Date: 12 July 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Rukobia

International non-proprietary name: fostemsavir
Pharmaceutical form: prolonged-release tablet
Dosage strength: 600 mg
Route(s) of administration: oral
Marketing Authorisation Holder: ViiV Healthcare GmbH
Marketing Authorisation No.: 67854
Decision and Decision date: approved on 28 September 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ART	Antiretroviral therapy
ARV	Antiretroviral
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BID	Twice daily
CD4+	Helper T cell (helper T lymphocyte)
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DDI	Drug-drug interaction
DSUR	Drug safety update report
DTG	Dolutegravir
EAP	Early access programme
ECG	Electrocardiogram
ERA	Environmental Risk Assessment
ER/PR	Extended release / prolonged release
FTR	Fostemsavir
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HI	Hepatic impairment
HIV	Human immunodeficiency virus
HPDE	High-density polyethylene
HTE	Heavily treatment-experienced
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
INSTI	Integrase strand transfer inhibitor
IR	Immediate release
IRIS	Immune reconstitution inflammatory syndrome
ITT-E	Intent-to-treat exposed
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MDR	Multi-drug resistant
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NRTI	Nucleoside reverse transcriptase inhibitor
OBT	Optimised background therapy
PD	Pharmacodynamics
PDVF	Protocol-defined virologic failure
PI	Protease Inhibitor
PIP	Paediatric Investigation Plan (EMA)

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PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US FDA)
QD	Once daily
QTc	Corrected QT
QTcF	Corrected QT using Fridericia's formula
RAL	Raltegravir
RI	Renal impairment
RNA	Ribonucleic acid
RMP	Risk Management Plan
RTV	Ritonavir
SAE	Serious adverse event
SMQ	Standardised MedDRA Queries
SOC	System organ class
SwissPAR	Swiss Public Assessment Report
TdP	Torsade de point
TMR	Temsavir
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance fostemsavir, (fostemsavir tromethamine) of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Rukobia, in combination with other antiretrovirals, is indicated for the treatment of intensively pretreated adults with multidrug resistant 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 *Properties / Effects*).

2.2.2 Approved Indication

Rukobia is indicated in combination with optimised background antiretroviral therapy against human immunodeficiency virus type 1 (HIV-1) infection for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced adults whose current antiviral regimen failed due to resistance and/or cannot be continued due to intolerance or safety reasons (*see Properties/Effects/Clinical Efficacy*).

2.2.3 Requested Dosage

Rukobia should be prescribed by physicians experienced in the management of HIV infection.
Posology
Adults
The recommended dose of Rukobia is one tablet (600 mg) twice daily with or without food intake.
Special dosage recommendations
Hepatic impairment
No dosage adjustment is required in patients with hepatic impairment (see *Kinetics in specific patient groups*).
Renal impairment
No dosage adjustment of Rukobia is required for patients with renal impairment or those on haemodialysis (see *Kinetics in specific patient groups*).
Elderly
There are limited data available on the use of Rukobia in patients aged 65 years and older. However, there is no evidence that elderly patients require a different dose than younger adult patients (see *Kinetics in specific patient groups*).
Paediatric population
Due to a lack of data on safety and efficacy, the use of Rukobia is not recommended in children aged under 18 years.
Method of administration
Rukobia can be taken at any time. The prolonged-release tablet should be swallowed whole, and not be chewed, crushed or split.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	3 February 2020
Formal control completed	20 February 2020
List of Questions (LoQ)	1 July 2020
Answers to LoQ	28 September 2020
Predecision	29 December 2020
Answers to Predecision	1 March 2021
Labelling corrections	27 May 2021
Answers to Labelling corrections:	25 June 2021
Final Decision	28 September 2021
Decision	approval

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3 Medical Context

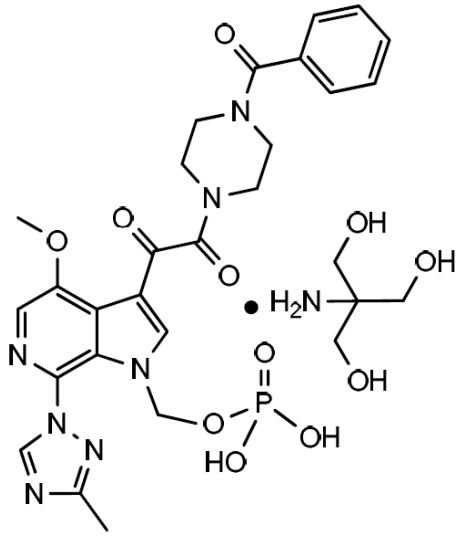
Management of HIV infection consists of a combination of antiretroviral drugs (ARVs), with the goal of suppressing and then maintaining the suppression of plasma HIV-RNA levels below the level of detection, restoring the immune system, reducing HIV-associated morbidity and preventing transmission.
Heavily treatment-experienced (HTE) patients infected with multi-drug resistant (MDR) HIV represent a small but important subset of patients living with HIV. The prevalence of patients with multi-drug resistant virus has decreased substantially in developed countries, in part due to increasing use of boosted protease inhibitors (PIs) and the overall enhanced potency of ARV regimens.
Patients with MDR HIV who cannot achieve complete virological suppression with antiretroviral therapy (ART) are at high risk for AIDS-related morbidity and mortality.
HTE patients may be on highly individualised combinations of ARV agents, and for some patients, virological suppression may not be possible. Nevertheless, even if suppression is not achievable, additional treatment objectives exist, including partial reduction of the viral load, preserving immunologic function, preventing clinical progression of disease and minimising additional resistance.

4 Quality Aspects

4.1 Drug Substance

Name:	Fostemsavir tromethamine
INN:	Fostemsavir (free acid)
Chemical name:	(3-((4-Benzoyl-1-piperazinyl)(oxo)acetyl)-4-methoxy- 7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3- c]pyridin-1-yl)methyl dihydrogen phosphate, 2-amino- 2-(hydroxymethyl)-1,3-propanediol (1:1)
Molecular formula:	$C_{25}H_{26}N_7O_8P \bullet C_4H_{11}NO_3$
Molecular mass:	704.62 (tromethamine salt) 583.49 (free acid)

Molecular structure:



Physico-chemical properties: Fostemsavir tromethamine is a white to almost-white powder and is freely soluble in water and aqueous buffers.**Synthesis:** The drug substance is manufactured by a multiple step chemical synthesis with final isolation by crystallisation.**Specification**: The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay and impurities.
Stability: Appropriate stability data have been presented and justify the established re-test period.

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4.2 Drug Product

Description and composition: Rukobia ER/PR Tablets, 600 mg, contain 725 mg of fostemsavir tromethamine, which is equivalent to 600 mg of fostemsavir free acid. Rukobia Tablets, 600 mg, are beige, biconvex, oval-shaped, film-coated tablets (approximately 10.2 mm x 19.0 mm) with “SV 1V7” debossed on one side and plain on the other side.
The excipients are: hydroxypropyl cellulose, hypromellose, silica and magnesium stearate.

Pharmaceutical development: The drug product is developed as a prolonged-release tablet for oral administration with a film-coating to protect from light and moisture.

Manufacture: The manufacturing process is described with a sufficient level of detail in order to achieve consistent quality of the tablets. Appropriate in-process controls are applied.

Specification: The finished product release specifications include appropriate tests for appearance, identification (HPLC, UV), dissolution, uniformity of mass of delivered dose, assay and related substances (HPLC), and microbiological purity. The test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container-closure system: The tablets are packed in an opaque, white, high-density polyethylene (HDPE) bottle with a polypropylene child-resistant closure that includes a polyethylene faced induction heat-seal liner.

Stability: Appropriate stability data including in-use stability are presented for industrial scale batches. Based on these data, a shelf life and was established for the Rukobia ER/PR Tablets, 600 mg. The storage recommendation is “Do not store above 30°C”.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

The applicant submitted a comprehensive nonclinical study package for Rukobia (fostemsavir, FTR). Pivotal toxicology studies were conducted in compliance with GLP.

Pharmacology

FTR is a prodrug that is converted into the active ingredient temsavir (TMR) by alkaline phosphatase (ALP) in the gastrointestinal lumen. TMR was shown to directly bind to the envelope glycoprotein gp160 on the surface of human immunodeficiency virus (HIV). TMR was shown to prevent the initial interaction between the virus and CD4+ cell surface receptors (IC_{50} 14 nM), and to inhibit virus entry into and infection of cells. TMR was active against the majority of the subtype B laboratory HIV strains and subtype B, C and D clinical isolates.

Studies on secondary pharmacodynamics with FTR and TMR did not reveal potential for relevant off-target interactions. In safety pharmacology studies, TMR inhibited the hERG channel by 52% at a concentration of 30 µM. *In vivo*, FTR at ≥ 40 mg/kg/day led to decreased blood pressure and QT prolongation in dogs. This is in line with clinical observations and is adequately addressed in the information for healthcare professionals. FTR treatment showed no effects on respiratory and CNS function in the long-term safety studies in rats and dogs.

Pharmacokinetics

FTR was hydrolysed by intestinal ALP to TMR in all species (rat, dog, cynomolgus monkey, chimpanzee and human). FTR rapidly cleared from circulation ($t_{1/2}$ < 1.5 min), and TMR formed within 2-5 min in all tested species (t_{max} ≤ 1h). TMR bioavailability after oral administration was 82%, 89%, 64% and 16% in rats, dogs, cynomolgus monkeys and chimpanzees, respectively. There was no accumulation upon repeated oral dosing. *In vitro* plasma protein binding was 70.4%, 84.7%, 87.7%, 92.2%, 95.9% and 98.6% in dogs, cynomolgus monkeys, mice, humans, rats and rabbits, respectively.
Following oral administration, [^{14}C]-FTR-related radioactivity was widely and quickly distributed in rats (t_{max} of 0.5 h), with the highest concentrations in the in alimentary canal contents, bile and urine. No specific uptake in red blood cells was seen. [^{14}C]-FTR-related radioactivity was detected for the longest period in the adrenal glands and kidneys in male and female rats, and in the liver of male rats. The compound displayed a specific association with melanin-containing tissues. In rats, TMR crossed the placental barrier and was transferred into milk.
TMR was stable in S9 liver fraction, liver microsomes and in rat, dog, monkey and human hepatocytes. M4 and M28 were the major circulating metabolites in humans, i.e. greater than 10% of total drug-related exposure at steady state. The enzymes responsible for their formation were not identified. All human plasma metabolites were found in animals at similar or higher levels.
TMR was a moderate *in vitro* inhibitor of human hepatic uptake transporter OCT1 and human renal uptake transporters MATE1 and MATE2-K, and was only a weak inhibitor of P-gp. The major TMR metabolite, M28, was an efflux transporter substrate in Caco-2 cells and had no effect on P-gp. It increased efflux ratio in the breast cancer resistance protein (BCRP) Efflux Transporter Substrate activity assay. It also was an inhibitor of OATP1B1, OATP1B3, BSEP, OAT3, hBCRP and MDR2 *in vitro* (more than 50% inhibition at C_{max} (50 µM)). The second major metabolite of TMR (M4) was a BCRP efflux transporter substrate.
Radioactivity was eliminated primarily in faeces in mice, rats and dogs, but both urinary and biliary elimination pathways were significant in mice, rats, dogs and humans.

Toxicity

Rats and dogs were chosen for the definitive repeated-dose toxicology studies up to 9 months based on the pharmacokinetic profile. Mice and rabbits were used as second species in carcinogenicity and developmental toxicity studies. The oral administration route and dosing frequency were consistent with the proposed clinical use. The duration of the repeated-dose studies supports the intended chronic use in humans.

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In single oral dose studies with FTR, mortality was recorded in mice after oral administration of 1000 mg/kg and in rats at 2000 mg/kg. Twice daily (BID) doses of more than 200 mg/kg led to mortality in dogs. Emesis was a common side effect in dogs.
The liver, kidneys and adrenal glands were the primary target organs. All histopathological FTR-related changes except for those in the liver disappeared partially or fully after the recovery period. In general, males were more sensitive than females. At the NOAELs for hepatic, renal and adrenal toxicity, safety margins of 2.1-, 25- and 5.9-fold the clinical exposure at the maximum recommended human dose (MRHD) were calculated.

No FTR-related adverse effects were observed at doses up to 300 mg/kg/day in rats in the six-month oral toxicity study. In a six-month study in CByB6F1 mice, FTR was tolerated up to 200 mg/kg/day in males and 300 mg/kg/day in females (15- and 32-fold clinical exposure, respectively).
FTR, TMR and the major metabolites were not genotoxic or clastogenic. FTR was not carcinogenic in a 26-week study in Tg *ras*H2 mice (exposure up to 36-fold clinical exposure) or in a two-year study in rats with 3.6-fold human exposure levels. FTR-related mortality occurred in males treated at ≥ 30 mg/kg/day, leading to dose reduction in all groups from Week 58 and termination of the high-dose group after 69 weeks. There were no neoplastic or non-neoplastic findings attributable to treatment with FTR in either male or females. The carcinogenicity study in rats was therefore acceptable.
In rats, adverse effects of FTR at ≥ 100 mg/kg/day on male reproductive organs included decreased prostate weight, small epididymides, correlating with microscopic findings of hypospermia or aspermia, and small testes, correlating with microscopic findings of moderate to marked seminiferous tubule atrophy, minimal to marked bilateral atrophy of the seminiferous tubule epithelium and minimal increases in cell debris in the epididymal ducts. Sperm analysis revealed reduced density and motility as well as increased abnormalities in sperm morphology. Mating and fertility of males were comparable to controls. The reproductive NOAEL in male rats was 10 mg/kg/day (6.4-fold the clinical exposure).
In an embryo-foetal development study in rats, when FTR was given to pregnant rats from Gestation Days (GD) 6 to 15 at doses ≤ 600 mg/kg/day (130-fold the clinical exposure), no adverse maternal or embryo-foetal findings were observed. FTR administration to pregnant rabbits from GD 7 to GD 19 was associated with maternal toxicity at doses ≥ 250 mg/kg/day and developmental toxicity at 100 mg/kg/day, including slightly increased post-implantation loss (8.7% compared to 2.4% in the controls). Plasma exposure at the NOAEL for maternal toxicity (25 mg/kg/day) and developmental toxicity (50 mg/kg/day) was 11- and 21-fold the clinical exposure, respectively. The issue of developmental toxicity is accurately covered in the information for healthcare professionals.
In a pre- and postnatal development study in rats, FTR administration to dams at 300 mg/kg/day from GD 6 until lactation day 20 was associated with decreased pup survival during the lactation period. Pup mortality could be related to lactational exposure to TMR. FTR had no effect on development or reproductive function of the F1 generation. Sexual maturation, motor activity, auditory startle habituation and water maze behaviour were unchanged in the F1 generation. Plasma exposure of the maternal animals at the NOAEL for pup survival (50 mg/kg/day) was 23-fold the clinical exposure.

Oral administration of FTR up to 100 mg/kg/day for 10 weeks to juvenile rats from postnatal days 21 to 90 was well tolerated. No overt differences to adult rats were detected, and changes in the blood chemistry parameters fully resolved by the end of the recovery period. The conversion of FTR to TMR was slower in younger rats, and the mean TMR AUC value of juvenile rats was similar to or 2-fold that achieved at the NOAELs in adult rats. These data suggest no increased sensitivity of juvenile rats to FTR.

There are no concerns with regard to excipients and impurities.
The environmental studies did not identify a risk at anticipated exposures.

Conclusion:
Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Rukobia with the new active substance fostemsavir in the proposed indication. The pharmacological properties as well as the pharmacokinetic and toxicity profiles of fostemsavir were adequately

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characterised. Low safety margins for liver and developmental toxicity are addressed adequately in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Temsavir (TMR) is a first-in-class, HIV-1 attachment inhibitor. Due to its low solubility, following oral administration only low plasma TMR concentrations were achieved in humans. Therefore, fostemsavir (FTR) was developed as a highly water-soluble prodrug of TMR.

Biopharmaceutical development
Various formulations of FTR were developed throughout the clinical development programme. The first was an immediate release (IR) oral capsule formulation, which was used in the very early Phase 1 studies. Since plasma TMR concentrations following administration of the immediate release capsules was lower than clinically desired, further formulation development focused on extended release (ER) formulations. Several ER tablet formulations were used throughout Phase 1, 2 and 3 studies. Bridging between these formulations was acceptable. The formulation used in the pivotal Phase 3 study is also the to-be-marketed formulation.

ADME
The PK of TMR was characterised following administration of either TMR itself or, in the majority of studies, following administration of the prodrug FTR to healthy subjects and HIV-infected patients.

Following IV administration, TMR plasma concentrations decreased in a biphasic manner, with a half-life of approx. 1.5h in the early phase and approx. 13h in the secondary phase of decline. The same biphasic decline was observed following oral administration of FTR at doses ≥ 140 mg, administered as FTR IR capsules. The change to an ER tablet formulation, however, resulted in a flatter concentration-time profile compared to the IR capsules, with a lower C_{max} and AUC, but higher C_{12} and C_{24} values.

Absorption
The absolute bioavailability of TMR following administration of the prodrug FTR, was 26.9%.
Maximum TMR plasma concentrations were reached at a median time of 2-3h after fasted administration of ER tablets. Following repeated administration of the requested dose of 600 mg ER tablets BID, the steady state was reached by Day 2-3, and TMR accumulated mildly with accumulation indices ranging from 1.3-1.6. TMR PK showed no time-dependency.
TMR C_{max} and AUC increased in a slightly more than dose-proportional manner following a single dose of 20-1000 mg of IR capsules.

Table 9 of the information for healthcare professionals presents the exposure in HIV-infected subjects following the requested dose of 600 mg ER tablets BID. As illustrated in that table, the between-subjects variability (%CV) in TMR C_{max}, AUC_{tau} and C_{tau} was moderate to high.

Food effect
Administration of a high-fat meal with FTR ER tablets delayed TMR t_{max} by 4.5 hours but had no effect on TMR C_{max}, while TMR AUC_{0-t} and AUC_{inf} increased to 1.8-fold. Mean C_{12} was increased to 5.7-fold. In the pivotal Phase 3 study, FTR ER tablets were administered without regard to meals. FTR ER tablets can be administered irrespective of food intake.

Distribution
TMR plasma protein binding was approx. 82-88% (primarily to albumin). Protein binding was decreased in subjects with impaired renal or hepatic function. TMR or its metabolites showed minimal distribution to red blood cells. The volume of distribution of TMR was 29.5 L.

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Elimination
TMR is cleared by extensive metabolism (74% of the administered dose), while urinary excretion of TMR is low (2% of the administered dose). Part of a radioactive FTR dose was also eliminated by biliary secretion (5% of a radioactive dose within 3-8 hours postdose). However, the exact total extent of biliary secretion is unclear.

Metabolism
The primary metabolic pathway for TMR is hydrolysis (by an unidentified esterase), which leads to formation of BMS-646915 (M4) and its metabolites (M1, M2, M3), accounting for elimination of 36.1% of the administered dose.

The secondary pathway for TMR elimination is CYP3A4-dependent metabolism, which results in formation of the metabolites BMS-930644 (M28), M10, M13, M14, M16, M22, M26 M27, and accounted for 21.2% of the administered dose (27.3% of the recovered dose)

Other metabolites (M7, M18, M20, M23, M24, M25) presumably generated by CYPs other than CYP3A4 accounted for 7.2% of the administered dose.
Less than 1% of the administered dose was recovered as glucuronide metabolites (M8 and M21) in bile.

Following oral administration of a single radioactive dose of 300 mg FTR with or without ritonavir (RTV), the prodrug FTR was detectable at low levels in plasma (1.6 - 6.1% within 8 hours postdose). TMR was the main species in plasma early postdose (> 62%). Without concomitant administration of RTV, BMS-930644 (M28) was the main metabolite in plasma at 8h postdose and later. However, with concomitant RTV, CYP3A4-dependent formation of M28 was reduced and instead TMR, M2, M4 and M23/24 were the abundant radioactive species in plasma at 8h postdose and later.

Excretion
In total, approx. 50% of the administered radioactive dose was recovered in urine, independent of concomitant intake of RTV. Only approx. 2% of the dose was excreted as TMR in urine. Metabolite M4 was the most abundant radioactive species in urine, accounting for 18.9% of the administered dose (25.2% when given with RTV). M1 was the second most abundant species in urine, accounting for 6.5% of the administered dose (10.6% when administered with RTV). 13 minor metabolites were also identified in urine, each of which accounted for < 3.2% of the dose, when administered without RTV.

Overall, approx. 30% of the radioactive dose was recovered in faeces, independent of concomitant intake of RTV. The prodrug FTR was not detected in faeces, and faecal excretion of TMR was also low (1.1% of the dose; 2.2% when given with RTV). There was no dominant radioactive species in faeces. M4 was the most abundant radioactive metabolite in faeces, accounting for 5.9% of the administered dose (8.2% when given with RTV). 12 other metabolites were identified in faeces, each of which accounted for < 5% of the administered dose.

The total CL of TMR was 17.9 L/h (study 206218). The mean terminal half-life following administration of 600 mg ER tablets varied between approx. 8-13h across studies.

Special Populations / Intrinsic Factors

Renal impairment
Total and unbound TMR plasma C_{max} and AUC values were mildly to moderately increased in subjects with renal impairment (RI) compared to subjects with normal renal function. In addition, the unbound fraction of TMR varied according to renal function and was highest for subjects with severe RI (18.6%) versus normal renal function (11.8%), mild RI (12.3%), moderate RI (13.2%) and ESRD (15.9%).

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Regression model-predicted average increases in TMR unbound AUC were 1.66-fold, 1.12-fold, 1.15-fold and 1.32-fold for the mild, moderate and severe RI groups and subjects with ESRD under dialysis, respectively. The increases in unbound C_{max} were less pronounced.
Considering that only a low percentage of TMR is cleared by renal secretion, the mild impact of renal impairment on TMR exposure is plausible and likely caused by indirect effects of uremic compounds on plasma protein binding and metabolic clearance. No dose adjustment is recommended for subjects with impaired renal function.

Hepatic impairment
Total and unbound plasma TMR C_{max} and AUC values were mildly to moderately increased in subjects with hepatic impairment (HI) compared to subjects with normal hepatic function. The unbound fraction of TMR was increased in subjects with severe HI (22.8%) but comparable in subjects with normal hepatic function (18.2%) and mild (19.9%) and moderate HI (17.5%).
Unbound TMR AUC_{last} values increased to 1.3-fold in subjects with mild HI, to 1.6-fold in subjects with moderate HI and to 2.2-fold in subjects with severe HI. Unbound C_{max} increased to a similar extent. No dose adjustment is recommended for subjects with impaired hepatic function.

The PK of TMR was similar in HIV-infected patients and healthy subjects, based on the Phase 3 PopPK analysis. Further, no significant effects of age, gender, race, creatinine clearance, ALT and AST were identified in the Phase 3 PopPK analysis.
Body weight was included as a covariate on the distribution volume and clearance parameters in the PopPK model. However, the effects on TMR exposure were small and do not require body weight-based dosing.

Interactions
TMR is a victim of clinically relevant drug-drug interactions (DDI), which resulted in contraindication for concomitant use with strong inducers. TMR and its metabolites also caused DDI effects on other drugs, which warranted dose adjustments/limitations for concomitant use with e.g. certain statins and oral contraceptives.

Further details on the interaction potential of TMR and its metabolites and recommendations with regard to concomitant medications are addressed in the attached information for healthcare professionals; see section 8.1 of this report.

Pharmacodynamics
Mechanism of Action and Primary Pharmacology

FTR is a methyl-phosphate prodrug that is hydrolysed to the active moiety temsavir (TMR), which binds directly to the gp120 envelope glycoprotein on the surface of HIV and prevents initial interaction between HIV and CD4+ cell-surface receptors, thereby preventing attachment.
The antiviral activity of TMR (administered as FTR) has been demonstrated as monotherapy in a Phase 2 study and as functional monotherapy in the pivotal Phase 3 study.
Details of the antiviral activity of TMR are addressed in the attached information for healthcare professionals (see section *"Properties/Effects - Pharmacodynamics").*

Secondary Pharmacology (Safety)
The results of a thorough QT study indicated that TMR has potential to cause clinically relevant prolongations of the QT interval at a supratherapeutic dose of 2400 mg FTR. The maximum prolongation of ΔΔQTcF of 11.18 msec (90% CI of 9.035 – 13.299) was observed 5h postdose.
At a dose of 1200 mg FTR QD, which corresponds to the requested daily therapeutic dose (600 mg BID), no clinically meaningful effect on the QTc interval was observed (the upper bounds of the two-sided 90% CIs for ΔΔQTcF did not exceed 10 msec).

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6.2 Dose Finding and Dose Recommendation

The dose applied for and evaluated in the Phase 3 study (in combination with failing ARV, followed by in combination with optimised background therapy [OBT]) was FTR 600 mg BID in combination with other ARVs.

This dose was based on an integrated approach, evaluating antiviral response, efficacy and safety/tolerability. This included data from the Phase 2a POC monotherapy study 206267 (conducted predominately in treatment-naïve adults), the Phase 2b study 205889 (Monotherapy substudy and Week 48 data from the full study in generally treatment-experienced adults), as well as the safety risk assessment from the Thorough QTc study 206275.

Based on a model-based simulation, the FTR 600 mg BID dose had the highest probability of resulting in 71% of subjects achieving >1 log decline and 100% of subjects achieving a >0.5 log decline in HIV-1 viral load on Day 8 following FTR as monotherapy.
To minimise the QT prolongation risk, results of the thorough QTc study 206275 were also analysed and the potentially frequent co-administration of RTV was taken into account.

6.3 Efficacy

A single pivotal Phase 3 study pertinent to the requested indication and dose was submitted.
Study 205888 was an ongoing Phase 3 multi-arm, randomised, placebo-controlled, double-blind clinical trial conducted in MDR HIV-1 infected HTE patients. It was a multicentre study at 108 sites in 22 countries around the world, with most sites in Europe and North and South America.
The study was still ongoing and the review was based on the submitted data with Week 96 results.

The study was conducted in two cohorts. The randomised cohort included HTE HIV-1 infected adults with one but no more than two fully active ARVs to combine with FTR. The randomised cohort had two arms in the blinded “Phase 1” part of the study. Eligible subjects were randomised 3:1 to treatment with FTR or placebo added to their open label failing ARV regimen. The primary objective was to demonstrate the superiority of the FTR treatment as assessed by the adjusted mean change from baseline HIV-1 RNA at Day 8 compared to the placebo group.
At the end of this functional monotherapy at Day 8, the primary endpoint was assessed. The study then progressed to the open-label “Phase 2” part, in which all subjects received 600 mg FTR BID with OBT. A non-randomised cohort, which included subjects who had no fully active, approved ARVs at baseline, was added as a third arm in the “Phase 2” part.
Notably, the population of the non-randomised cohort was not identical with the population of the proposed indication. The aim of the non-randomised cohort was to offer an investigational therapy option for patients with no available treatment options and to further assess the safety profile of FTR. Formal hypothesis testing was not performed in this cohort; however, efficacy results can be considered supportive. Subjects in the non-randomised cohort also received open-label 600 mg FTR BID in combination with OBT.

The design of a short-duration, placebo-controlled functional monotherapy phase followed by a single-arm assessment on durability of effect for ≥24-96 weeks is acceptable for HTE patients with few/no alternative approved therapies and consistent with the FDA guidance.

The study included adults over 18 years of age who were ARV-experienced, with documented historical or baseline resistance, intolerability and/or contraindications to ARVs in at least four of the six classes, and were failing their current ARV regimen with a confirmed plasma HIV-1 RNA ≥400 c/mL.
The study excluded patients who had HIV-2 infection, chronic untreated HBV infection, ALT or AST>7 xULN, ALP> 5xULN, decompensated cirrhosis, a history of congestive heart failure or congenital prolonged QT.
The virological response of the FTR-based regimens was assessed in the open-label “Phase 2” part of the study by the Snapshot algorithm at Weeks 24, 48 and 96.

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A total of 272 patients were included in the randomised cohort, with 69 in the placebo and 203 in the FTR group. 26% of the randomised cohort were women, with more women in the FTR group compared to the placebo group (30% vs 17%).
More subjects over 50 years of age were included in the FTR arm compared to the placebo arm (43% vs 33%). Baseline characteristics, including HIV-1 RNA load and CD4+ count, were balanced between the FTR and placebo groups. The enrolled population were generally similar across the cohorts as regards ethnicity and race.
In the non-randomised cohort, 99 patients were enrolled, 10% of whom were women. The baseline characteristics of the non-randomised subjects were consistent with an MDR HTE population with advanced disease. They were slightly older compared to the subjects in the randomised cohort (mean age 48.1 years vs 44.7) and more subjects had CD4+ <20 (40% vs 26%) and lower mean CD4+ count (99.4 vs 152) compared to the randomised cohort. 81% of subjects had been treated for more than 15 years (vs 67% in the randomised cohort), and 60% had a treatment history of more than 20 years.
85% of subjects in the randomised and 90% in the non-randomised cohort had a history of AIDS.
A tabulated version presenting the main demographic and baseline characteristics can be found in the approved information for healthcare professionals (Table 6.).

Most of the patients had subtype B HIV-1 infection, almost exclusively in the non-randomised cohort and 80% in the randomised FTR group, while 7% had the F1, 5% the F1B, 3% the C and 0.5% the AE subtype.
Most of the enrolled patients were hepatitis B and C negative at entry, 4% of subjects were hepatitis B positive and 4% were hepatitis C positive. Only moderately hepatically impaired patients were allowed to enter the study.
Almost all subjects took concomitant medications other than the ARV medications.
The most commonly used were trimethoprim/sulfametoxazole (46% in the randomised, 62% in the non-randomised cohort), azithromoycin, fluconazole, paracetamol, ibuprofen and aciclovir.
83% of subjects in the randomised cohort had had more than five prior ARV treatments, including the current failing regimen. In the non-randomised cohort 91% of patients had had more than five ARV treatments.
The placebo and FTR treatment groups were in general similar as regards prior ARV treatment, with the exception of tenefovir alafenamide, which was administered to 10% of subjects in the FTR group vs 3% in the placebo group.
The prior ARV treatment also reflects the observed baseline characteristics of the non-randomised cohort in comparison to the randomised cohort.

Subjects in the non-randomised cohort were pre-treated with dolutegravir, emtricitabine, darunavir, tipranavir, etravirine, entry inhibitors, CCR5 antagonists and other investigational ARTs at a higher rate compared to the randomised cohort.
81% of the subjects were on NRTI (in most cases, tenofovir, 59%), 66% had PI (mostly darunavir, 45%) and 42% of patients were on INSTI (26% raltegravir) in the failing regimen in the FTR group.
Subjects in the placebo group had a failing regimen that contained NRTI in 81% of cases, similarly to the FTR group (49% tenofovir and 51% lamivudine), PI in 70% of cases (mostly darunavir 51%) and INSTI in 48% (RAL 39%).

The primary endpoint was assessed in the randomised cohort by the adjusted mean decline in baseline HIV-1 RNA at Day 8 in the functional monotherapy group compared to the placebo group.
The adjusted mean decline in baseline HIV-1 RNA was 0.79 log10 c/mL for the randomised subjects receiving blinded FTR + the open-label failing regimen versus 0.17 log10 c/mL for subjects on blinded placebo plus failing regimen (p <0.0001) in the ITT-E population, and showed statistical superiority (difference of -0.625, p <0.0001).
The results of the analysis in the per-protocol population were consistent with the results in the ITT-E population.

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The viral load monitoring is considered as a clinically relevant endpoint and even the early assessment on Day 8 is acceptable. Longer (more than two weeks) placebo-controlled studies are not appropriate, since continued use of a failing regimen increases the risk that the failing regimen might induce additional resistance and/or the risk of the investigational drug developing resistance might become significant. Early viral load reduction has been shown to predict long-term response.

Additionally, the FDA performed a sensitivity analysis to assess the efficacy of FTR after removing subjects who were not eligible based on specific entry criteria. Plasma HIV-1 RNA log10 (copies/mL) changes from Day 1 to day 8 were (separately) assessed, excluding subjects with HIV-1 RNA <400 copies/mL at baseline, subjects with HIV-1 RNA decline >0.4 log10 copies/mL from screening to baseline and subjects not eligible by resistance criteria. All three analyses demonstrated that excluding subjects who did not meet criteria did not substantially change the efficacy outcome.

Viral load decline was lower (0.143 log10 c/ml) at Day 8 for subjects with HIV-1 RNA ≤1000 c/ml at baseline in the FTR monotherapy group compared to those with higher baseline HIV-1 RNA >1000 c/ml.

The rates of the virological response at Day 8 were adversely affected by low baseline CD4+ count (below 20/ml), as patients with the lowest baseline CD4+ cell count (<20 cells/mm^3) within the FTR treatment group had the lowest mean viral load reduction at Day 8.

No relevant differences in virological response (plasma HIV-1RNA), were observed by age, race and region in the FTR 600 mg BID group on Day 8 but the numbers were limited. The treatment difference between FTR and placebo was lower for females versus males.

6.4 Safety

A total of 1,465 subjects have been exposed to at least one dose of FTR or TMR across the entire clinical development programme (624 HIV-1-infected adults and 841 uninfected adults) up to the data cut-off date for the Week 96 analysis of Phase 3 study 205888 (14 August 2018).
The FTR safety cohort comprises all HIV-1-infected subjects who have received FTR at a cumulative daily dose of ≥1200 mg. This includes all treated subjects (across both the randomised and non-randomised cohorts) from the FTR Phase 3 study as well as any subject in the Phase 2b study who received at least a single dose of FTR at either a 800 mg BID or 1200 mg once daily dose (including those subjects who switched to the 1200 mg QDay continuation dose). A total of 553 subjects (study 205888, 370 subjects; study 205889, 183 subjects) received at least one dose of ≥1200 mg FTR once daily and are included in the FTR safety cohort.
The FTR safety cohort includes 503 subjects who have received ≥1200 mg FTR daily for ≥24 weeks in Phase 2b study 205889 (165/200, 83%) and Phase 3 study 205888 (338/370, 91%). The mean (SD) duration of exposure was 130.45 (74.282), range 0.1-293.1 weeks, median 119.29 weeks.
In general, a larger safety population would be preferred to evaluate the safety profile. The present safety database is not sufficient to reliably capture less common adverse events (AE). On the other hand, long-term safety data are available for a large part of the safety population.

The most frequently reported AEs (>10%) were diarrhoea (20%), nausea (14%), upper respiratory tract infection (13%), nasopharyngitis (13%) and headache (13%). AEs from the “Infections and infestations” SOC accounted for most of the events. Most AEs were of mild to moderate severity (Grade 1 or 2, 64%). A higher frequency of more severe AEs were seen in the non-randomised cohort of study 205888 (Grade 3 or 4, 49%) compared to the randomised cohort (Grade 3 or 4, 29%) and study 205889 (Grade 3 or 4, 18%).
The most frequently reported drug-related AEs (>1%) were nausea (7%), diarrhoea (4%), headache (3%), fatigue (2%), dyspepsia (2%) and vomiting (2%). Similar proportions of subjects across both the Phase 2b and 3 (both cohorts) studies reported any drug-related or any drug-related AEs of Grade 3 or 4 severity.

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Serious adverse events (SAE)

In the FTR safety cohort, approximately one-third of subjects experienced an SAE, most commonly reported from the “Infections and infestations” SOC. Pneumonia, cellulitis and acute kidney injury were reported as SAEs by >1% of subjects. Seventeen drug-related SAEs were reported in 13 subjects. Two cases of immune reconstitution inflammatory syndrome (IRIS) and two cases of nephrolithiasis were reported, while other drug-related SAEs were reported once without a clear pattern.

Deaths

Relatively many deaths were reported in the FTR clinical development programme (35 on study and one during screening). Three of the deaths occurred in subjects who had never received FTR. Details of the remaining cases are as follows:

- Phase 3 study: 29 deaths as of cut-off of the Week 96 analysis:
  - 7 AIDS-related
  - 11 due to acute infections
  - 6 due to non-AIDS-related malignancies
  - 5 due to other conditions

Out of the 29 deaths, one fatal SAE of IRIS, related to recurrent atypical mycobacterial infection and considered by the investigator to be drug-related, was reported.

The majority of deaths occurred in subjects with very low baseline CD4+ cell counts (baseline CD4+ T-cell counts <20 cells/mm3: 66%).

- Phase 2b study: three deaths; none considered by the investigator to be drug-related.

A relation to FTR can, however, not be ruled out for one subject who had a fatal SAE of suicide on study day 1125.

- Phase 2a study: no deaths reported
- Clinical pharmacology studies: no deaths reported among subjects who received FTR
- Early access programme: two deaths until the cut-off date for the most recent DSUR (4 December 2018); none considered by the investigator to be drug-related.

AEs of special interest

IRIS, *hypersensitivity reaction and rash*, *ventricular tachyarrhythmias*, and *musculoskeletal events and CPK elevation* were identified as adverse events of special interest (AESIs) for FTR based on emerging nonclinical/clinical safety data, disease and/or population events, and/or regulatory requirements.

IRIS

Events of IRIS were only observed in the Phase 3 study, which included the most heavily pre-treated and immune suppressed population. Eight IRIS events (2%) of moderate to severe severity were observed. All but one of those were considered related to FTR and the OBT. Three events were considered SAEs, and one was fatal.

Given the study population, more events of IRIS might have been expected. This safety issue is adequately addressed in the information for healthcare professionals, in line with the product information of other approved ARVs.

Hypersensitivity reaction (HSR) and rash

A photodegradant impurity in the FTR tablets contains a beta-lactam ring and might, therefore, cause hypersensitivity reactions. Based on the recommendations of an expert panel, the applicant concluded that this is unlikely given the low antigenicity together with very low maximum serum concentrations. In the preclinical review, this position was supported.

174 HSR- and rash-related AEs were reported in 112 (20%) subjects in the FTR safety cohort. The majority of these AEs were non-serious, of mild or moderate severity, and resolved on continued treatment with FTR. In 14% of subjects, events were considered drug-related. Three events were considered SAEs; none was considered to be drug-related.

In the Phase 3 study, there were nine reports of hypersensitivity, all of mild to moderate severity, and all considered unrelated to FTR treatment. Two subjects reported a history of allergy to penicillin. In the single serious case, the event was thought to be related to ACE inhibitor treatment, and FTR was interrupted for one day.

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As there were no drug-related events of hypersensitivity reported in the Phase 3 study (data set used for labelling), this was not included in the information for healthcare professionals. However, one SAE of severe Grade 3 drug allergy was reported in a subject with a history of sulfonamide allergy in the early access programme. The subject was discontinued from the programme. The event was considered possibly related to FTR, darunovir, dolutegavir (DTG) and ibalizumab. Furthermore, in the Phase I studies, two reports were suggestive of a potential hypersensitivity reaction, one of which was considered drug-related: SAE of Grade 2 anaphylactic reaction. FTR and RTV were discontinued and the events fully resolved after several hours following treatment. A causal relationship could not be excluded for either study drug. However, given the delayed onset, this event was considered unlikely to be a Type 1 hypersensitivity reaction.
The exact relation of these events to FTR cannot be determined, as subjects were treated with a regimen of ARVs including FTR. These findings, therefore, cannot confirm or rule out a risk of hypersensitivity reactions.
Findings in the Phase 3 study do not indicate a potential for Type I hypersensitivity. However, given the two SAEs suggestive of hypersensitivity reaction observed in the early access programme (EAP) and in the Phase I studies, this risk cannot be ruled out.
“Severe Type 1 hypersensitivity“ is included in the PSUR and will be further evaluated through routine pharmacovigilance activities.

Ventricular tachyarrhythmias

- A total of eight subjects reported an AE of ECG QT prolongation: seven in Phase 3 study 205888 and one in the Phase 2b study 205889.
- For eight subjects in the Phase 3 study, the investigator reported an AE from the Torsade de pointes (TdP) SMQ. For seven of the eight subjects, the events were considered unrelated to the study drug.

There was one serious AE of loss of consciousness and disorientation (both Grade 3, duration two days) considered related to treatment. Treatment was continued without interruption. This subject recorded an ECG abnormality of sinus bradycardia at baseline, and during the study recorded a QTcF >30 ms increase (to 447 msec) from baseline on one occasion.
Another subject in the 1200 mg once daily dose group in the Phase 2b study, experienced syncope (Grade 3) and septicaemia (Grade 4) of unknown origin with onset on study day 855. The subject died due to septicaemia on the same day. The events were considered unrelated to FTR. Myocardial ischaemia (screening) and other non-specific ST/T (study day 1) ECG abnormalities were recorded in this subject.

- Seven subjects (7/371, 1.9%) were discontinued from the Phase 3 study due to reaching protocol-specified QTc prolongation stopping criteria before the Week 96 data cut-off. For four of the seven subjects a non-serious AE of ECG QT prolongation was reported.
- Six of the seven subjects who met protocol-stopping criteria for QTc prolongation were transitioned to the EAP (207214) and continued dosing with FTR outside of the Phase 3 study. One of these subjects reported an SAE of complete atrioventricular block on Day 58 in the EAP, which resulted in hospitalisation and resolved two days later with placement of a pacemaker. This was considered unrelated to FTR, and FTR dosing continued without change.

Although the findings from the tQT study indicated a clinically relevant effect on QTc interval at a supratherapeutic dose only, several subjects in the clinical studies met stopping criteria for QTc prolongation and/or reported ventricular arrhythmia-related AEs. Although most events were considered non-serious, not related to the study drug or resulted in permanent discontinuation of FTR treatment, a risk for TdP cannot be ruled out. Most of these events were observed in the Phase 3 study, despite concomitant use of drugs known to cause TdP being prohibited.

Musculoskeletal events and CPK elevation

Overall, the observed safety profile was less good in comparison to other oral (combinations of) ARVs approved for the treatment of treatment-naïve and virologically suppressed patients. In part, the more frequent AEs, SAEs and deaths reflect advanced HIV infection with associated immune suppression

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and complications in the study population. This was also seen for Trogarzo, a recently FDA-approved monoclonal antibody (ibalizumab-uiyk) for treatment of HIV infection in heavily pre-treated patients with multi-drug-resistant HIV.
Specific safety issues are the potential for QT prolongation and hypersensitivity reactions. In addition, changes in laboratory parameters indicating a decline in kidney and liver function were observed. This was most pronounced in patients who had pre-existing risk factors for renal or hepatic impairment. These findings are, however, hard to interpret due to the advanced disease status, associated conditions and concomitant medication. The exact relation to FTR cannot be determined as the Phase 2b/3 studies included no comparisons to a control arm in the primary studies. Furthermore, FTR was combined with an OBT consisting of different ARVs depending on the patients' treatment-history and the resistance of their HIV.
Although a better understanding of the safety issues related to FTR treatment would be preferred, the safety data can be accepted, given the need for treatment options in the target population of treatment-experienced patients with multi-drug-resistant HIV.
Furthermore, the possible risks are not considered prohibitive, but can be managed with adequate information in the information for healthcare professionals.

6.5 Final Clinical and Clinical Pharmacology Benefit-Risk Assessment

Rukobia (FTR) is a first-in-class HIV-1 attachment inhibitor. FTR is a methyl-phosphate oral prodrug, which is hydrolysed to the active moiety TMR by alkaline phosphatase in the gastrointestinal lumen. TMR binds directly to the gp120 envelope glycoprotein on the surface of HIV, preventing initial interaction between HIV and CD4+ cell-surface receptors, thereby preventing entry into host T-cells and other immune cells.

The treatment of HIV infection is based on the combination of antiretroviral drugs. The goal of the treatment is to suppress and then maintain the suppression of plasma HIV-RNA levels below the level of detection (of sensitive HIV-RNA assays), restore the immune system, reduce HIV-associated morbidity and prevent transmission.
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 and tolerability problems, and poor adherence. Treatment failure may result in selection of virus with resistance to one or more ARV agents. Furthermore, resistance mutations selected by one ARV agent often confer resistance to multiple drugs within a given ARV class, significantly limiting future therapeutic options.
HTE patients infected with MDR HIV represent a rather small but important subset of patients living with HIV. Patients with MDR HIV who cannot achieve complete virological suppression with ART are at high risk for AIDS-related morbidity and mortality.
HTE patients are on highly individualised combinations of ARV agents that lack the efficacy, safety and tolerability profiles of ARVs used in earlier lines of therapy. While the primary goal of ARV therapy is to achieve complete virological control, if suppression is not achievable, additional treatment objectives exist, including partial reduction of the viral load, preserving immunological function, preventing clinical progression of disease and minimising additional resistance to agents important to future treatment options.

TMR was active *in vitro* against both CCR5 and CXCR4 and dual tropic viruses; however, the range of susceptibility for CXCR4 and dual tropic viruses was wider.

The pharmacokinetics of the prodrug FTR and the active metabolite TMR have been well characterised in healthy subjects and HIV-infected patients.

FTR has demonstrated short-term virological activity in HTE patients infected with MDR HIV. In the pivotal Phase 3 study (study 205888), patients in the functional monotherapy group receiving blinded FTR 600 mg BID in addition to their failing antiretroviral regimen achieved a significantly higher mean

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decrease in the HIV-1 RNA compared to the placebo group, who received placebo in addition to the failing regimen.
The mean decline in HIV-1 RNA is consistent with the findings from the Phase two study 205889. Following the functional monotherapy period, the patients in the randomised cohort received open-label FTR and OBT. This open-label period showed the durability of the virological activity through to Week 96. The immunological response showed a continued increase in the CD4+ counts and an increase in the CD4/CD8 ratio as well. Notably, the durability of viral suppression is a result of an entire drug regimen rather than of an individual drug.

The definition of the target population in the initially proposed indication:
"Rukobia, in combination with other antiretrovirals, is indicated for the treatment of intensively pretreated adults with multidrug resistant 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 Properties / Effects)"
was not represented by the population studied in the randomised cohort of the pivotal Phase 3 study. In fact, the randomised cohort included subjects with MDR HIV-1 infection who had at least one, but no more than two, remaining fully active ARVs. Therefore, a viable new but suboptimal regimen was accessible for the majority of the study population. The primary endpoint was also analysed in this randomised cohort. As a consequence, the efficacy of fostemsavir was primarily shown in these patients. Thus, the indication was modified accordingly and to point out that Rukobia is indicated in combination with an optimised antiretroviral treatment.

Phase 2b study 205889 provided supportive data (in generally treatment-experienced patients with a TMR IC50<100 nM) on the long-term durability of FTR through to Week 192, with demonstration of comparable efficacy and immunological response to the control ATV/r group (both groups in combination with RAL+TDF).

Impaired hepatic or renal function is associated with a mild to moderate increase in TMR exposure. However, the extent of efficacy and safety data in patients with impaired organ function is currently unclear.

A single Phase 3 study was submitted in the intent-to-use population and with the requested dose. Two adequate and well-controlled studies conducted in the population proposed for the requested indication would be preferable.
The study design of the Phase 3 study is considered acceptable. However, as it is not controlled beyond the functional monotherapy part that assessed the primary endpoint of the study and individualised optimised background regimens were administered instead of a standardised background therapy due to the nature of the HTE populations, uncertainty remains regarding the contribution of FTR in maintaining virological effect. Additionally, most of the subjects in the randomised cohort received DTG (84%) in the initial OBT with the majority of subjects taking it twice daily (63%).

In the Phase 3 study, the rates of the virological response at Day 8 were adversely affected by low baseline CD4+ count (below 20/ml) and low baseline HIV-1 RNA load. The treatment differences were lower in these groups. Thus, the virological efficacy of FTR in these subgroups seems to be limited.

The demonstrated efficacy of FTR is confined to a selected group of patients. Most of the study subjects had subtype B infection, only 3% had subtype C, 7% subtype F1 and 0.5% subtype AE. Subjects with baseline pre-defined genotypic substitutions achieved smaller median change in the viral load at Day 8 compared to those with no gp160 substitutions.
Baseline susceptibility of TMR was highly variable and seemed to be higher than observed for other entry inhibitors. The exposure-response relationship indicated that the baseline sensitivity as

measured by phenotyping is an influential factor in determining the magnitude of decline of the HIV-1 RNA.
Based on the patient population of the Phase 3 study, there is very limited information on patients infected with HBV or HCV. However, co-infection is not uncommon in patients living with HIV.

Regarding the two Phase 2 studies intended to support the viral activity of FTR, neither the population nor the dose were in line with those of the to Phase 3 study.
In study 205889 a potential overestimation of the efficacy might be present as no patients with a TMR IC50 greater than 100 nM were included.

In the Phase 3 efficacy study and the supporting Phase 2b study, genotypic testing at baseline and in the PDVF population was limited to pre-defined amino acids at sites of interest.
The clinical data did not provide consistent evidence that the *genotypic* substitutions identified from the exploratory analysis modelling were associated with a significant reduction in susceptibility to TMR. However, the substitution S375N was significantly associated with reduced response and emerged in 18/62 (29%) of subjects with PDVF through to Week 24 in study 205888.

Based on *in vitro* data, the recombinant subtype CRF01_AE might exhibit inherent resistance to TMR.

TMR causes a clinically relevant prolongation of the QT interval at a supratherapeutic dose but not at the requested daily dose. In the clinical studies, several subjects met stopping criteria for QTc prolongation and/or reported ventricular arrhythmia-related AEs. However, the clinical relevance of these events seems limited. The risk can be addressed by a warning in the information for healthcare professionals.
Based on the answer to the LoQ, it was mostly patients with renal/hepatic impairment who had QTc prolongation leading to withdrawal. Subjects who withdrew due to QT prolongation did not appear to have higher plasma TMR C_{max} compared to subjects who did not meet protocol stopping criteria for QT.

TMR is a victim of clinically relevant DDIs, which results in a contraindication for concomitant use with strong inducers. TMR and its metabolites also cause DDI effects on other drugs, which warrants dose adjustments/limitations for concomitant use with e.g. certain statins and oral contraceptives.

Clinical isolates of nine viruses from subtype CRF01_AE, two viruses from Group O and one HIV-2 virus that were examined displayed no susceptibility to TMR at the highest concentration tested.
The observed safety profile was not as good as that of other oral (combinations of) ARVs approved for the treatment of treatment-naïve and virologically suppressed patients. The more frequent AEs, SAEs and deaths reflect advanced disease status with associated immune suppression and complications in the study population. The most frequently reported drug-related AEs (>1%) were nausea (7%), diarrhoea (4%), headache (3%), fatigue (2%), dyspepsia (2%) and vomiting (2%). Specific safety issues are the potential for QT prolongation, hypersensitivity reaction, and changes in laboratory parameters indicating a decline in kidney and liver function.

A safety margin for QT prolongations of approx. 4-fold (only 1.8 fold in subjects with increased TMR exposure due to hepatic impairment + CYP3A4 inhibitor use) above the mean therapeutic exposure has been determined based on exposure-response simulations. There are a lack of clinical data to confirm this margin.
Due to the study population, the lack of a control arm and the evaluation of FTR in combination with individualised optimised background regimens dependent on the patients' treatment history in the Phase 3 study, the extent to which the observed safety issues are related to FTR treatment, concomitant medication or advanced HIV infection with associated conditions cannot be determined.
Increased exposure was seen in patients with various degrees of renal impairment and hepatic impairment in the dedicated PK studies. Furthermore, observed changes in laboratory parameters indicating a decline in kidney and liver function were most pronounced in patients who had pre-

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existing risk factors for renal or hepatic impairment. In the Phase 3 study, the proportion of subjects reporting any Grade 3 - 4 AE, AEs leading to discontinuation or SAEs was higher in all renally impaired and hepatically impaired analysis groups when compared to subjects with neither RI nor HI. However, no consistent pattern of specific AEs was observed by baseline RI or HI status, and the level of the FTR contribution or the underlying medical conditions is difficult to assess.

The treatment of heavily treatment-experienced MDR HIV-1 infected patients is complex and challenging, as they have limited remaining treatment options and MDR HIV infection. Virological suppression cannot be achieved or maintained with a failing ARV regimen, resulting in higher risk for AIDS-related morbidity and mortality. There is an obvious medical need for the small group of HTE patients to have new therapy options available.

FTR offers a new mode of action, by inhibiting the HIV-1 attachment without cross resistance to current ARVs.

FTR demonstrated virological efficacy in a short-term functional monotherapy substudy in the intent-to-use population and also provided some evidence of durable virological suppression until Week 96. However, there are uncertainties regarding the contribution of FTR to long-term efficacy.

Although a better understanding of the safety issues related to FTR treatment would be preferred, the safety data can be accepted, given the need for treatment options in the target population of treatment-experienced patients with multi-drug resistant HIV. Furthermore, the possible risks are not considered to be prohibitive and can be mitigated with adequate information into the information for healthcare professionals.

The overall benefit-risk profile of Rukobia in the target population is positive.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Rukobia was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Rukobia

Composition

Active substances

Fostemsavir (as Fostemsavir Tromethamine)

Excipients

Tablet core: hydroxypropyl cellulose, hypromellose, colloidal anhydrous silica, magnesium stearate
Film coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172), iron oxide red (E172)

Pharmaceutical form and active substance quantity per unit

Prolonged-release tablet containing 600 mg of fostemsavir (as fostemsavir tromethamine).
Beige, biconvex, oval film-coated tablet which may have a slight odour (vinegar-like), debossed with ‘SV 1V7’ on one side.

Indications/Uses

Rukobia is indicated in combination with optimised background antiretroviral therapy against human immunodeficiency virus type 1 (HIV-1) infection for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced adults whose current antiviral regimen failed due to resistance and/or cannot be continued due to intolerance or safety reasons (*see Properties/Effects/Clinical Efficacy*).

Dosage/Administration

Therapy should be initiated and monitored by a physician experienced in the management of HIV infection.

Usual dosage

Adults
The recommended dosage of Rukobia is 600 mg tablet, twice daily, taken orally with or without food.

Special dosage instructions

Patients with impaired hepatic function

No dosage adjustment is required in patients with hepatic impairment (*see Pharmacokinetics — Special Patient Populations*).

Patients with impaired renal function

No dosage adjustment of Rukobia is required for patients with renal impairment and those on haemodialysis (*see Pharmacokinetics — Special Patient Populations*).

Elderly patients

There are limited data available on the use of Rukobia in patients aged 65 years and older. However, there is no evidence that elderly patients require a different dose than younger adult patients (*see Pharmacokinetics – Special Patient Populations*).

Children and adolescents

Rukobia is not recommended in children below 18 years of age due to a lack of safety and efficacy data.

Mode of administration

Rukobia can be taken independently of meals.
Rukobia tablets should be swallowed whole, and should not be chewed, crushed or split.

Contraindications

Rukobia is contraindicated in patients who have demonstrated hypersensitivity to fostemsavir or any of the other components of the preparation.
Rukobia is contraindicated in combination with strong CYP3A inducers including, but not limited to carbamazepine, phenytoin (anticonvulsants), mitotane (antineoplastic), enzalutamide (androgen receptor inhibitor), rifampicin (antimycobacterial) and St John's wort (Hypericum perforatum, herbal supplement), which may result in a loss of therapeutic effect of Rukobia (*see Interactions*).

Warnings and precautions

Immune Reconstitution Syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months after initiation of ART. Relevant examples are CMV retinitis, generalised and/or focal mycobacterial infections and Pneumocystis jiroveci pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

QTc Prolongation

In healthy study participants, a supratherapeutic dose of fostemsavir (2400 mg twice daily) has been shown to significantly prolong the QTc interval of the electrocardiogram (*see Pharmacodynamics*). Rukobia should be used with caution in patients with a history of QT interval prolongation, when co-administered with a drug which is also known to cause QT interval prolongation or Torsade de Pointes (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, or sotalol) or in patients with relevant pre-existing cardiac disease. Caution is needed when Rukobia use is being considered in patients with hepatic or renal impairment who are receiving concomitant strong CYP3A4 inhibitors. In combination, these factors can possibly lead to increases in TMR exposure. Elderly patients may be more susceptible to drug-induced QT interval prolongation (*see Interactions, Pharmacokinetics* and *Undesirable Effects*).

Patients with Hepatitis B or C Virus Co-infection

Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co- infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting Rukobia therapy in HIV-hepatitis B co-infected patients.

Opportunistic infections

Patients receiving Rukobia or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission of infection

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Interactions with other drug products

Caution should be given to co-administering medications (prescription and non- prescription) that may change the exposure to temsavir, the active moiety of fostemsavir, or medications that may have their exposure changed by temsavir (*see Contraindications*, *Interactions*). Increased exposure to temsavir may increase the risk of QTc interval prolongation (*see Warnings and Precautions, Pharmacodynamics*).

Co-administration of fostemsavir with elbasvir/grazoprevir is not recommended as increased grazoprevir concentrations may increase the risk of ALT elevations (*see Interactions*).

Dose modifications and/or careful titration of dose is recommended for certain statins that are substrates of OATP1B1/3 or BCRP (rosuvastatin, atorvastatin, pitavastatin, simvastatin and fluvastatin) when co-administered with fostemsavir (*see Interactions*).
When fostemsavir was co-administered with oral contraceptives, temsavir increased concentrations of ethinyl estradiol and caution is advised particularly in patients with additional risk factors for thromboembolic events. Doses of estrogen-based therapies, including oral contraceptives, should not contain more than 30 µg of ethinyl estradiol per day in patients who are receiving fostemsavir (*see Interactions*).

Interactions

Effect of Fostemsavir on the Pharmacokinetics of Other Agents

Substrates of the transporters OATP1B1, OATP1B3 and BCRP
In vitro, temsavir inhibited organic anion transporter polypeptides (OATP)1B1 and OATP1B3 (IC_{50} = 32 and 16 µM, respectively). Additionally, temsavir and its two metabolites (BMS-646915 and BMS-930644) inhibited breast cancer resistance protein (BCRP) (IC_{50} = 12, 35, and 3.5 to 6.3 µM, respectively). Based on these data, temsavir is expected to increase the exposure of drugs that are substrates of OATP1B1/3 or BCRP. Therefore, dose modifications and/or careful titration of dose is recommended for certain statins.

Substrates of CYP3A4
Based on in vitro data, BMS-930644 inhibited CYP3A4 with IC_{50} values <10 µM. However, in clinical studies, the circulating concentrations of BMS-930644 are low [C_{max} of approximately 458 ng/mL (~1 µM) with fostemsavir 600 mg twice daily], and thus a clinically relevant interaction is unlikely. Co-administration of fostemsavir with substrates of CYP3A4 (e.g. maraviroc) showed a slight inhibition of CYP3A4. However, this increase in exposure is not clinically relevant.

Substrates of the transporters MATE1/2 -K and OCT1/2
Based on in vitro data, temsavir and its two metabolites (BMS-930644 and BMS-646915) inhibited multidrug and toxin extrusion protein (MATE)1/2-K. BMS-930644 inhibited OCT1 with IC_{50} values <10 µM, However, clinically relevant interactions are unlikely.

Other interactions
Relevant interactions are not expected when fostemsavir is co-administered with substrates of cytochrome P_{450} (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6), uridine diphosphate glucuronosyl transferases (i.e. UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7), P-glycoprotein (P-gp), multidrug resistance protein (MRP)2, bile salt export pump (BSEP), sodium

taurocholate co-transporting polypeptide (NTCP), organic anion transporters (OAT)1, OAT3, and organic cation transporter-OCT2 based on in vitro and clinical drug interaction data. In addition, temsavir did not induce CYP enzymes in vitro.

Effect of Other Agents on the Pharmacokinetics of Temsavir

Temsavir is a substrate of P-gp and BCRP, but not of OATP1B1 or OATP1B3. Its biotransformation to two metabolites, BMS-646915 and BMS-930644, is mediated by unidentified esterases (36.1%) and by CYP3A4 enzyme (21.2%), respectively. Temsavir exposures may be influenced by modulators of CYP3A4, P-gp and/or BCRP activity.

Concurrent use contraindicated

Strong inducers of CYP3A4

When fostemsavir was co-administered with a strong CYP3A inducer rifampicin, a significant reduction in temsavir plasma concentrations was observed. Significant decreases in temsavir plasma concentrations may also occur when fostemsavir is co-administered with other strong CYP3A inducers, and may result in loss of virologic response (*see Contraindications*).

Concurrent use not recommended

Grazoprevir

Temsavir may increase grazoprevir plasma concentrations to a clinically relevant extent caused by OATP1B1/3 inhibition by temsavir (*see Warnings and Precautions*).

Further interactions

Moderate inducers of CYP3A4

A reduction in plasma concentrations of temsavir was observed when fostemsavir was co-administered with moderate CYP3A inducers (i.e., rifabutin and etravirine). Limited clinical data on efficacy when co-administered with etravirine suggest that virological response is not adversely affected.

When used concomitantly with other moderate inducers, no data are available and therefore an impact on virological response cannot be excluded. Therefore, the need for concomitant use should be considered.

Medicines that prolong the QT interval

Coadministration of Rukobia with a drug with a known risk of Torsade de Pointes may increase the risk of Torsade de Pointes (*see Warnings and Precautions*). Use Rukobia with caution when coadministered with drugs with a known risk of Torsade de Pointes.

Inhibitors of CYP3A4

Fostemsavir may be co-administered with strong CYP3A4, BCRP and/or Pgp inhibitors (e.g. clarithromycin, itraconazole, posaconazole, and voriconazole) without dose adjustment based on the results of clinical drug interaction studies with cobicistat and ritonavir.

Selected drug interactions are presented in Table 1. Table 1 gives the geometric mean ratio (GMR) with 90% confidence intervals (CI) of the pharmacokinetic variables when taken with/without concomitant medication. Recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of the interaction and/or potential for serious adverse events or loss of efficacy.

Table 1 Drug Interactions

Active substance by therapeutic area (dosage scheme)	Effects on drug concentration GMR (90% CI) (Possible interaction mechanism)	Recommendation for concomitant use
HIV-1 Antiviral Agents		
Entry-Inhibitoren: Maraviroc (MVC) (300 mg twice daily)	Temsavir C_{max} 1.13 (0.962, 1.32) AUC 1.10 (0.993, 1.23) $C\tau$ 0.901 (0.691, 1.17) MVC AUC 1.25 (1.08, 1.44) C_{max} 1.01 (0.844, 1.20) $C\tau$ 1.37 (1.26, 1.48)	No dose adjustment of either drug is necessary.
Integrase-Inhibitor: Raltegravir (RAL) (400 mg twice daily)	Temsavir ↔* RAL ↔*	No dose adjustment of either drug is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Temsavir ↓ This interaction has not been studied. Expected: Decrease in temsavir exposure (Induction of CYP3A enzymes)	Efavirenz is expected to decrease temsavir plasma concentrations. No dose adjustment is recommended. However, the need for concomitant use should be considered *(see Further Interactions/Moderate Inducers of CYP3A4).*

Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR) without boosted protease inhibitors (200 mg twice daily)	Temsavir AUC 0.502 (0.442, 0.571) C_{max} 0.516 (0.454, 0.587) $C\tau$ 0.483 (0.324, 0.720) (Induction of CYP3A enzymes) ETR AUC 1.11 (1.05, 1.17) C_{max} 1.11 (1.04, 1.19) $C\tau$ 1.14 (1.08, 1.21)	Etravirine decreased temsavir plasma concentrations. This reduction is not clinically relevant based on limited data. No dose adjustment is recommended.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine (NVP)	Temsavir ↓ This interaction has not been studied. Expected: Decrease in temsavir exposure (Induction of CYP3A enzymes)	Nevirapine is expected to decrease temsavir plasma concentrations. No dose adjustment is recommended. However, the need for concomitant use should be considered *(see Further Interactions/Moderate Inducers of CYP3A4).*
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDF) (300 mg once daily)	Temsavir AUC 1.00 (0.910,1.11) C_{max} 0.986 (0.861, 1.13) $C\tau$ 1.13 (0.773, 1.66) TDF AUC 1.19 (1.12, 1.25) C_{max} 1.18 (1.12, 1.25) $C\tau$ 1.28 (1.20, 1.38) (Inhibition of P-gp and/or BCRP)	No dose adjustment of either drug is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir alafenamide (TAF)	TAF ↑ This interaction has not been studied. Expected: Temsavir should increase plasma concentrations of tenofovir alafenamide (Inhibition of OATP1B1/3 and/or BCRP)	With regard to dose adjustments, consult the full prescribing information for TAF-containing medications when co-administered.

Pharmacokinetic Enhancer: Cobicistat (COBI) (150 mg once daily)	Temsavir AUC 1.93 (1.75, 2.12) C_{max} 1.71 (1.54, 1.90) $C\tau$ 2.36 (2.03, 2.75) (Inhibition of CYP3A enzymes, P-gp and/or BCRP)	No dose adjustment is necessary.
Pharmacokinetic Enhancer: Ritonavir (100 mg once daily)	Temsavir AUC 1.45 (1.29, 1.61) C_{max} 1.53 (1.31, 1.79) $C\tau$ 1.44 (1.00, 2.08) (Inhibition of CYP3A and P-gp) RTV $\leftrightarrow$	No dose adjustment of either drug is necessary.
Protease Inhibitor: Atazanavir (ATV)/ritonavir (RTV) (300 mg/100 mg once daily)	Temsavir AUC 1.54 (1.44, 1.65) C_{max} 1.68 (1.58, 1.79) $C\tau$ 1.57 (1.28, 1.91) (Inhibition of CYP3A enzymes and P-gp) ATV AUC 1.09 (1.03, 1.15) C_{max} 1.03 (0.963, 1.10) $C\tau$ 1.19 (1.10, 1.30) RTV AUC 1.07 (1.03, 1.10) C_{max} 1.02 (0.957, 1.09) $C\tau$ 1.22 (1.12, 1.32)	No dose adjustment of either drug is necessary.
Protease Inhibitor: Darunavir (DRV)/cobicistat (800 mg/150 mg once daily)	Temsavir AUC 1.97 (1.78, 2.18) C_{max} 1.79 (1.62, 1.98) $C\tau$ 2.24 (1.75, 2.88) (Inhibition of CYP3A enzymes, P-gp and/or BCRP)	No dose adjustment is necessary.

Protease Inhibitor: Darunavir (DRV)/ritonavir (600 mg/100 mg twice daily)	Temsavir AUC 1.63 (1.42, 1.88) C_{max} 1.52 (1.28, 1.82) $C\tau$ 1.88 (1.09, 3.22) (Inhibition of CYP3A enzymes and P-gp) DRV AUC 0.944 (0.894, 0.996) C_{max} 0.983 (0.931, 1.04) $C\tau$ 0.948 (0.865, 1.04) RTV AUC 1.15 (0.992, 1.33) C_{max} 0.995 (0.856, 1.16) $C\tau$ 1.19 (1.06, 1.35)	No dose adjustment is necessary for any drug when co-administered.
Protease Inhibitor: Darunavir (DRV)/ritonavir + Etravirine (600 mg/100 mg/200 mg twice daily)	Temsavir AUC 1.34 (1.17, 1.53) C_{max} 1.53 (1.32, 1.77) $C\tau$ 1.33 (0.980, 1.81) DRV AUC 0.938 (0.888, 0.991) C_{max} 0.954 (0.903, 1.01) $C\tau$ 0.881 (0.769, 1.01) RTV AUC 1.09 (0.979, 1.22) C_{max} 1.14 (0.960, 1.35) $C\tau$ 1.07 (0.972, 1.17) Etravirine AUC 1.28 (1.20, 1.36) C_{max} 1.18 (1.10, 1.27) $C\tau$ 1.28 (1.18, 1.39)	No dose adjustment is necessary for any drug when co- administered.
Other Agents		
Androgen receptor inhibitor: Enzalutamide	Temsavir ↓ Not studied. Expected: Significant decrease in temsavir exposure caused by strong CYP3A induction. (Induction of CYP3A enzymes)	Concomitant use of fostemsavir is contraindicated.

Anticonvulsants: Carbamazepine Phenytoin	Temsavir ↓ Not studied. Expected: Significant decrease in temsavir exposure caused by strong CYP3A induction. (Induction of CYP3A enzymes)	Concomitant use of fostemsavir is contraindicated.
Antineoplastic: Mitotane	Temsavir ↓ Not studied. Expected: Significant decrease in temsavir exposure caused by strong CYP3A induction. (Induction of CYP3A enzymes)	Concomitant use of fostemsavir is contraindicated.
Buprenorphine/naloxone (8/2 to 24/6 mg once daily)	Buprenorphine AUC 1.30 (1.17, 1.45) C_{max} 1.24 (1.06, 1.46) Norbuprenorphine AUC 1.39 (1.16, 1.67) C_{max} 1.24 (1.03, 1.51)	No dose adjustment is necessary.
Methadone (40-120 mg once daily)	Methadone R-Methadone AUC 1.13 (1.07, 1.19) C_{max} 1.15 (1.11, 1.20) S-Methadone AUC 1.15 (1.09, 1.21) C_{max} 1.15 (1.10, 1.19)	No dose adjustment is necessary.
H_2-Receptor Antagonists: Famotidine (40 mg single dose given 2 hours before fostemsavir)	Temsavir AUC 1.04 (0.867, 1.25) C_{max} 1.01 (0.845, 1.21) $C\tau$ 0.903 (0.636, 1.28)	No dose adjustment is necessary when combined with drugs that increase gastric pH.

Oral contraceptives: Ethinyl estradiol (EE) (30 µg once daily) Norethindrone acetate (NE) (1.5 mg once daily)	EE AUC 1.40 (1.29, 1.51) C_{max} 1.39 (1.28, 1.51) (Inhibition of CYP enzymes and/or BCRP) NE AUC 1.08 (1.03, 1.14) C_{max} 1.08 (1.01, 1.16)	For hormone therapies containing EE, the total daily dose of ethinyl estradiol should not exceed 30 µg. Caution is advised particularly in patients with additional risk factors for thromboembolic events (*see Warnings and Precautions*). No dose adjustment for NE is necessary.
Rifabutin (300 mg once daily)	Temsavir AUC 0.698 (0.642, 0.760) C_{max} 0.732 (0.647, 0.829) $C\tau$ 0.594 (0.461, 0.766) (Induction of CYP3A enzymes)	Rifabutin decreased temsavir plasma concentrations. No dose adjustment is recommended. However, the need for concomitant use should be considered *(see Further Interactions/Moderate Inducers of CYP3A4).*
Rifabutin + Ritonavir (150 mg/100 mg once daily)	Temsavir AUC 1.66 (1.52, 1.81) C_{max} 1.50 (1.38, 1.64) $C\tau$ 2.58 (1.95, 3.42)	Ritonavir, when co-administered with rifabutin, increased the plasma concentrations of temsavir. No dose adjustment is necessary.
Rifampicin (600 mg once daily)	Temsavir AUC 0.181 (0.163, 0.200) C_{max} 0.241 (0.208, 0.279) (Induction of CYP3A enzymes)	The concomitant use of fostemsavir and rifampicin is contraindicated.
HMG-CoA Reductase Inhibitors : Rosuvastatin (10 mg single dose) Atorvastatin Pitavastatin Fluvastatin Simvastatin	Rosuvastatin AUC 1.69 (1.44, 1.99) C_{max} 1.78 (1.52, 2.09) (Inhibition of OATP1B1/3 and/or BCRP)	Use the lowest possible starting dose of rosuvastatin with careful monitoring, for statin associated adverse events. Although not studied, use the lowest possible starting dose of other statins that are substrates of OATP1B1/3 and/or BCRP with careful monitoring for HMG-CoA reductase inhibitor-associated adverse events.
Pravastatin	Pravastatin ↔	Although not studied, clinically relevant increases in plasma concentrations of pravastatin are not expected as it is not a

		substrate of BCRP. No dose adjustment is anticipated.
Hepatitis C Virus Direct-Acting Antivirals (HCV DAAs): Elbasvir/Grazoprevir	Grazoprevir ↑ Not studied. Expected: Temsavir may increase grazoprevir plasma concentrations to a clinically relevant extent caused by OATP1B1/3 inhibition by temsavir.	Co-administration of fostemsavir with elbasvir/grazoprevir is not recommended as increased grazoprevir concentrations may increase the risk of ALT elevations.
Sofosbuvir Ledipasvir Velpatasvir Voxilaprevir Ombitasvir Paritaprevir Dasabuvir Glecaprevir Pibrentasvir Daclatasvir	HCV DAA ↑ Not studied. Temsavir may increase plasma concentrations of other HCV DAAs.	No dose adjustment is necessary.

Abbreviations: ↑ = Increase; ↓ =decrease; ↔ = no significant change; AUC=area under the concentration versus time curve; C_{max}=maximum observed concentration, Cτ=concentration at the end of dosing interval.
* = Using cross-study comparisons to historical pharmacokinetic data.

Pregnancy, lactation

Pregnancy

There are no adequate and well-controlled studies of fostemsavir in pregnant women. The effect of fostemsavir on human pregnancy is unknown.

Animal studies indicate no effects of fostemsavir on embryo-foetal development at clinically relevant exposures (*see Preclinical Data*).

Rukobia should not be used during pregnancy unless absolutely necessary.

Lactation

It is expected that temsavir will be secreted into human milk based on animal data, although this has not been confirmed in humans *(see Preclinical Data).*

Therefore, women should not breastfeed during treatment with Rukobia if possible.

Health experts generally recommend that where possible, HIV-infected women do not breast feed their infants in order to avoid transmission of HIV.

Fertility

There are no data on the effects of fostemsavir on human male or female fertility. Animal studies indicate no effects of fostemsavir on male or female fertility at clinically relevant doses (*see Preclinical Data).*

Effects on ability to drive and use machines

There have been no studies to investigate the effect of fostemsavir on driving performance or the ability to operate machinery. Rukobia can cause dizziness, headaches, drowsiness and nausea. The clinical status of the patient and the adverse event profile of Rukobia should be borne in mind when considering the patient's ability to drive or operate machinery.

Undesirable effects

Clinical trial data

A total of 620 HIV-1 infected subjects received at least one dose of fostemsavir as part of a controlled clinical trial.

The safety and tolerability of fostemsavir was evaluated in a Phase III, partially-randomised, double-blind, placebo-controlled trial (BRIGHTE [205888]) conducted in 371 heavily treatment-experienced adult subjects (*see Clinical efficacy*). In the Randomised Cohort, 272 subjects received either blinded fostemsavir, 600 mg twice daily (n = 203), or placebo (n = 69), in addition to their current failing regimen, for 8 days of functional monotherapy. Beyond Day 8, randomised subjects received open-label fostemsavir, 600 mg twice daily, plus an optimised background therapy. In the Non-randomised Cohort, 99 subjects received open-label fostemsavir, 600 mg twice daily, plus optimised background therapy from Day 1 onward.

Adverse drug reactions (ADRs) identified in the Phase III clinical trial, which included a total of 370 subjects receiving at least 1 dose of fostemsavir 600 mg twice daily, are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports. For many of the adverse drug reactions listed, it is unclear whether they are related to fostemsavir, or the other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process.

Table 2 Adverse Reactions with Fostemsavir

System	Frequency	Adverse reactions
Immune system disorders	Common	Immune Reconstitution Inflammatory Syndrome[1] (*see Warnings and Precautions*)

Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Headache (13%)
	Common	Dizziness, Neuropathy peripheral[2], Somnolence, Dysgeusia
Cardiac disorders	Common	Electrocardiogram QT prolonged[3] *(see Warnings and Precautions)*
Gastrointestinal disorders	Very common	Diarrhoea (24%), Nausea (18%), Abdominal pain[4] (12%), Vomiting (11%)
	Common	Dyspepsia
Hepatobiliary disorders	Common	Transaminases increased[5,6]
Skin and subcutaneous tissue disorders	Very common	Rash[7] (10%)
	Common	Pruritus[8]
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administration site conditions	Common	Fatigue, Asthenia
Investigations	Common	Blood creatinine increased[6], Blood creatine phosphokinase increased[6]

[1] Includes Central Nervous System Immune Reconstitution Inflammatory Response and Immune Reconstitution Inflammatory Syndrome.

[2] Includes neuropathy peripheral and peripheral sensory neuropathy.

[3] Based on number of subjects who met QTc discontinuation criteria; all reports were asymptomatic.

[4] Includes abdominal discomfort, abdominal pain and abdominal pain upper.

[5] Includes ALT increased, AST increased, hepatic enzymes increased, and transaminases increased.

[6] Asymptomatic elevations in creatinine, creatine phosphokinase and liver enzymes were mainly grade 1 or 2 and did not require interruption of treatment.

[7] Includes rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic and rash vesicular.

[8] Includes pruritus and pruritus generalised.

Changes in laboratory chemistries
Increases in creatine phosphokinase (CPK) were observed following treatment with fostemsavir, which were mainly mild or moderate. These changes were rarely associated with musculoskeletal complaints.
Clinically relevant increases in serum creatinine have primarily occurred in patients with identifiable risk factors for reduced renal function, including pre-existing medical history of renal disease and/or concomitant medications known to cause increases in creatinine. A causal association between fostemsavir and elevation in serum creatinine has not been established.
Increases in direct (conjugated) bilirubin have been observed following treatment with fostemsavir. Cases of clinical significance were uncommon and were confounded by the presence of intercurrent serious comorbid events not related to dosing with study medication (e.g. sepsis, cholangiocarcinoma or other complications of viral hepatitis co-infection). In the remaining reports, elevations in direct bilirubin (without clinical jaundice) were typically transient, occurred without increases in liver transaminases and resolved on continued fostemsavir.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms
There is currently limited experience of overdosage with fostemsavir.
Treatment
There is no specific treatment for overdose with fostemsavir. After an overdose, the patient must receive the appropriate supportive treatment and be monitored as appropriate. If overdose occurs, the temsavir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.
Further management should be as clinically indicated or as recommended by the national toxicology information centre, where available.

Properties/Effects

ATC code

J05AX29

Mechanism of action

Fostemsavir is a prodrug without significant biochemical or antiviral activity that is hydrolyzed to the active moiety, temsavir, upon cleavage of a phosphonooxymethyl group in vivo. Temsavir binds directly to the gp120 subunit within the HIV-1 envelope glycoprotein gp160 and selectively inhibits the interaction between the virus and cellular CD4 receptors, thereby preventing attachment and subsequent viral entry into host cells. Temsavir inhibited the binding of soluble CD4 to surface immobilized gp120 with an IC_{50} of 14 to 30 nM using an enzyme-linked immunosorbent assay (ELISA).

Pharmacodynamics

Antiviral Activity in Cell Culture

Temsavir exhibited antiviral activity against CCR5- (n=3; EC_{50} range 0.4 to 1.7 nM), CXCR4- tropic (n=5; EC_{50} range 0.7 to >2,000 nM) and dual/mixed-tropic (n=1; EC_{50} 58 nM) laboratory strains of subtype B HIV-1.

A total of 103 clinical isolates were examined for susceptibility to temsavir using peripheral blood mononuclear cells (PBMCs) as the host cell. These viruses spanned multiple Group M subtypes. In addition, 2 Group O viruses and one HIV-2 virus were tested for temsavir susceptibility. The cohort contained mostly CCR5- tropic viruses, but there were also some CXCR4-tropic and dual-tropic strains. For most of the subtypes, temsavir exhibited variable activity, with EC_{50} ranges for subtype A (n=13) 0.38 to >2,000 nM, subtype B (n=47) 0.01 to >2,000 nM, subtype B' (n=3) 4.2 to >2,000 nM, subtype C (n=17) <91 to >5,000 nM, subtype D (n=6) <0.46 to >2,000 nM, subtype F (n=2) 11.9 to >2,000 nM, subtype CRF01_AE (n=9) ≥1,814 to >2,000 nM and subtype G (n=3) 33.6 to >2,000 nM. However, both viruses examined from Group O and the lone HIV-2 virus all displayed no susceptibility to temsavir, while all nine viruses examined from subtype CRF01_AE showed significantly impaired susceptibility to temsavir at the highest concentration tested.

A total of 1337 isolates have been examined to date in the PhenoSense Entry Assay. These include viruses from all subjects in the Phase IIa (206267), Phase IIb (205889) and Phase III (205888) studies, plus other samples obtained from plasma samples of infected individuals. A total of 881 of these samples were from subtype B, 156 samples from subtype C, 43 samples from subtype A, 17 samples from subtype A1, 48 samples from subtype F1, 29 samples from subtype BF1 and 19 samples from subtype BF infected individuals. In addition, there were 5 CRF01_AE samples: four of these samples exhibited IC_{50} values above the maximum concentration of the assays used (100 nM or 5,000 nM), while one sample exhibited an IC_{50} of ~222.9 nM.

CRF_01_AE is classified as having intrinsic reduced susceptibility to temsavir based on available data and the presence of polymorphisms at positions S375H and M475I (see below).

Each of the subtypes displayed variable susceptibility to temsavir with a wide range in IC_{50} values from 0.018 nM to > 5,000 nM. For the subtype B viruses, IC_{50}s ranged from the low pM to > 5,000 nM.

The other subtypes had similar ranges. Geometric mean IC_{50}s ranged from 1.15 nM for subtype B virus to 34.91 nM for the BF1 subtype.

Antiviral activity against subtype AE

Within HIV-1 group M, temsavir showed significantly impaired antiviral activity against isolates of subtypes AE. Genotyping of the AE subtype virus identified polymorphisms at amino acid positions S375H and M475I in the gp120 domain, which was associated with reduced susceptibility to fostemsavir.

Subtype AE is a predominant subtype in Southeast Asia, but is not common elsewhere. At screening, two patients in the randomised cohort had subtype AE virus. One patient (EC_{50} fold-change > 4747-fold and gp120 substitutions at positions S375H and M475I at baseline) showed no response to fostemsavir at day 8. The second patient (EC_{50} fold-change 298-fold and gp120 substitution at position S375N at baseline) received placebo during functional monotherapy. Both patients had an HIV RNA of <40 copies/ml at week 96 while receiving fostemsavir plus OBT, which included dolutegravir.

Antiviral Activity in Combination with Other Antiviral Agents

No drugs with inherent anti-HIV activity were antagonistic with temsavir (in vitro assessments were performed in combination with abacavir, didanosine, zalcitabine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, zidovudine, efavirenz, nevirapine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, enfuvirtide, maraviroc, ibalizumab, delavirdine, rilpivirine, darunavir, dolutegravir or raltegravir). In addition, antivirals without inherent anti-HIV activity (entecavir, ribavirin) have no apparent effect on temsavir activity.

Resistance in vitro

HIV-1 variants with reduced susceptibility to temsavir were selected in cell culture following passage of NL4-3, LAI and BaL viruses in a T-cell line. Emerging amino acids in gp120 that reduced susceptibility were identified and included L116P/Q, A204D, M426L, M434I, and M475I (S375I/N substitutions were identified based on in vivo data with a related attachment inhibitor).

Single-substitution recombinant viruses were engineered into the HIV-1 LAI viral background, and the resultant recombinants were examined against temsavir (Table 3).

Table 3. Phenotypes of recombinant LAI viruses with clinically relevant gp120 substitutions

Substitutions	**Fold-Change vs Wild type EC50**
Wild type	1
S375H	48
S375I	17

S375M	47
S375N	1
S375T	1
S375V	5,5
S375Y	> 10000
M426L	81
M426V	3,3
M434I	11
M434T	15
M475I	4,8
M475L	17
M475V	9.5

Two other amino acid substitutions, L116P and A204D, located distal to the CD4 binding pocket of glycoprotein gp120, conferred high levels of resistance to temsavir in a LAI background (>340-fold decrease). However, both amino acids are strictly conserved within clinical envelope genes and these specific polymorphisms at these positions have not been observed clinically during treatment with fostemsavir.
Temsavir remained active against laboratory derived CD4-independent viruses.

Cross resistance
There was no evidence of cross-resistance to other ARVs. Temsavir retained wild-type activity against viruses resistant to tenofovir, abacavir, zidovudine, lamivudine, rilpivirine, atazanavir, darunavir and raltegravir and viruses resistant to enfuvirtide retained susceptibility to temsavir.
Both the CD4+ -targeted post-attachment inhibitor ibalizumab and the gp120-targeted pre-attachment inhibitor fostemsavir develop resistance-associated mutations in the gp120 domain. In clinical isolates, five of seven viruses with resistance to ibalizumab maintained susceptibility to temsavir, while the other two viruses showed reduced susceptibility to both temsavir (>1400-fold reduction in susceptibility) and ibalizumab.
Some CCR5-tropic, maraviroc-resistant viruses showed reduced susceptibility to temsavir. Additionally, maraviroc, ibalizumab and enfuvirtide retained activity against site-directed mutants with reduced susceptibility to temsavir, or against clinical envelopes that had low baseline susceptibility to temsavir and contained S375H, M426L, or M426L plus M475I substitutions.

Virologic response by genotype and phenotype in BRIGHTE
Results of the Phase III study (BRIGHTE [205888]) in heavily treatment-experienced adult subjects demonstrated that, overall, virologic response at Day 8 and subsequent timepoints (Weeks 24, 48,

and 96) in the Randomised Cohort was not reliably predicted by baseline temsavir IC_{50}-fold change value or the presence of a gp160 substitution of interest, as described below.

Temsavir IC_{50} FC >100-fold was associated with a median change in HIV-1 RNA from Day 1 to Day 8 of <0.5 log10 copies/mL. Similarly, the presence at baseline of pre-defined gp160 substitutions, identified as potentially important for determining phenotypic susceptibility to temsavir (S375H/I/M/N/T, M426L/P, M434I/K and M475I), was associated with a lower decline in HIV-1 RNA (Table 4). However, increased baseline temsavir IC_{50} FC, or the presence of pre-defined gp160 substitutions, did not preclude subjects from achieving a response of >0.5 log10 copies/mL at Day 8 (Tables 4 and 5). Indeed, 8 of 21 (38%) subjects with IC_{50} FC >100-fold did achieve a Day 8 response >0.5 log10 copies/mL and 7/21 (33%) subjects achieved a >1 log10 copies/mL decline in viral load. Subjects with no pre-defined gp160 substitutions present at baseline achieved a median change in HIV-1 RNA of -1.032 log10 copies/mL at Day 8, compared to -0.652 log_{10} copies/mL change in viral load in subjects with pre-defined gp160 substitutions present. Baseline gp160 substitutions most associated with response <0.5 log10 copies/mL at Day 8 were S375H/M, M426L and M475I.

Table 4: Virologic Response at Day 8 (Randomised Cohort) by Presence of gp160 Substitutions at Baseline (ITT-E Population)

		Randomised Cohort FTR 600 mg BID (N=203)[a]	
		Change in HIV-1 RNA from Day 1 to Day 8	
	n	**>0.5 Log_{10} Decline n (%)**	**Median Log_{10}**
No pre-defined gp160 substitutions at positions of interest	103	79 (77)	-1.032
Pre-defined gp160 substitutions (S375H/I/M/N/T, M426L, M434I, M475I)[b]	85	48 (56)	-0.652
S375H/I/M/N/T	61	38 (62)	-0.820
S375H	1	0	0.473
S375I	4	3 (75)	-0.928
S375M	5	1 (20)	-0.317
S375N	21	13 (62)	-0.735
S375Y[c]	2	1 (50)	-0.546
M426L	22	10 (45)	-0.364
M434I	9	5 (56)	-1.043
M475I	1	0	0.473
More than 1 pre-defined gp160 substitutions present	8	5 (63)	-1.175

a. 188 of 203 Randomised subjects had analysable results for each the following: baseline gp160 sequencing, Day 1 HIV-1 RNA, and Day 8 HIV-1 RNA.
b. No M426P or M434K substitutions were observed at baseline.
c. S375Y was not included in the list of substitutions pre-defined for analysis in the Phase III study, although it was subsequently identified as a novel polymorphism and shown to substantially decrease temsavir susceptibility in a LAI envelope in vitro.

Table 5: Virologic Response Category at Day 8 (Randomised Cohort) by Phenotype at Baseline (ITT-E Population)

Baseline Temsavir IC_{50} Fold Change Category	n	Randomised Cohort FTR 600 mg BID (N=203)[a]	
		Change in HIV-1 RNA from Day 1 to Day 8	
		>0.5 Log_{10} Decline n (%)	Median Log_{10}
IC_{50} FC value not reported	7	5 (71)	-1.324
0 – 1	95	71 (75)	-1.053
>1 – 10	52	36 (69)	-0.893
>10 – 100	20	11 (55)	-0.625
>100 - 1,000	10	4 (40)	-0.179
>1,000	11	4 (36)	-0.317

a. 195 of 203 Randomised subjects had analysable results for each the following: baseline gp160 sequencing, Day 1 HIV-1 RNA, and Day 8 HIV-1 RNA.

With the addition of an optimised background therapy, increased baseline temsavir IC_{50} FC, or the presence of pre-defined gp160 substitutions, did not influence durability of response (HIV-1 RNA <40 copies/mL) through Week 96.

The percentage of subjects who experienced virologic failure through the Week 96 analysis was 25% (69/272) in the randomised cohort. Overall, 50% (26/52) of the viruses of evaluable subjects with virologic failure in the Randomised Cohort had treatment-emergent gp120 genotypic substitutions at 4 key sites (S375, M426, M434, and M475). The median temsavir EC_{50} fold change at failure in randomised evaluable subject isolates with emergent gp120 substitutions at positions 375, 426, 434, or 475 (n = 26) was 1,755-fold compared to 3-fold for isolates with no emergent gp120 substitutions at these positions (n = 26). Of the 25 evaluable subjects in the Randomised Cohort with virologic failure and emergent substitutions S375N and M426L and (less frequently) S375H/M, M434I and M475I, 88% (22/25) had temsavir IC_{50} FC Ratio >3-fold (FC Ratio is temsavir IC_{50} FC on-treatment compared to baseline and FC Ratio >3-fold is outside of the usual variability observed in the PhenoSense Entry assay). Overall, 21/69 (30%) of the virus isolates of patients with virologic failure in the Randomised Cohort had genotypic or phenotypic resistance to at least one drug in the OBT at screening and in 48% (31/64) of the virologic failures with post-baseline data the virus isolates had emergent resistance to at least one drug in the OBT.

In the Non-randomised Cohort virologic failures were observed in 51% (50/99) through Week 96. While the proportion of viruses with gp120 resistance-associated substitutions at screening was similar between patients in the Randomised and Non-randomised Cohorts, the proportion of virus isolates with emergent gp120 resistance-associated substitutions at the time of failure was higher among Non-randomised patients (75% vs. 50%). The median temsavir EC_{50} fold change at failure in

Non-randomised evaluable subject isolates with emergent substitutions at positions 375, 426, 434, or 475 (n = 33) was 4,216-fold and compared to 402-fold for isolates without substitutions at these positions (n = 11). Of the 32 evaluable virologic failures in the Non-randomised Cohort with emergent substitutions S375N and M426L and (less frequently) S375H/M, M434I and M475I, 91% (29/32) had temsavir IC_{50} FC Ratio >3-fold. Overall, 45/50 (90%) of the viruses of patients with virologic failure in the Non-randomised Cohort had genotypic or phenotypic resistance to at least one drug in the OBT at screening and in 55% (27/49) of the virologic failures with post-baseline data the virus isolates had emergent resistance to at least one drug in the OBT.

Effects on Electrocardiogram

In a randomised, placebo- and active-controlled, double-blind, cross-over thorough QT study, 60 healthy subjects received oral administration of placebo, fostemsavir 1200 mg once daily, fostemsavir 2400 mg twice daily and moxifloxacin 400 mg (active control) in random sequence. Fostemsavir administered at 1200 mg once daily did not have a clinically meaningful effect on the QTc interval as the maximum mean time-matched (2-sided 90% upper confidence bound) placebo-adjusted QTc change from baseline based on Fridericia's correction method (QTcF) was 4.3 (6.3) milliseconds (below the clinically important threshold of 10 milliseconds). However, fostemsavir administered at 2400 mg twice daily for 7 days was associated with a clinically meaningful prolongation of the QTc interval as the maximum mean time-matched (2-sided 90% upper confidence bound) for the placebo-adjusted change from baseline in QTcF interval was 11.2 (13.3) milliseconds. Steady-state administration of fostemsavir 600 mg twice daily resulted in a mean temsavir C_{max} approximately 4.2-fold lower than the temsavir concentration predicted to increase QTcF interval 10 milliseconds (*see Warnings and Precautions)*.

Clinical efficacy

The efficacy of fostemsavir in HIV-infected, heavily treatment-experienced adult subjects is based on data from a Phase III, partially-randomised, international, double-blind, placebo-controlled trial (BRIGHTE [205888]).

The BRIGHTE study was conducted in 371 heavily-treatment experienced HIV-1 infected subjects with multi-class resistance. All subjects were required to have a viral load greater than or equal to 400 copies/mL and ≤2 antiretroviral classes remaining at baseline due to resistance, intolerability, contraindication, or other safety concerns. At Screening, subjects from the Randomised Cohort had one, but no more than two, fully active and available antiretroviral agents which could be combined as part of an efficacious background regimen. Within the Randomised Cohort, 272 subjects received either blinded fostemsavir, 600 mg twice daily (n= 203), or placebo (n= 69), in addition to their current failing regimen, for 8 days of functional monotherapy. Beyond Day 8, Randomised subjects received open-label fostemsavir, 600 mg twice daily, plus an optimised background therapy selected by the

Principal Investigator. The Randomised Cohort provides primary evidence of efficacy of fostemsavir. Within the Non-randomised Cohort, 99 subjects with no fully active and approved antiretroviral agents available at Screening, were treated with open-label fostemsavir, 600 mg twice daily, plus an optimised background therapy from Day 1 onward. The use of an investigational drug(s) as a component of the optimised background therapy was permitted in the Non-randomised Cohort.

Table 6: Summary of Demographic and Baseline Characteristics in BRIGHTE trial-ITT-E Population

		Randomised Cohort (N=272)	Non-Randomised Cohort (N=99)	TOTAL (N=371)
	Sex, n (%)			
Male		200 (74)	89 (90)	289 (78)
	Age (yrs[a])			
Median		48.0	50.0	49.0
≥ 65, n (%)		10 (4)	2 (2)	12 (3)
	Race, n (%)			
White		185 (68)	74 (75)	259 (70)
	Baseline HIV-1 RNA (log10 copies/mL)			
Median		4.7	4.3	4.6
	Baseline CD4+ (cells/mm^3)			
Median		99.5	41.0	80.0
	Baseline CD4+ (cells/mm^3), n (%)			
<20		72 (26)	40 (40)	112 (30)
<200		199 (72)	79 (79)	278 (75)
AIDS History, n (%)[b]				
Yes		231 (85)	89 (90)	320 (86)
	Number of Years Treated for HIV Infection, n (%)			
>15		182 (67)	80 (81)	262 (71)
	Number of Prior ART Regimens (including current failing regimen) n (%)			
5 or more		226 (83)	90 (91)	316 (85)
	Number fully active agents in their original OBT n (%)			
0		16 (6)	80 (81)	96 (26)
1		142 (52)	19 (19)[c]	161 (43)
2		114 (42)	0	114 (31)
	Number with history of hepatitis B and/or C co-infection			
n (%)		21 (8)	8 (9)	29 (8)

a. Age is imputed when full date of birth is not provided.
b. History of AIDS = Yes if a subject has Nadir CD4+ count <200 cells/mm^3, or if response to "Does subject have AIDS?" on Disease History CRF is Yes.
c. N=15 (15 %) received ibalizumab, which was an investigational agent at the start of BRIGHTE

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 vs. 0.17 log10 decline, respectively; p<0.0001, Intent To Treat-Exposed [ITT-E] population) (Table 7).

Table 7 Plasma HIV-1 RNA Log_{10} (copies/mL) Change from Day 1 at Day 8 (Randomised Cohort) in BRIGHTE trial – ITT-E 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.

At Day 8, 65% (131/203) and 46% (93/203) of subjects had a reduction in viral load from baseline > 0.5 log_{10} copies/mL and > 1 log_{10} copies/mL, respectively, in the fostemsavir group, compared with 19% (13/69) and 10% (7/69) of subjects, respectively, in the placebo group.

By subgroup analysis, fostemsavir-treated Randomised subjects with baseline HIV-1 RNA >1,000 copies/mL achieved a mean decline in viral load of 0.86 log_{10} copies/mL at Day 8, compared with 0.20 log_{10} copies/mL decline in subjects treated with blinded placebo. Subjects with baseline HIV-1 RNA ≤ 1,000 copies/mL achieved a mean decline in viral load of 0.22 log_{10} copies/mL at Day 8 compared with a mean increase of 0.10 log_{10} copies/mL in subjects treated with blinded placebo.

Virologic outcomes by ITT-E Snapshot Analysis at Weeks 24, 48 and 96 in the BRIGHTE trial (including outcomes by key baseline covariates) are shown in Table 8 for the Randomised Cohort. There was considerable variability in the antiretroviral agents included in the OBT regimens. The majority of subjects (84%) received dolutegravir as a component of OBT, of which approximately half (51% overall) also received darunavir with ritonavir or cobicistat.

Table 8 Virologic Outcomes (HIV-1 RNA <40 copies/mL) at Weeks 24, 48 and 96 with Fostemsavir (600 mg twice daily) plus Optimised Background Treatment (Randomised Cohort) in BRIGHTE trial (ITT-E Population, Snapshot Algorithm)

	Fostemsavir 600 mg twice daily		
	Week 24 (N = 272)	**Week 48 (N = 272)**	**Week 96 (N = 272)**
HIV-1 RNA <40 copies/mL	53%	54%	60%
HIV-1 RNA ≥40 copies/mL	40%	38%	30%
Data in window not <40 copies/mL	32%	26%	12%
Discontinued for lack of efficacy	<1%	2%	4%
Discontinued for other reasons while not suppressed	1%	3%	6%
Change in ART regimen	6%	7%	8%
No virologic data	7%	8%	10%

Reasons			
Discontinued study/study drug due to adverse event or death	4%	5%	6%
Discontinued study/study drug for other reasons	2%	3%	3%
Missing data during window but on study	1%	<1%	2%
HIV-1 RNA <40 copies/mL by Baseline Covariates n/N (%)			
Baseline Plasma viral load (copies/mL)			
<100,000	116 / 192 (60%)	118 / 192 (61%)	124 / 192 (65%)
≥100,000	28 / 80 (35%)	28 / 80 (35%)	39 / 80 (49%)
Baseline CD4+ (cells/mm^3)			
<20	23 / 72 (32%)	25 / 72 (35%)	33 / 72 (46%)
20 to <50	12 / 25 (48%)	12 / 25 (48%)	14 / 25 (56%)
50 to <200	59 / 102 (58%)	59 / 102 (58%)	62 / 102 (61%)
≥200	50 / 73 (68%)	50 / 73 (68%)	54 / 73 (74%)
Number of Fully Active and Available Antiretroviral (ARV) Classes in initial OBT			
0*	5 / 16 (31%)	5 / 16 (31%)	3 / 16 (19%)
1	80 / 142 (56%)	82 / 142 (58%)	92 / 142 (65%)
2	59 / 114 (52%)	59 / 114 (52%)	68 / 114 (60%)
Use of DTG and DRV as a component of OBT**			
DTG and DRV	68/117 (58%)	60/117 (51%)	75/117 (64%)
With DTG, without DRV	61/112 (54%)	67/112 (60%)	71/112 (63%)
Without DTG, with DRV	5/17 (29%)	8/17 (47%)	8/17 (47%)
Without DTG or DRV	10/26 (38%)	11/26 (42%)	9/26 (35%)
Gender			
Male	104 / 200 (52%)	102 / 200 (51%)	118 / 200 (59%)
Female	40 / 72 (56%)	44 / 72 (61%)	45 / 72 (63%)
Race			
White	90 / 185 (49%)	92 / 185 (50%)	103 / 185 (56%)
Black or African-American/Others	54 / 87 (62%)	54 / 87 (62%)	60 / 87 (69%)
Age (years)			
<50	81 / 162 (50%)	81 / 162 (50%)	96 / 162 (59%)
≥50	63 / 110 (57%)	65 / 110 (59%)	67 / 110 (61%)

N = Number of subjects in the Randomised Cohort. OBT = Optimised Background Therapy.
DTG = Dolutegravir, DRV = Darunavir.
* Includes subjects who never initiated OBT, were incorrectly assigned to the Randomised Cohort or had one or more active ARV agents available at screening but did not use these as part of the initial OBT.
** Darunavir was coadministered with ritonavir or cobicistat.

In the Randomised Cohort, viral load <200 HIV-1 RNA copies/mL was achieved in 68%, 69% and 64% of subjects at Weeks 24, 48 and 96, respectively. At these timepoints, the proportion of subjects with viral load <400 HIV-1 RNA copies/mL was 75%, 70% and 64%, respectively (ITT-E, Snapshot algorithm). Mean changes in CD4+ T-cell count from baseline continued to increase over time (i.e. 90 cells/mm^3 at Week 24, 139 cells/mm^3 at Week 48 and 205 cells/mm^3 at Week 96). Based on a sub-analysis in the Randomised Cohort, subjects with the lowest baseline CD4+ T-cell counts (<20 cells/mm^3) had a similar increase in CD4+ count over time compared with subjects with higher baseline CD4+ T-cell count (>50, >100, >200 cells/mm^3).

In the Non-randomised Cohort (subjects with no fully active and approved antiretroviral agents available at Screening), HIV-1 RNA <40 copies/mL was achieved in 37%, 38% and 37% of subjects

at Weeks 24, 48 and 96, respectively. At these timepoints, the proportion of subjects with HIV-1 RNA <200 copies/mL was 42%, 43% and 39%, and the proportion of subjects with HIV-1 RNA <400 copies/mL was 44%, 44% and 40%, respectively (ITT-E, Snapshot algorithm). Mean changes in CD4+ cell count from baseline increased over time: 41 cells/mm^3 at Week 24, 64 cells/mm^3 at Week 48 and 119 cells/mm^3 at Week 96.

Pharmacokinetics

The pharmacokinetics of temsavir following administration of fostemsavir are similar between healthy and HIV-infected subjects. Between-subject variability (%CV) in plasma temsavir C_{max} and AUC ranged from 22% to 50% and $C\tau$ from 50% to 127% across Phase I studies in healthy subjects. The magnitude of variability was similar in HIV infected subjects (%CV in plasma temsavir C_{max} and AUC ranged from 20.5% to 63% and $C\tau$ from 20% to 165%). Between-subject variability in oral clearance and central oral volume of distribution estimated from population pharmacokinetic analysis of healthy subjects from selected Phase I studies and HIV-1 infected patients were 43% and 48%, respectively.

Absorption

Fostemsavir is a highly soluble prodrug that is metabolized to temsavir by alkaline phosphatase at the luminal surface of the small intestine. The majority (98-99%) of plasma concentrations of fostemsavir were below the limit of detection following oral administration. The active moiety, temsavir, is rapidly absorbed and reaches maximum plasma concentrations after a median time (Tmax) of 2 hours post dose (fasted). The absolute bioavailability of temsavir was 26.9% following oral administration of a single 600 mg dose of fostemsavir.

Following oral administration, plasma temsavir exposure (C_{max} and AUC) increased slightly dose disproportionately over the range of 600 mg to 1,800 mg of fostemsavir. Temsavir is absorbed across the small intestine and cecum/proximal ascending colon.

Pharmacokinetic parameters following multiple oral doses of fostemsavir 600 mg twice daily in healthy and HIV-1 infected, heavily-treatment experienced adult subjects are shown in Table 9.

Table 9 Multiple-Dose Pharmacokinetic Parameters of Temsavir following oral administration of Fostemsavir 600 mg twice daily

Parameter Mean (CV%)	Healthy subjects[a]	Heavily Treatment-Experienced HIV-1 infected subjects[b]
C_{max} (μg/mL)	1.64 (45)	1.77 (39.9)
AUC (μg.hr/mL)	9.70 (42)	12.90 (46.4)
C_{12} (μg/mL)	0.312 (45)	0.478 (81.5)

a. With a standard meal.

b. Based on population pharmacokinetic analyses with or without food, in combination with other antiretroviral drugs. CV = Coefficient of Variation.

Effect of Food

Temsavir bioavailability (AUC) was not impacted by a standard meal (approximately 423 kcal, 36% fat) but increased 81% with a high-fat meal (approximately 985 kcal, 60% fat). This increase is not considered clinically significant. Regardless of calorie and fat content, food had no impact on plasma temsavir C_{max}.

Distribution

Temsavir is approximately 82-88% bound to human plasma proteins based on in vivo data. Human serum albumin is the major contributor to plasma protein binding of temsavir in humans. The volume of distribution of temsavir at steady state (Vss) following intravenous administration is estimated at 29.5 L. The blood-to-plasma total radiocarbon C_{max} ratio was approximately 0.74, indicating minimal association of temsavir or its metabolites with red blood cells.

Metabolism

Temsavir is extensively metabolized, accounting for the fact that only 3% of the administered dose is recovered in human urine and faeces. In vivo, temsavir is primarily metabolised via esterase hydrolysis to BMS-646915 and to further secondary metabolites (36.1% of administered dose) and secondarily oxizided by CYP3A4 oxidation to BMS-930644 and to further secondary metabolites (21.2% of administered dose). Other non-CYP3A4-mediated metabolic pathways contribute to the elimination of 7.2% of the administered dose. Glucuronidation is a minor metabolic pathway (<1% of administered dose). The metabolites BMS-646915 (a product of hydrolysis) and BMS-930644 (a product of N-dealkylation) are the main metabolites in plasma.

Elimination

Temsavir has a terminal half-life of approximately 11 hours. Plasma clearance of temsavir following intravenous administration was 17.9 L/hr, and the apparent clearance (CL/F) following oral dosing was 66.4 L/hr. After oral administration of a single 300 mg dose of ^{14}C-labeled fostemsavir in a human mass balance study, 51% and 33% of the radioactivity, mainly in the form of metabolites, was retrieved in the urine and faeces, respectively. Based on limited bile collection in this study (3 to 8 hours post dose), biliary clearance accounted for 5% of the radioactive dose, suggesting that a fraction of faecal excretion is from biliary excretion.

Kinetics in specific patient groups

Hepatic impairment

The effect of hepatic impairment on the exposure of temsavir after a single 600 mg dose of fostemsavir was evaluated in an open-label study in 30 adult subjects with normal (n=12), mild (Child-Pugh Score A, n=6), moderate (Child- Pugh Score B, n=6), and severe (Child-Pugh Score C, n=6) hepatic impairment. Total and unbound temsavir exposures increased with increasing severity of hepatic impairment classified by Child-Pugh classes. In comparison to subjects with normal hepatic function, unbound temsavir AUC values are increased to 1.3-fold, 1.6-fold and 2.2-fold in subjects with mild, moderate and severe hepatic impairment, respectively. Free fraction of temsavir in plasma was higher for subjects with severe hepatic impairment (23%) than subjects with normal hepatic function (18%), mild (20%) or moderate (18%) hepatic impairment.

Renal impairment

The effect of renal impairment on the exposure of temsavir after a single 600 mg dose of fostemsavir was evaluated in an open-label study in 30 adult subjects with normal renal function, mild, moderate, and severe renal impairment, and subjects with ESRD or haemodialysis (n=6 per group). Classification of renal function was based on estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2), as follows: 60 ≤eGFR ≤89 (mild), 30 ≤eGFR <60 (moderate), eGFR <30 (severe, and ESRD with haemodialysis). In comparison to subjects with normal renal function, unbound TMR AUC values are increased to 1.06-fold, 1.12-fold and 1.15-fold in subjects with mild, moderate and severe renal impairment, respectively, and to 1.32-fold in subjects with end stage renal disease (ESRD) under dialysis. Free fraction of temsavir in plasma was higher for subjects with severe renal impairment (19%) compared with normal renal function (12%), mild (12%) or moderate (13%) renal impairment, and ESRD (16%). Fostemsavir may be administered to patients with ESRD without regard to time of haemodialysis because temsavir was not readily cleared by haemodialysis, with approximately 12.3% of the administered dose removed during the 4-hour haemodialysis session. Haemodialysis initiated 4 hours after temsavir dosing was associated with an average 46% increase in plasma total temsavir C_{max} and an average 11% decrease in AUC relative to pharmacokinetics off haemodialysis.

Elderly patients

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. Pharmacokinetic data for temsavir in subjects aged 65 years and older are limited. Of the 764 subjects included in the analysis, 11 subjects

(1.4%) were ≥65 years of age. Elderly patients may be more susceptible to drug-induced QT interval prolongation (*see Warnings and Precautions)*.

Children and adolescents
The pharmacokinetics of temsavir have not been evaluated in children younger than 18 years.

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

Race
Population pharmacokinetic analyses indicated no clinically relevant effect of race on the exposure of temsavir. Of the 764 subjects included in the analysis, 490 (64%) were White, 177 (23%) were Black/African American, 5 (1%) were Asian, and 92 (12%) were of other race.

Co-infection with Hepatitis B or C
Pharmacokinetic data for temsavir in patients co-infected with hepatitis B and/or C virus are limited. Of the 364 subjects with temsavir pharmacokinetic data available in the Phase III study, 29 (8%) were co-infected with hepatitis B and/or C virus.

Preclinical data

Long-term toxicity (or repeat dose toxicity)

Fostemsavir has been evaluated in repeat dose toxicity studies in rats (up to 26 weeks) and in dogs (up to 39 weeks). In rats, effects were observed on the adrenal glands (angiectasis, increased gland size and weight), testicles (degeneration of seminiferous epithelium, decreases in sperm motility and sperm morphologic alterations) and kidneys (decreases in urine pH, renal tubular dilatation, increase kidney weight and urine volume) at systemic exposures ≥70 times the human clinical exposure based on AUC at 600 mg twice daily (MRHD). In dogs, liver toxicity (hepatic canalicular bile pigment deposits and lipofuscin pigment deposits in Kupffer cells) was observed at systemic exposures ≥6 times the human exposure at the MRHD.

Mutagenicity

Neither fostemsavir nor temsavir were mutagenic or clastogenic using in vitro tests in bacteria and cultured mammalian cells and an in vivo rat micronucleus assay.

Carcinogenicity

Fostemsavir was not carcinogenic in long term, oral gavage administration studies in the mouse (following 26 weeks of dosing) and rat (following 100 weeks of dosing). The systemic exposure multiples (based on MHRD) in mice ranged from 1.6 to 17.4 in males based on doses of 25 to 200 mg/kg/day, and 2.9 to 36.7 in females based on doses of 30 to 300 mg/kg/day. The systemic exposure multiples (based on MHRD) in rats ranged from 4.1 to 17.1 in males based on doses of 5 to 20 mg/kg/day, and 11.3 to 107 in females based on doses of 10 to 100 mg/kg/day.

Reproductive Toxicology

Fertility

Oral administration of fostemsavir had no adverse effects on fertility in rats at doses up to 300 mg/kg/day in males and 600 mg/kg/day in females (this is equivalent to >95 times the MRHD based on AUC). Effects in males included dose-dependent gross and microscopic pathological findings in the testes and epididymides, reductions in prostate gland/seminal vesicle weights, and decreased sperm density (at >70 times the MRHD), with decreased motility and increased abnormal sperm. In male rats the reproductive NOAEL is found at 10 mg/kg/day (7-fold of human exposure at the MRHD).

Embryo-fetal development

Following oral administration of fostemsavir to pregnant rats during organogenesis at 600 mg/kg/day and when fostemsavir was administered at oral doses up to 300 mg/kg/day through pregnancy and lactation (>90 times the human exposure at the MRHD) no adverse effects were observed on pregnancy, delivery or foetal and early offspring development. However, oral administration of fostemsavir to pregnant rats did result in foetal abnormalities (cleft palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw and protruding tongue) and reductions in foetal body weights in the presence of maternal toxicity (reductions in body weights and food consumption) when dosed at 1000 mg/kg/day (>180 times the human exposure at the MRHD).

No adverse effects on embryonic survival and foetal weights were evident following oral administration of fostemsavir to pregnant rabbits during organogenesis at 50 mg/kg/day (>24 times the human exposure at the MRHD). Decreases in foetal body weights and embryonic deaths were evident at >50 times the exposure at the MRHD.

Oral administration of fostemsavir from 250 mg/kg/day (>100-fold of human exposure to MRHD) to pregnant rabbits resulted in severe maternal toxicity (deaths and inappetence, body weight loss) while at 100 mg/kg/day increased embryonic death in the presence of maternal toxicity (transient inappetence and decreased weight gain) was observed.

In a distribution study in pregnant rats, fostemsavir-derived radioactivity (i.e. temsavir and/or temsavir derived metabolites) crossed the placenta and was detectable in milk and foetal tissue.

Pre- and postnatal development

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

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C. Store in the original packaging. Keep out of the reach of children.

Authorisation number

67854 (Swissmedic)

Packs

Rukobia: 60 film-coated tablets

Marketing authorisation holder

ViiV Healthcare GmbH, 3053 Münchenbuchsee

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