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.
United States of America	4 December 2019	Approved on 2 July 2020	*Rukobia, a human immunodeficiency virus type 1 (HIV-1) gp120-directed attachment inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-02898-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2020
First round evaluation completed	12 March 2021
Sponsor provides responses on questions raised in first round evaluation	12 May 2021
Second round evaluation completed	18 May 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 May 2021
Sponsor's pre-Advisory Committee response	17 May 2021
Advisory Committee meeting	3 and 4 June 2021
Registration decision (Outcome)	9 July 2021
Completion of administrative activities and registration on the ARTG	14 July 2021
Number of working days from submission dossier acceptance to registration decision*	191

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Fostemsavir is a novel prodrug of the active moiety temsavir, which binds directly to gp120 subunits within the envelope glycoprotein on the surface of HIV. The chemical structure of the drug substance and the active moiety temsavir are below in Figure 1 and Figure 2.

The drug substance is in a salt form with trometamol (also known as tromethamine, or Tris), and is a salt form used in currently registered medicines. Fostemsavir tromethamine is the USA adopted name for the drug product, whereas the European Medicines Agency (EMA) refers to fostemsavir trometamol. The TGA considers fostemsavir trometamol to be the more appropriate terminology for the drug substance and aligns with the currently registered medicines (for example, fosfomycin trometamol and ketorolac trometamol).

The drug product is an extended release tablet formulation and the recommended dose is 600 mg taken twice orally daily, with or without food. The proposed product is to be supplied in an opaque, bottle with child-resistant, with a pack size of 60 tablets.

Figure 1: Chemical structure for fostemsavir trometamol

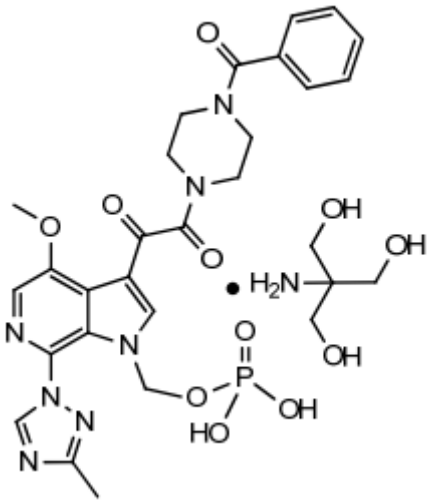
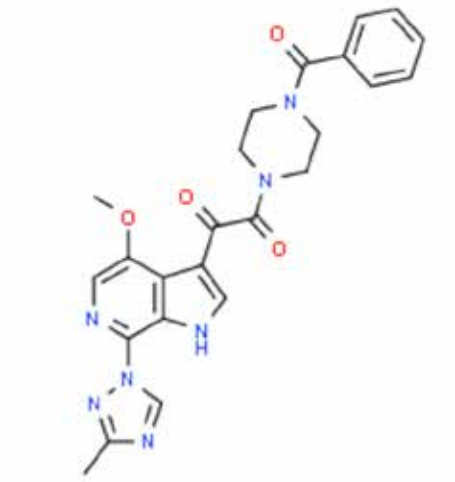


Figure 2: Chemical structure for temsavir



In conclusion, the quality evaluator recommended approval for registration of the proposed product from a pharmaceutical chemistry perspective.

Nonclinical

The submitted nonclinical dossier was in accordance with the relevant International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for the nonclinical assessment of pharmaceuticals.[4] The overall quality of the dossier was reasonable with all pivotal safety studies conducted under Good Laboratory Practice conditions.

Fostemsavir has minimal antiviral activity and is cleaved to temsavir by alkaline phosphatase in the intestinal epithelia. Due to fostemsavir's very limited pharmacological activity (temsavir has ≥ 700 times more potency than fostemsavir), almost all of the nonclinical pharmacodynamics data used the active moiety temsavir. Temsavir did not have activity against reverse transcriptase, protease and integrase, showing specificity for the glycoprotein gp160 complex. Many laboratory virus strains (C-X-C motif chemokine

[4] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals Step 5. EMA/CPMP/ICH/286/1995.

receptor 4 (CXCR4))-tropic, C-C chemokine receptor type 5 (CCR5)-tropic, and dual tropic) showed susceptibility to temsavir, but the RF strain (CXCR4-tropic) was not susceptible. Not all clinical isolates (from different countries) examined were susceptible to temsavir. Although most viruses are susceptible to temsavir, these results suggest that there is a large range of intrinsic susceptibility to temsavir in baseline envelopes within the population.

Substitutions in the HIV-1 envelope glycoprotein gp160 gene increased resistance to temsavir. Temsavir did not demonstrate i*n vitro* cross-resistance to other antiretroviral agents and was active against HIV-1 virus regardless of tropism (that is CCR5-, CXCR4-, or dual-tropic virus). In summary, the pharmacology studies submitted provide support to the proposed clinical indication.

Based on a comprehensive screen against several receptors, ion channels and transporters, no off-target effects were identified for the proposed clinical use of fostemsavir. Fostemsavir and temsavir were not cytotoxic to various human cell lines and peripheral blood mononuclear cells.

The examination of antiviral activity of temsavir, in combination with other antiretroviral drugs, did not reveal any antagonism or cytotoxicity. Temsavir exhibited additive and synergistic activity when in combination with other antiretroviral drugs. The drugs tested for pharmacodynamic drug interactions with temsavir included nucleoside reverse transcriptase (NRTI), non-nucleoside reverse transcriptase (NNRTI), protease (PI), integrase strand transfer inhibitor (INSTI), and entry inhibitor classes.

Safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous system (CNS). CNS and respiratory functions in rats were unaffected by treatment. Temsavir inhibited hERG K^+ tail currents with an half maximal inhibitory concentration (IC_{50}) equivalent to about 64 times the free clinical maximum concentration (C_{max}) in plasma of temsavir at the maximum recommended human dose (MRHD) of fostemsavir. Tachycardia was observed in rats and dogs in the repeat dose toxicity studies at high exposure margins (temsavir ERAUC ≥ 25);[5] whereas increases in the QT interval occurred at lower relative exposures in safety pharmacology studies in dogs.[6] Since QT prolongation was also observed in patients receiving fostemsavir (2400 mg twice daily), changes in heart rate and electrocardiogram parameters may be present during clinical use.

Fostemsavir is a prodrug. It is rapidly and extensively converted to temsavir. Temsavir is the predominant substance in the systemic circulation, whereas only trace levels of the prodrug are detected in the circulation. Fostemsavir has high solubility, low permeability, and short elimination half-life, whereas temsavir has low solubility, high permeability and longer elimination half-life. No meaningful sex differences were observed in pharmacokinetic (PK) analysis. Bioavailability of temsavir was higher in animals (> 80%) species than humans (< 30%). The extent of protein binding was high in rabbits (98.6%), rats (95.9%), mice (87.7%) and humans (88.4%), and moderate in dogs (70.4%). Due to the differences in free fractions, animal to human exposure margins were determined based on the calculated unbound plasma concentrations. Temsavir had a large volume of distribution but had minimal penetration of the blood-brain barrier. Fostemsavir-related radioactivity was present in the placenta and milk in rats. The PK profile in non-human primates was qualitatively similar to that of humans, except for the fact that metabolites BMS-646915 (M4; debenzolylated temsavir, created by hydrolysis) and BMS-930644 (M28; N-dealkylated temsavir, created via N-dealkylation)) were identified in plasma and

[5] **ERAUC** = exposure ratio based on the area under the concentration versus time curve.
[6] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

accounted for approximately half the drug-related radioactivity in humans, but were only a minor component in the rat and dog. Nevertheless, exposure to these 2 metabolites was higher than their respective human exposure in the nonclinical toxicity studies. In all species teste and after administration of fostemsavir, temsavir was eliminated mainly via biotransformation (by CYP3A4);[7] followed by elimination unchanged in urine, faeces and bile.

Fostemsavir has low acute oral toxicity in rats and dogs.

Repeat-dose toxicity studies by the oral route were conducted in mice (4 weeks), rats (up to 26 weeks) and dogs (up to 39 weeks). Maximum exposures (area under the concentration-time curve (AUC)) to temsavir following dosing with fostemsavir were generally high multiples of the clinical AUC, reaching > 37 in the pivotal studies in rats and dogs. Target organs for toxicity included:

- The liver was the main target organ identified in dogs, with increased bilirubin, not fully reversible multifocal canalicular pigment deposits, as well as increases in alkaline phosphatase (ALP) and aspartate transaminase (AST). Rats displayed increased liver weights and ALP levels.
- The adrenal gland was the main target organ identified in rats, with increased organ weights, angiectasis and adrenal necrosis, and increased incidence (although not statistically significant) of pheochromocytoma in rats. These effects occurred mostly in females. Dogs displayed adrenal necrosis and inflammation.
- Renal changes occurred only in rats (tubular dilatation multifocal, involving cortical tubules and increased kidney weights) and were partially (in females) to fully reversible (in males).
- Effects in testicular tissues in rats (decreased sperm count/dysmorphology and degenerative seminiferous tubule epithelium; not fully reversible) and dogs (debris in epididymis and atrophy of seminiferous epithelium).

Temsavir and its prodrug fostemsavir were not mutagenic in the bacterial mutation assay or clastogenic *in vivo* (in the rat micronucleus test). No treatment related increase in tumour incidence was observed in transgenic mice in a six months oral carcinogenicity study, or rats in two years oral carcinogenicity studies. Relative exposure to temsavir (based on AUC) at the no observable adverse effect level (NOAEL) (maximum doses used) was six in male rats, 38 in female rats, 18 in male transgenic mice and 39 in female transgenic mice.

Fostemsavir decreased sperm density values, and prostate (with seminal vesicles) weights, at temsavir ERAUC ≥ 21. At temsavir ERAUC 33, fostemsavir increased abnormalities in sperm morphology and decreases in epididymal weights and sperm motility, although male reproductive performance and embryonic viability were unaffected. The NOAEL for reproductive effects was 600 mg/kg/day fostemsavir in female rats (temsavir ERAUC 49). At a maternotoxic dose of 1000 mg/kg/day (temsavir ERAUC 65), fostemsavir caused fetal malformations of the head and jaw, and reduced fetal body

[7] **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

weights to pregnant rats. The NOAEL for developmental toxicity was 300 mg/kg/day (temsavir ERAUC 37). In rats, fostemsavir-related radioactivity crossed the placenta. In rabbits, fostemsavir's NOAEL for maternal toxicity was 25 mg/kg/day (temsavir ERAUC 1.7), and for developmental toxicity was 50 mg/kg/day (temsavir ERAUC 2-3). No teratogenicity was observed at maternotoxic doses of 250 mg/kg/day (temsavir ERAUC 13). Although the sponsor has proposed Pregnancy Category B1;[8] Pregnancy Category B3 is recommended;[9] since fetal damage was observed (for example, fetal malformations of the head and jaw in rats and increased post-implantation losses/early resorptions in rabbits). In female rats treated with fostemsavir from early gestation through to weaning, reduced neonatal survival from post-natal day (PND) 7 to PND 14 was observed, in the absence of maternal toxicity, at 300 mg/kg/day fostemsavir (temsavir ERAUC 35). The NOAEL for neonatal toxicity was 50 mg/kg/day (temsavir ERAUC 9.4). Temsavir was excreted in milk in rats.

There are no objections on nonclinical grounds to the proposed registration of Rukobia for the proposed indication.

Clinical

Pharmacology

Pharmacokinetics

The PK of fostemsavir is focused on the active moiety, temsavir.

[8] **Pregnancy category B1**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.

[9] **Pregnancy category B3**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Table 3: Conversion of fostemsavir to temsavir

Conversion of FTR (pro-drug) to TMR (active moiety)		
FTR is hydrolyzed to TMR by alkaline phosphatase in the gastrointestinal lumen; the conversion is predominantly pre-systemic.		
Absorption		
Absolute Bioavailability	26.9%	
tmax (fasted)	2.0 hours	
Food Effect	Standard Meal (423 kcal, 36% fat) vs. Fasted	High-Fat Meal (985 kcal, 60% fat) vs. Fasted
Cmax	No change	No change
AUC	No change	1.81
Ctau	1.68	5.66
tmax	↑2 hours	↑4.5 hours
↑Gastric pH Effect		
Cmax	No change	
AUCinf	No change	
Distribution		
Vss	29.5 L	
Plasma protein binding (ex vivo)	88.4% primarily to HSA	
blood:plasma ratio	0.74	
Transporters involved in TMR distribution	BCRP, Pgp	
Metabolism & Excretion		
t1/2	11 hours	
CL	17.9 L/h	
Route of Elimination	Metabolism	
Metabolic Pathways (percent of administered dose)	Esterase hydrolysis (primary, 36.1%)[a] CYP3A4 (secondary, 21.2%)[a] Other CYP (non-CYP3A4) (minor, 7.2%)[a] Glucuronidation (minor, <1%)[b]	
Excretion (predominantly as metabolites)	Recovery of radioactivity (% of administered dose)	
	without bile collection[a]	with bile collection[b]
	44% urine 33% feces	51% urine 33% feces 5% bile

FTR = fostemsavir; TMR = temsavir; Cmax = maximum concentration; AUC = area under the concentration-time curve; C_{tau} = concentration in plasma at the end of a dosing interval; Tmax = time of maximum concentration; AUC_{inf} = area under the concentration-time curve from time 0 to infinity; Vss = volume of distribution at steady state; HSA = human serum albumin; BCRP = breast cancer related protein; Pgp = P-glycoprotein; t1/2 = terminal half flice; CL = cleareance; CYP = cytochrome P450 system enzyme

Similar plasma temsavir. exposure between healthy and HIV-1 infected subjects supports extrapolation of data generated in healthy subjects, such as drug and food interactions and the thorough QT/QTc study, to the HIV-1 infected population. Plasma temsavir PK parameter values following repeat dose administration of fostemsavir extended released tablets are similar between healthy and HIV-1 infected subjects based on results of cross-study comparisons.

Special Populations

Elderly

Population pharmacokinetic analysis of temsavir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on temsavir exposure. PK data for temsavir in subjects greater than 65 years old are limited. Elderly patients may be more susceptible to drug-induced QT interval prolongation.

Renal impairment

There was no clinically relevant effect of renal impairment on pharmacokinetic exposure parameters (C_{max} and AUC) of temsavir (total and unbound).

Hepatic impairment

In patients with mild to severe hepatic impairment, the increased exposure to both unbound and total C_{max} and AUC was in the range of 1.2 to 2.2 fold. However, the upper bounds of the two sided 90% confidence interval (CI) for the impact of hepatic impairment on plasma total and unbound temsavir C_{max} are lower than the C_{max} threshold of an approximate 4.2 fold increase (7500 ng/ml) established based on temsavir exposure response.

Gender and Race

Population pharmacokinetic analyses indicated no clinically relevant effect of gender or race on the exposure of temsavir. Of the 764 subjects included in the analysis, 216 (28%) were female.

Pharmacokinetic interactions

Significant interactions are not expected when fostemsavir is co-administered with substrates of CYPs, uridine diphosphate glucuronosyl transferases, permeability glycoprotein, multidrug resistance protein 2, bile salt export pump , sodium taurocholate co-transporting polypeptide, organic anion transporter (OAT)1, OAT3, organic cation transporters (OCT)1, and OCT2 based on *in vitro* and clinical drug interaction data.

Population pharmacokinetic data

The sponsor conducted a population pharmacokinetics (popPK) analysis of fostemsavir following administration of fostemsavir tablets using the plasma temsavir concentration data from healthy adult subjects and adult patients with HIV-1 enrolled in Phase I, Phase II, and Phase III trials.

The final popPK model was a two compartments model with dual zero and first order absorption and first order elimination with CYP3A inducers and CYP3A inhibitors as covariates on apparent total clearance of the drug from plasma after oral administration (CL/F) and allometrically scaled body weight as a covariate on CL/F, V2/F, Q/F and V3/F.

All popPK parameters were estimated with good precision, as measured by relative standard errors <15% for both fixed and random effects, model fit to the observed data at population and individual level was reasonable. The visual predictive check showed that the model adequately described the time course of plasma temsavir concentrations for key studies which were included in the exposure-response (E-R) analysis (Phase IIb Study 205889 and Phase III Study 205888), best for the 400 mg and 600 mg twice daily doses.

Over a body weight range of 40 to 150 kg, plasma temsavir trough plasma concentration at the end of a dosing interval (C_{tau}) was estimated as 1.4 to 0.70 fold the reference exposure for 72 kg. The sponsor's covariate analysis suggests that HIV status, age, gender, race, formulation, and baseline clinical laboratory parameters (creatinine clearance, alanine transaminase (ALT), AST, ALP, and direct bilirubin) had no effect on temsavir PK. Temsavir PK data in subjects ≥ 65 years old (n =11) and in some racial groups (especially Asian subjects) were limited. Plasma temsavir PK parameters for fostemsavir 600 mg twice a day are summarised based on data collected on Day 8 in subjects with HIV-1 enrolled in the randomised cohort of the Phase III trial, Study 205888.

Summary of exposure-response analysis for efficacy

This analysis was based on the data from the randomised cohort of the Phase III (Study 205888) which was conducted in the intended population with HIV-1 at the proposed regimen of fostemsavir 600 mg twice daily. The final E-R model was a maximum effect inhibitory model where the response variable was change in plasma HIV-1 RNA from Day 1 to Day 8 and explanatory variables were the exposure metric (*post hoc* C_{tau}) and the two baseline characteristics (baseline plasma HIV-1 RNA and $CD4^+$ T cell counts >

20 cells/mm^3). The sponsor noted that age, gender, race, body weight, geographic region, and the following baseline factors: IC_{50}, IC_{50} fold change (FC), number of predefined genotypic substitutions of interest within the gp160 domain, and $CD8^+$ T cell count had no effect on Day 8 virologic response. The sponsor concluded that the final E-R model suggests the E-R relationship between plasma temsavir C_{tau} and change in plasma HIV-1 RNA on Day 8 is shallow and highly variable.

Summary of Exposure-Response Analysis for Safety

A graphical analysis was conducted to evaluate the relationship between *post hoc* plasma temsavir exposure metrics from the final popPK model and select safety parameters. It was concluded that exposure-safety relationships were not evident between temsavir exposure metrics (average concentration and C_{max}) and safety endpoints of interest.

Pharmacodynamics

The primary pharmacodynamic (PD) effect is reduction in plasma HIV-1 RNA. This was examined in the two Phase II antiretroviral (ARV)-naïve and ARV treatment-experienced HIV-1 infected populations. Temsavir exhibited variable activity across HIV-1 subtypes. Temsavir half-maximal inhibitory concentration (IC_{50}) value ranged from 0.01 to > 2000 nM against clinical isolates of subtypes A, B, B', C, D, F, G and CRF01_AE strain in peripheral blood mononuclear cells. Temsavir was not active against HIV-2. Due to high frequencies of polymorphism S375H (98%) and S375M/M426L/M434I (100%) temsavir is not active against Group O and Group N.

Steady state plasma temsavir concentrations are achieved by Day 2 to 3 following administration of fostemsavir 600 mg twice daily. Concentrations are related to HIV activity as well as the effect of lengthening the QTc.

Simulation showed that there was no E-R relationship evident between plasma temsavir C_{tau} and Week 24 efficacy endpoints or between plasma temsavir C_{tau} and change in $CD4^+$ T cell count from Day 1 at each visit through Week 24. The exploratory E-R relationship from the Phase IIa monotherapy study indicated that baseline viral drug susceptibility (expressed as IC_{50}) was the most influential factor in determining the magnitude of decline in HIV RNA. In that study, IC_{50} baseline values ≥ 100 nM seemed to be associated with a decreased antiviral activity.[10]

A supratherapeutic dose (at a C_{max} approximately 4.2 fold the therapeutic dose) of fostemsavir has been shown to significantly prolong the QTc interval. Fostemsavir should be used with caution in patients with a history of QT interval prolongation, when co-administered with a medicine with a known risk of torsade de pointes or in patients with relevant pre-existing cardiac disease. This was reflected as a warning in Section 4.4 of the PI.

Efficacy

Dose finding for the pivotal study

The proposed dose of fostemsavir 600 mg twice daily utilised in the Phase III Study 205888 in HTE patients infected with MDR HIV-1 was developed from data from the Phase IIa proof of concept monotherapy Study 206267 and the Phase IIb Study 205889, together with QT data from different fostemsavir concentrations obtained from Study 206275. It was based on PK, efficacy, and safety data from two Phase II trials in subjects with HIV-1 infection. Study 206267 was a Phase IIa trial that evaluated fostemsavir 600

[10] Sponsor clarification: However, data from the pivotal Phase III study, showed that while there did appear to be a trend toward reduced clinical response at higher temsavir IC_{50} values, following 8 days of fostemsavir functional monotherapy, this baseline variable failed to reliably predict efficacy outcomes over time in the intended use population

mg twice daily and 1200 mg daily at bedtime in treatment-naïve subjects and fostemsavir 1200 mg twice daily in treatment-experienced (but not considered HTE) subjects. Study 205889 was a Phase IIb trial that evaluated fostemsavir 400 mg twice daily, 600 mg twice daily, 800 mg twice daily, 600 mg once a day, and 1,200 mg once daily. The primary endpoint for the Phase IIa trial was a mean decline in plasma HIV-1 RNA from Day 1 to Day 8 with fostemsavir monotherapy, while the primary endpoint for Phase IIb trial is the proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24.

The sponsor performed an E-R analysis using the monotherapy data from the Phase IIa and IIb trials and selected 600 mg twice daily for the Phase III trial. The sponsor's proposed dose, 600 mg twice daily, was the dose evaluated in the pivotal study, Study 205888, also known as the BRIGHTE trial, and is considered acceptable.

Study 2058880 (BRIGTE trial) (pivotal study)

Study 2058880, also known as the BRIGHTE trial, is an ongoing Phase III study conducted in HIV-1-infected highly treatment experience (the) adult subjects infected with MDR HIV-1. Subjects were assigned to the randomised or non-randomised cohort based on the number of fully active ARV agents that could be used to construct a background regimen.

The primary objective was to demonstrate the antiviral effect of fostemsavir relative to placebo, when given on the background of a failing regimen from Day 1 to Day 8 in the randomised cohort. Secondary objectives were assessment of durability of response and assessment of safety.

The randomised and non-randomised cohorts are described as follows, and the Study 205888 study schema is shown in Figure 3, below.

Cohorts

Randomised cohort

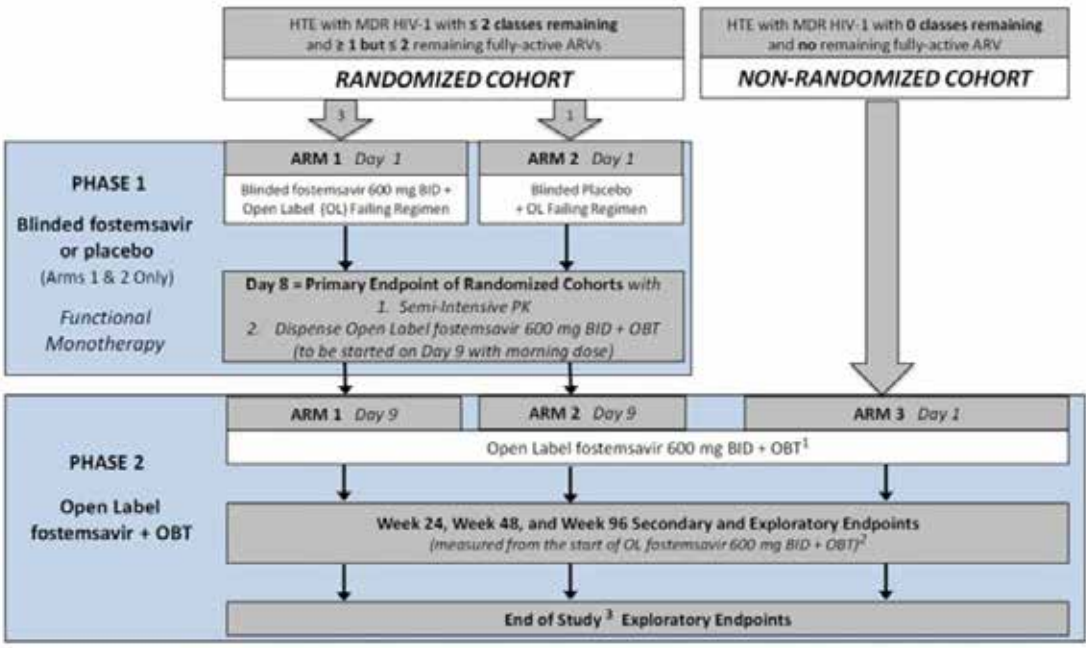
- Highly treatment experienced subjects with MDR HIV-1 infection on a failing ARV regimen. Subjects had ≤ 2 ARV classes remaining with at least one but no more than two remaining fully active ARVs which could be effectively combined to form a viable new regimen, based on baseline or documented historical resistance testing and tolerability and safety concerns.
- Subjects were randomised 3:1 to treatment with fostemsavir 600 mg twice daily or placebo, respectively, in addition to their failing regimen for 8 days.
- Randomisation was stratified by baseline HIV-1 RNA (≤ 1000 copies/mL or > 1000 copies/mL).
- The primary endpoint was assessed on Day 8 after which all subjects began open label fostemsavir 600 mg twice daily in combination with optimised background therapy (OBT).
- Virologic and immunologic responses were followed for at least 96 weeks to assess the durability of treatment with fostemsavir.
- Data from the randomised cohort provide the basis for determination of efficacy. This cohort also serves as the primary safety population.

Non-randomised cohort:

- Subjects began open label fostemsavir 600 mg twice daily and OBT starting on Day 1.
- Virologic and immunologic responses were followed for at least 96 weeks to assess the durability of treatment with fostemsavir.
- The purpose of this cohort was to allow access to fostemsavir for individuals with no remaining therapeutic options.

- Data from the non-randomised cohort provide safety and supplementary efficacy information. No formal hypothesis testing was conducted.

Figure 3: Study 2058880 Design schema



Treatments

Subjects in the randomised cohort received one tablet 600 mg fostemsavir or placebo orally twice daily from Day 1 to Day 8 together with their current failing regimen. From Day 9, subjects were administered one tablet 600 mg fostemsavir orally twice daily plus the OBT. Patients of the non-randomised cohort started taking 600 mg fostemsavir orally twice daily with OBT from Day 1. Fostemsavir was taken with or without food. Other investigational products were only allowed in the non-randomised cohort.

The formulation used in the Phase III is equivalent to the marketed 600 mg prolonged release formulation which differs from the formulation used in the Phase IIb study. The 600 mg twice daily prolonged release regimen had not been studied clinically prior to Phase III, but was selected based on modelling of E-R relationships on the one hand and on the assessment of risk of QT-interval prolongation on the other hand, using an integrated approach.

The primary endpoint of the Phase III Study 2058880 was the mean change of $\log_{10}$ HIV-1 RNA (copies/ml) relative to placebo from Day 1 (Baseline) to Day 8 in the randomised cohort. The key secondary endpoint was the proportion of subjects with HIV-1 RNA < 40 copies/ml over time (Week 24, 48 and 96) in both cohorts using the US Food and Drug Administration (FDA) snapshot algorithm in which subjects without an HIV-1 RNA value at the relevant time point or those who changed OBT due to lack of efficacy were considered as failures.

Inclusion criteria

- Men and nonpregnant women at least 18 years of age
- Antiretroviral-experienced with documented historical or baseline resistance, intolerability, and/or contraindications to ARVs in at least three classes.
- Failing current ARV regimen with a confirmed plasma HIV-1 RNA ≥ 400 copies/mL (first value from Investigator within 6 months of Screening visit, with the second value obtained from screening labs). Subjects with a Screening HIV-1 RNA < 400 copies/mL should be counted as screen failures; repeat testing is not permissible.

- Subjects in the randomised cohort must have at least one fully active and available agent in ≤ two ARV classes, based on current and/or documented historical resistance testing, taking into account tolerability and other safety concerns. Subjects without any remaining fully active approved antiretrovirals may be enrolled in the non-randomised cohort. Details regarding the determination of ARV activity are provided in element eight of the inclusion criteria

Exclusion criteria

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

Statistical analysis plan

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

Key secondary efficacy analyses of the randomised double blind phase at Day 8 included a comparison of the percentage of subjects with an HIV-1 RNA decline > 0.5 log_{10} and > 1 log_{10} copies/mL from Baseline in the fostemsavir and placebo groups. Secondary assessments also included safety, durability of virologic response, immunologic response, and emergence of resistance to the investigational drug and other drugs in the regimen. These secondary assessments occurred 24, 48, and 96 weeks from the time point subjects in both groups of the randomised cohort received open label fostemsavir in combination with OBT (extension phase).

For the open label, single arm, Non-randomised cohort, the durability of virologic response and immunologic response with fostemsavir in combination with OBT was summarised at Week 24, 48, and 96.

Subgroup analyses were performed to assess the consistency of the primary efficacy analysis in the randomised cohort. Subgroups of interest included HIV-1 RNA categories at Day 1, $CD4^+$ T cell categories at Day 1, HIV-1 subtype, age group, gender, race, geographic region, number of fully active ARVs in the initial OBT, number of baseline polymorphisms of interest in the gp160 domain, and TMR IC_{50}.

Results

Slightly more than 50% of the patients screened for participation were enrolled in the trial. The majority of subjects (78%) in each randomised treatment group remained in the trial at the Week 96 data cut off. The most frequent reasons for discontinuation in both the randomised and non-randomised cohorts were lack of efficacy, non-adherence to study drug, and death.

The primary efficacy analysis compares the decline in HIV-1 RNA with fostemsavir compared to placebo in the randomised cohort. Demographic factors and baseline disease characteristics were generally balanced between these two groups. Baseline median HIV-1 RNA was comparable across the study groups as well, ranging from 4.3 to 4.7 $\log_{10}$ copies/mL. Median baseline $CD4^+$ T cell count was notably lower in the non-randomised cohort compared to the randomised cohort (41 cells/mm^3 and 100 cells/mm^3, respectively) which is reflective of the differences in available ARV options between the two cohorts. Similarly, subjects in the non-randomised cohort had longer lifetime ART with more prior ARV regimens compared to randomised subjects.

The primary endpoint analysis, based on the adjusted mean decline in HIV-1 RNA from Day 1 at Day 8 in the randomised cohort, demonstrated superiority of fostemsavir to placebo (0.79 versus0 0.17 $\log_{10}$ decline, respectively; p< 0.0001, ITT-exposed (ITT-E) population).

Table 4: Study 2058880 Primary Analysis, plasma HIV-1 RNA $\log_{10}$ (copies/mL) change from Day 1 and Day 8 using one way analysis of covariance with homogeneous slopes and variances (randomised cohort); intent to treat-exposed population

Randomised Treatment	n	Adjusted Mean[a] (95% CI)	Difference[b] (95% CI)	p-value[c]
Placebo	69	-0.166 (-0.326, -0.007)	-	-
Fostemsavir 600 mg twice daily	201 [d]	-0.791 (-0.885, -0.698)	-0.625 (-0.810, -0.441)	<0.0001

a. Mean adjusted by Day 1 $\log_{10}$ HIV-1 RNA.

b. Difference: Fostemsavir - Placebo.

c. Mean value of viral load change from baseline (Fostemsavir = Placebo).
Note: p-value from Levene's Test of Homogeneity of variance 0.2082.

d. Two subjects (both in the fostemsavir arm) who had missing Day 1 HIV-1 RNA values were not included in the analysis.

The planned per-protocol sensitivity analysis was performed to assess efficacy of blinded fostemsavir, relative to blinded placebo, for subjects with values within the Day 8 window (Day 6 to Day 10) who did not deviate in any meaningful way from the protocol during the blinded period. These support the primary efficacy endpoint results; difference of adjusted mean between the two populations = 0.633 (-0.833, -0.432); p < 0.0001. The primary endpoint result is also supported by the sensitivity analyses of the ITT-E population using a two-way analysis of covariance which demonstrated a significantly larger decline in HIV-1 RNA from Day 1 to Day 8 for fostemsavir compared with placebo, in combination with a subject's failing ARV regimen.

In two key secondary efficacy analyses, significantly more subjects in the fostemsavir arm compared to the placebo arm had > 0.5 $\log_{10}$ and > 1 $\log_{10}$ decreases from Day 1 to Day 8, further supporting the efficacy of fostemsavir

Table 5: Secondary analysis, proportion of subjects with > 0.5 log_{10} and > 1 log_{10} declines in plasma HIV-1 RNA (copies/mL) from Day 1 to Day 8 using last observation carried forward Phase III trial. (intent to treat-exposed population)

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

As the HTE population had not been able to achieve virologic suppression with currently available therapy, the durability of virologic response in HTE subjects is important to analyse particularly as some of the drugs in the OBT were still fully or partially active. For example, the ARVs that were used in the OBT in order of percentage in the randomised cohort were integrase strand transfer inhibitors (INSTI; primarily dolutegravir), protease inhibitors (primarily darunavir) and nucleoside reverse transcriptase inhibitors (NRTI). The C-C motif chemokine receptor 5 (CCR5) antagonist,maraviroc, and non-nucleoside reverse transcriptase inhibitors (NNRTI) were used less frequently, while entry inhibitors (enfuvirtide or ibalizumab) were used the least frequently. In the non-randomised cohort, NRTIs and protease inhibitors were the most common class of drugs in the OBT, followed by INSTIs (primarily dolutegravir). Entry inhibitors and NNRTIs were used less frequently, and the CCR5 antagonist was used least frequently.

From Day 8 onward, all subjects were transitioned from their initial (failing) background regimen to an optimised regimen in combination with open label fostemsavir 600 mg twice daily.

The most important finding is that virologic suppression was achieved and maintained with fostemsavir plus OBT through Week 96 in a majority of subjects previously unable to achieve virologic suppression although the specific contribution of fostemsavir in this OBT is not known (after 8 days it was not monotherapy).

Virologic response was evaluated using the FDA snapshot algorithm (November 2015) after the final subject in each cohort (randomised and non-randomised cohort) completed the Week 24, 48 and Week 96 visit.

Table 6: Study 2058880 Virologic outcomes (HIV-1 RNA < 40 copies/mL) at Week 24, 48, and 96 for the randomised cohort; intent to treat-exposed population

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

Examining the snapshot analysis for the randomised cohort (combined placebo and fostemsavir groups as all subjects were receiving OBT during the open label phase of the trial).

Table 7: Study 2058880 Virologic outcomes for the randomised cohort; intent to treat- exposed population

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

Outcomes by US FDA snapshot algorithm; ART = antiretroviral therapy/treatment; AE = adverse event.

Immunologic response

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

Baseline $CD4^+$ T cell counts were lower in the non-randomised cohort compared to the randomised cohort but steadily increased over time across both cohorts. In the non-randomised cohort, mean changes in $CD4^+$ T cell counts from Baseline increased over time by 41, 63.5, and 119 cells/mm^3 at Weeks 24, 48, and 96 respectively. However, it is important to note that the number of subjects continually decreased (for example, dropouts due to death, adverse events (AEs), lack of benefit), so the gains in $CD4^+$ T cell counts largely reflect those with virologic success.[11]

Table 8: Study 2058880 Summary of mean change from Baseline in absolute $CD4^+$ T cell count (cells/mm^3) by visit; observed, intent to treat-exposed population

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

Subgroup analyses were conducted to assess the potential for differences in the treatment effect for various demographic groups. Overall, the treatment effect of fostemsavir 600 mg twice daily compared to placebo appeared consistent across demographic subgroups of age, gender, race, ethnicity, and geographic region, although the sample sizes for some subgroups were small.

Safety

The overall assessment of safety of fostemsavir is informed by early phase clinical studies, the Phase III, conducted in the target heavily treatment experienced (HTE) population, and

[11] Sponsor clarification: 59% of non-randomised cohort participants and 79% of randomised cohort participants were virologically suppressed at the Week 96 timepoint by observed analysis. That indicates that >40% of non-randomised cohort and >20% of randomised cohort participants were not suppressed when the W96 CD4 count was considered

the Phase IIb trial, which was conducted in a treatment-experienced population that retained susceptibility to several ARVs.

Key clinical safety issues identified are:

- hepatobiliary adverse events (AE)
- prolongation of the QT interval
- immune reconstitution inflammatory syndrome
- rash and hypersensitivity reactions
- elevations in serum creatine kinase and reports of myalgia
- neuropsychiatric events
- drug drug interactions, HIV therapies and other drugs.

These aspects are well documented and overall fostemsavir has demonstrated acceptable safety profile in HTE subjects with MDR HIV-1 infection at the dose of 600mg twice daily. Overall, there is no clear pattern of high grade fostemsavir related safety issues, but the causality assessment is complicated by lack of comparator group and confounding from poor health status and concomitant medications.

In the Phase III HTE trial, infections and malignancies were the leading causes of death and events requiring hospitalisation, which is consistent with expectations for this population. Infections and gastrointestinal (GI) events were reported most commonly, but rarely resulted in discontinuation.

No safety concerns emerged in the Phase IIb trial that were not apparent in the Phase III trial. Overall, safety events, particularly high grade events, occurred with much less frequency in the Phase IIb population. Deaths were uncommon and there was no pattern observed among serious adverse events (SAE) or AEs resulting in discontinuation of fostemsavir. Similar to the Phase III trial, the most commonly reported AEs were infections or GI events. As patients in the Phase III study had a more advanced HIV disease at Baseline, (for example, less $CD4^+$ T cells) compared to the Phase IIb study, the observation that patients in the Phase III study reported higher rates of AEs of increased severity was considered expected.

Adverse drug reactions (any Grade) were reported in 38%, 34%, 34% in the randomised cohort and the non-randomised cohort of the Phase III study, and in the Phase IIb study, respectively. For the randomised cohort of the Phase III study, the most commonly reported drug related AEs (any Grade) ≥ 1% were nausea (10%), diarrhoea (4%), headache (4%), dyspepsia (3%), fatigue (2%), insomnia (2%), depression (2%), incident reporting & investigation scheme (2%), blood creatinine increased (2%), abdominal pain (1%), rash (1%) and electrocardiogram QT prolonged (< 1%).

These issues can be managed through the risk management plan (RMP) and the warnings and precautions and adverse reactions sections of the PI.

Risk management plan

Viiv Healthcare Pty Ltd has submitted EU-RMP version 0.1 (data lock point (DLP) 14 August 2018) and Australian specific annex (ASA) version 1.0 (dated June 2020) in support of this application. At second round of evaluation, the sponsor submitted EU-RMP version 1.0 (dated 15 January 2021; DLP 6 September 2019) and ASA version 1.1 (dated March 2021). Lastly, the sponsor submitted ASA version 1.2 (dated April 2021) at third round of evaluation.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 9.[12]

Table 9: Summary of safety concerns and their associated risk monitoring and mitigation strategies.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Virologic failure and resistance ‡	ü	–	ü	–
Important potential risks	Ventricular tachyarrhythmias due to QT prolongation	ü	ü†	ü	–
	Drug interactions (particularly with optimised background therapy) (OBT) ‡	ü	–	ü	–
	Hepatobiliary Adverse Events ‡	ü	–	ü	–
	Musculoskeletal Adverse Events (including myalgia) ‡	ü	–	ü	–
	Neuropsychiatric Adverse Events (including sleep) ‡	ü	–	ü	–
	Uncertainties around dosing at extremes of weight and in the elderly ‡	ü	–	ü	–
Missing information	Use in pregnant and lactating women	ü	ü*	ü	–

[12] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Long term safety data	ü	ü†	–	–

* Antiretroviral Pregnancy Registry

† BRIGHT-E study

‡ AU only

The summary of safety concerns has been further assessed at the second round of evaluation following the sponsor's response to recommendations made by the clinical evaluator, and changes to align with an updated, approved EU-RMP. At the second round of evaluation, the sponsor removed 'Type 1 hypersensitivity' from the summary of safety concerns and renamed 'Ventricular tachyarrhythmias' to 'Ventricular tachyarrhythmias due to QT prolongation'. At third round of evaluation, the sponsor added the safety concerns requested by the clinical evaluator to the ASA. The summary of safety concerns is acceptable.

Routine pharmacovigilance is proposed for all safety concerns, and the pharmacovigilance plan has been updated at second round of evaluation to also include additional pharmacovigilance for all safety concerns. The pharmacovigilance plan will be further reviewed when the sponsor describes how health care professionals will be made aware of the pregnancy registry. At third round of evaluation, the sponsor has referred to the pregnancy registry in the PI. Routine pharmacovigilance only has been proposed for all of the Australian specific safety concerns requested by the clinical evaluator. The pharmacovigilance plan is now acceptable.

Routine risk minimisation is proposed for the important potential risk of 'ventricular tachyarrhythmias' and the missing information 'use in pregnant and lactating women'. Routine risk minimisation measures are not proposed for the important potential risk of 'Type 1 hypersensitivity' and 'long term safety data'. Additional risk minimisation activities are not proposed. The sponsor has provided a Consumer Medicines Information (CMI) in the new format as requested. At third round of evaluation, the CMI is acceptable, pending possible changes to the pregnancy category as recommended by the nonclinical evaluator which will require revision of pregnancy information. The sponsor proposes routine risk minimisation only for the Australian specific safety concerns. The risk minimisation plan is now acceptable.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Rukobia EU-Risk Management Plan (RMP) (version 1.0, dated 15 January 2021, data lock point 6 September 2019), with Australian Specific Annex (version 1.2, dated April 2021), included with submission PM-2020-02898-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As Rukobia is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Rukobia (fostemsavir) is to be included in the Black Triangle Scheme. The PI and CMI for Rukobia must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

The Delegate makes a decision under the Therapeutic Goods Act in relation to quality, safety and efficacy.

Quality

In relation to quality: Approval for registration of the proposed product has been recommended from the quality and nonclinical perspective by the respective evaluators.

Efficacy

In relation to efficacy: The sponsor's popPK model adequately describes temsavir PK of HIV patients enrolled in Phase IIb and Phase III studies. The assessment on the formulations effect is reasonable based on the current data supporting the bioequivalent bridging between the two formulations and the dissolution bridging between the two formulations. Overall, no exposure dependent signal was identified graphically.

The BRIGHTE trial consisted of a short term, placebo controlled, functional monotherapy phase over 8 days in the randomised cohort and an open label phase for at least 96 weeks in both cohorts. The design of the study can be considered adequate to show an early, short term effect of fostemsavir functional monotherapy on plasma HIV RNA concentrations, but the study was not designed to determine a long term effect of fostemsavir over OBT alone. A comparator arm with patients receiving active OBT without fostemsavir was lacking and the variety of OBTs in both cohorts rendered it difficult to estimate the contribution of fostemsavir on the overall efficacy (viral load and $CD4^+$ T cell count). It is understood that components of the OBT affect the rates of virologic suppression and that the treatment effect cannot be attributed to fostemsavir exclusively. This does not appear to affect the overall interpretation of the efficacy of fostemsavir, as the need for multiple drugs for effective treatment of HIV-1 infection is well established. Virologic suppression was achieved and maintained with fostemsavir plus OBT through Week 96 in a majority of subjects previously unable to achieve virologic suppression. From a clinical perspective, this observation suggests the contribution of fostemsavir, but the trial was not designed to demonstrate the contribution of fostemsavir as an individual drug to the OBT after Day 8.

A number of subjects did not meet important eligibility criteria for the BRIGHTE trial including evidence of being heavily treatment experienced or failure on their current ARV. Inclusion of these subjects could have affected the assessment of efficacy of fostemsavir. The proportion of subjects who did not meet eligibility criteria was balanced between the fostemsavir and placebo groups, and sensitivity analyses demonstrated that excluding subjects who did not meet criteria did not substantially change the efficacy outcome. Therefore, it can be concluded that inclusion of subjects who were not truly failing their baseline ARV regimen in the BRIGHTE trial did not affect the overall efficacy assessment of fostemsavir for treatment of MDR HIV-1 infection.

The BRIGHTE trial is currently ongoing, and three interim analyses were conducted so far. The Week 96 study report is inclusive of all data from previous interim analyses and supersedes the prior reports. Interim analyses were based on snapshots of the database which were subject to subsequent change (that is datasets were not locked for analyses) and consequently, the results slightly differed between the respective reports (Week 24, Week 48 and Week 96 report). The analysis may be impacted by results and introduce bias. However, this issue did not affect the validity of the primary endpoint results, as laboratory values upon which the primary and secondary endpoints were based were not changed and the primary endpoint results were identical regardless of the snapshot (Week 24, 48 or 96) used and the results for virologic response were not relevantly impacted.

There were some limitations to the data regarding the efficacy of fostemsavir and correlation between baseline factors and rate of virologic response. In particular, virologic response to fostemsavir could not be reliably predicted from any pre-treatment viral attributes (gp120 substitutions; temsavir IC_{50} values). However, attempting to restrict the use according to pre-treatment substitutions or IC_{50} would lead to unnecessarily excluding patients with MDR HIV-1 that might derive some benefit from treatment.

A more pronounced decrease in $\log_{10}$ plasma HIV-1 RNA was observed for fostemsavir in the monotherapy Phase IIa and IIb trials, but these studies were conducted in different patient populations (ART-naïve patients infected with HIV-1 subtype B or generally treatment-experienced patients with $IC_{50} < 0.1$ μM, respectively), with different regimens and using a different fostemsavir extended released formulation.

Safety

In relation to safety: The safety assessment was mainly based on the 96 weeks analysis of the ongoing Phase III study (cutoff date:14 August 2018) and end of study analysis of the completed Phase IIb study. Overall, Rukobia has demonstrated acceptable safety profile in HTE subjects with MDR HIV-1 infection at the dose of 600mg twice daily. The nature and frequency of significant safety events (deaths, SAEs, and discontinuations due to AEs) and the rate of virologic failure reported in the BRIGHTE trial reflect the targeted patient population: heavily treatment-experienced patients with advanced HIV/AIDS who are failing current ART and have very few remaining treatment options.

The identified safety concerns will be managed through the RMP and the 'Warnings and Precautions' and 'Adverse reactions' sections of the PI. Routine pharmacovigilance will be utilised to further characterise the safety of fostemsavir post-authorisation.

Proposed action

Despite the availability of different classes of ARV agents in 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.

The adjusted mean difference for change in HIV-1 RNA $\log_{10}$ copies/mL from Day 1 to Day 8 (fostemsavir minus placebo) was -0.63 (95% CI, -0.81, -0.44), demonstrating

superiority of fostemsavir compared to placebo. Reductions in HIV-1 RNA levels are predictive of meaningful clinical benefit, and fostemsavir functional monotherapy was superior to placebo for reducing HIV-1 RNA over 8 days. Virologic suppression was achieved and maintained with fostemsavir plus OBT through Week 96 in a majority of subjects previously unable to achieve virologic suppression. The lack of a control group after Day 8 in the BRIGHTE trial limits the ability to precisely quantify the contribution of fostemsavir to long-term virologic suppression. However, the contribution of fostemsavir is reflected by the relatively high rate of virologic suppression achieved with fostemsavir plus OBT through Week 96 in a population previously unable to achieve virologic suppression.

Despite some limitations and uncertainties of the safety data as discussed above, no serious safety risks emerged, and a favourable safety profile has been established. Safety findings can be adequately addressed in labelling and by routine pharmacovigilance.

Based on the review of data on safety and efficacy, the Delegate considers that the benefit-risk balance of Rukobia is favourable in the following indication:

> *Rukobia is indicated in combination with other antiretroviral agents for the treatment of heavily treatment-experienced adults with multidrug-resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance or safety considerations.*

Advisory Committee considerations[13]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Is the inability to estimate the contribution of fostemsavir on the overall efficacy, due to lack of a comparator arm, acceptable?

The ACM stated that the study was designed to assess fostemsavir-based strategies rather than fostemsavir monotherapy. They acknowledged that it is unlikely that fostemsavir would be used as a monotherapy, noting that the objective of HIV ARV therapy is to prevent development of drug resistance by preventing replication, using active drugs from multiple drug categories.

Additionally, the ACM noted that these patients have exhausted many treatment options. It would be difficult to design a suitable randomised controlled trial, and a prolonged study of fostemsavir monotherapy and a comparator could not be justified for this population.

Overall, the ACM advised that the lack of a comparator arm within the pivotal study is reasonable in this instance and agreed that the fostemsavir-containing regimen demonstrated sustained efficacy over the study period.

[13] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

2. ***Is the lack of being able to identify the patient population that would benefit most from an fostemsavir-containing regimen acceptable? (due to lack of data regarding the efficacy of fostemsavir and correlation between baseline factors and rate of virologic response)***

The ACM discussed the broad range of optimal background treatment choices utilised within Study 2058880 and flagged that the study was conducted in 23 countries.

Based on this information, the ACM agreed on the generalisability of findings and were of the view that it is reasonable to use an fostemsavir-containing regimen within various patient populations.

3. ***The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.***

The ACM noted that page 3 of the Consumer Medicines Information (CMI) states '… medicines may decrease the effectiveness of Rubokia' and lists examples. It goes on to state 'Don't take Rubokia with these medicines'. The ACM were of the view that it would be better to encourage patients to discuss these matters with their ARV prescriber and suggested the CMI wording be rephrased to encourage treatment option discussion.

The ACM also noted that in Australia, patients with MDR HIV-1 are a small subset of total HIV patients and are generally being managed within tertiary care centres with access to specialist multi-disciplinary teams and genetic testing.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Rukobia is indicated in combination with other antiretroviral agents for the treatment of heavily treatment-experienced adults with multidrug-resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance or safety considerations.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Rukobia (fostemsavir trometamol) 600 mg, extended release tablet, bottle, indicated for:

> *Rukobia is indicated in combination with other antiretroviral agents for the treatment of heavily treatment-experienced adults with multidrug-resistant human immunodeficiency virus-1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance or safety considerations (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).*

Specific conditions of registration applying to these goods

- Rukobia (fostemsavir) is to be included in the Black Triangle Scheme. The PI and CMI for Rukobia must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Rukobia EU- RMP (version 1.0, dated 15 January 2021, data lock point 6 September 2019), with ASA (version 1.2, dated April 2021), included with submission PM-2020-02898-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Rukobia approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au