RUKOBIA
Professional Information (PI)

SCHEDULING STATUS:

S4

1. NAME OF MEDICINE:

RUKOBIA

Prolonged-release tablets

(600 mg fostemsavir)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains 600 mg of fostemsavir (as fostemsavir tromethamine).

Sugar-free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Prolonged release tablets.

Beige, film-coated, biconvex, oval tablets which may have a slight odour (vinegar-like), debossed with ‘SV 1V7’ on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

4.2 Posology and method of administration:

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Posology:

Adults: The recommended dosage of RUKOBIA is 600 mg orally twice daily.

Method of administration:

RUKOBIA can be taken with or without food.

RUKOBIA tablets should be swallowed whole, and should not be chewed, crushed, or split.

If the patient misses a dose of RUKOBIA, the patient should take it as soon as they remember, if it is more than 12 hours until the next dose. If the next dose is due within 12 hours, the patient should skip the missed dose and resume the usual dosing schedule.

Special populations:

Elderly: There are limited data available on the use of RUKOBIA in patients aged 65 years and older and should be used with caution (see section 5.2).

Renal impairment: No dosage adjustment of RUKOBIA is required for patients with renal impairment and those on haemodialysis (see section 5.2).

Hepatic impairment: No dosage adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population:

RUKOBIA should not be given to adolescents and children below 18 years of age, due to lack of safety and efficacy data.

4.3 Contraindications:

RUKOBIA is contraindicated in patients who have demonstrated hypersensitivity to fostemsavir or any excipient in the formulation of RUKOBIA (see section 6.1).

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) (see section 4.5).

4.4 Special warnings and precautions for use:

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 of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. 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 Clinical Pharmacology). RUKOBIA should be used with caution in patients with a history of QT interval prolongation, when co-administered with a medicine with a known risk of Torsade de Pointes (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, or sotalol) or in patients with relevant pre-existing cardiac disease. Elderly patients may be more susceptible to medicine-induced QT interval prolongation.

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 medical practitioners 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:

Caution should be given to co-administering medicines (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 section 4.3 and section *4.5*). Increased exposure to temsavir may increase the risk of QTc interval prolongation (see QTc interval prolongation and Clinical Pharmacology).

Co-administration of RUKOBIA with elbasvir/grazoprevir is not recommended as increased grazoprevir concentrations may increase the risk of ALT elevations (see section 4.5).

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 section 4.5).

When RUKOBIA was co-administered with oral contraceptives, temsavir increased concentrations of ethinyl oestradiol and caution is advised particularly in patients with additional risk factors for thromboembolic events. Doses of oestrogen-based therapies, including oral contraceptives, should not contain more than 30 µg of ethinyl estradiol per day in patients who are receiving fostemsavir (see section 4.5).

4.5 Interactions with other medicines and other forms of interaction:

Effect of Fostemsavir on the Pharmacokinetics of Other Medicines:

Significant interactions are not expected when fostemsavir is co-administered with substrates of cytochrome P_{450} (CYPs), uridine diphosphate glucuronosyl transferases (UGTs), 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, organic cation transporters (OCT)1, and OCT2 based on *in vitro* and clinical interaction data.

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 affect the pharmacokinetics of medicines that are substrates of OATP1B1/3 or BCRP (e.g. rosuvastatin, atorvastatin, simvastatin, pitavastatin and fluvastatin). Therefore, dose modifications and/or careful titration of dose is recommended for certain statins.

Based on *in vitro* data, temsavir and its two metabolites (BMS-930644 and BMS-646915) inhibited multidrug and toxin extrusion protein (MATE)1/2K. However, this interaction is unlikely to be of clinical significance.

BMS-930644, a metabolite of temsavir, inhibited CYP3A4, BCRP, MATE2K, and OCT1 with IC_{50} values < 10 µM. However, as circulating concentrations of BMS-930644 are low [C_{max} of approximately 458 ng/ml (~1 µM) with RUKOBIA 600 mg twice daily], clinically significant interactions are unlikely.

Effect of Other Medicines on the Pharmacokinetics of Temsavir:

Temsavir is a substrate of P-gp and BCRP, but not of OATP1B1 or OATP1B3. Its biotransformation to two circulating 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. However, because of the primary esterase metabolism pathway, effects are expected to be less than that of substrates primarily metabolized by CYP3A4. When RUKOBIA 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 RUKOBIA is co-administered with other strong CYP3A inducers and may result in loss of virologic response (see section 4.3).

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

Selected medicine interactions are presented in Table 1. Recommendations are based on either medicine 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 Medicine Interactions

Concomitant Medicine Class: Medicine Name	Effect on Concentration of temsavir or Concomitant Medicine	Clinical Comment
HIV-1 Antiviral Medicines		
Entry Inhibitor: Maraviroc (MVC)	Temsavir ↔ C_{max} ↑ 13 % AUC ↑ 10% Cτ ↓ 10% MVC ↔ AUC ↑ 25 % C_{max} ↑ 1 % Cτ ↑ 3 7%	No dose adjustment of either medicine is necessary.
Integrase Inhibitor: Raltegravir (RAL)	Temsavir ↔* RAL ↔*	No dose adjustment of either medicine is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Temsavir ↓	This interaction has not been studied. Efavirenz is expected to decrease temsavir plasma concentrations with no clinically relevant impact. No dose adjustment is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR) without boosted protease inhibitors	Temsavir ↓ AUC ↓ 50 % C_{max} ↓ 48 % Cτ ↓ 52 % ETR ↔	Etravirine decreased temsavir plasma concentrations. As this decrease was not clinically relevant, no dose adjustment of either medicine is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine (NVP)	Temsavir ↓	This interaction has not been studied. Nevirapine is expected to decrease temsavir plasma concentrations with no clinically relevant impact. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of temsavir or Concomitant Medicine	Clinical Comment
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDF)	Temsavir ↔ AUC ↔ C_{max} ↓ 1 % Cτ ↑ 13 % TDF ↑ AUC ↑ 19 % C_{max} ↑ 18 % Cτ ↑ 28 %	No dose adjustment of either medicine is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir alafenamide (TAF)	TAF ↑	This interaction has not been studied. Temsavir is expected to increase tenofovir alafenamide plasma concentrations with no clinically relevant impact. Consult the full prescribing information for TAF-containing medicines when co-administered.
Pharmacokinetic Enhancer: Cobicistat (COBI)	Temsavir ↑ AUC ↑ 93 % C_{max} ↑ 71 % Cτ ↑ 136 %	Cobicistat increased temsavir plasma concentrations with no clinically relevant impact. No dose adjustment is necessary.
Pharmacokinetic Enhancer: Ritonavir	Temsavir ↑ AUC ↑ 45 % C_{max} ↑ 53 % Cτ ↑ 44 % RTV ↔	Ritonavir increased temsavir plasma concentrations with no clinically relevant impact. No dose adjustment of either medicine is necessary.
Protease Inhibitor: Atazanavir (ATV)/ritonavir (RTV)	Temsavir ↑ AUC ↑ 54 % C_{max} ↑ 68 % Cτ ↑ 57 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased temsavir concentrations with no clinically relevant impact. No dose adjustment of either medicine is necessary.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of temsavir or Concomitant Medicine	Clinical Comment
Protease Inhibitor: Darunavir (DRV)/cobicistat	Temsavir ↑ AUC ↑ 97 % C_{max} ↑ 79 % Cτ ↑ 124 %	Darunavir/cobicistat increased temsavir plasma concentrations with no clinically relevant impact. No dose adjustment is necessary.
Protease Inhibitor: Darunavir (DRV)/ritonavir	Temsavir ↑ AUC ↑ 63 % C_{max} ↑ 52 % Cτ ↑ 88 % DRV ↔ AUC ↓ 6 % C_{max} ↓ 2 % Cτ ↓ 5 % RTV ↔ AUC ↑ 15 % C_{max} ↔ Cτ ↑ 19 %	Darunavir/ritonavir increased temsavir plasma concentrations with no clinically relevant impact. No dose adjustment is necessary for any medicine when co-administered.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of temsavir or Concomitant Medicine	Clinical Comment
Protease Inhibitor: Darunavir (DRV)/ritonavir + Etravirine	Temsavir ↑ AUC ↑ 34 % C_{max} ↑ 53 % Cτ ↑ 33 % Darunavir ↓ AUC ↓ 6 % C_{max} ↓ 5 % Cτ ↓ 12 % Ritonavir ↑ AUC ↑ 9 % C_{max} ↑ 14 % Cτ ↑ 7 % Etravirine ↔ AUC ↑ 28 % C_{max} ↑ 18 % Cτ ↑ 28 %	Darunavir/ritonavir co-administered with etravirine increased temsavir plasma concentrations with no clinically relevant impact. No dose adjustment is necessary for any medicine when co-administered.
Other Medicines		
Buprenorphine/naloxone	Buprenorphine ↔ AUC ↑ 30 % C_{max} ↑ 24 % Norbuprenorphine ↔ AUC ↑ 39 % C_{max} ↑ 24 %	No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of temsavir or Concomitant Medicine	Clinical Comment
Methadone	Methadone ↔ R-Methadone AUC ↑ 13 % C_{max} ↑ 15 % S-Methadone AUC ↑ 15 % C_{max} ↑ 15 %	No dose adjustment is necessary.
H_2-Receptor Antagonists: Famotidine	Temsavir ↔ AUC ↑ 4 % C_{max} ↑ 1 % Cτ ↓ 10 %	No dose adjustment is necessary when combined with medicines that decrease gastric pH.
Oral contraceptives: Ethinyl estradiol (EE)	EE ↑ AUC ↑ 39 % C_{max} ↑ 40 %	Ethinyl oestradiol should not exceed 30 µg daily. Caution is advised particularly in patients with additional risk factors for thromboembolic events (see section 4.4).
Norethindrone acetate (NE)	NE ↔ AUC ↑ 8 % C_{max} ↑ 8 %	No dose adjustment is necessary.
Rifabutin	Temsavir ↓ AUC ↓ 30 % C_{max} ↓ 27 % Cτ ↓ 41 %	Rifabutin decreased temsavir plasma concentrations with no clinically relevant impact. No dose adjustment is necessary.
Rifabutin + Ritonavir	Temsavir ↑ AUC ↑ 66 % C_{max} ↑ 50 % Cτ ↑ 158 %	Rifabutin co-administered with ritonavir increased temsavir plasma concentrations with no clinically relevant impact. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of temsavir or Concomitant Medicine	Clinical Comment
Rifampicin	Temsavir ↓ AUC ↓ 82 % C_{max} ↓ 76 %	May lead to loss of virologic response to fostemsavir due to significant decreases in temsavir plasma concentrations caused by strong CYP3A induction. Therefore, the concomitant use of RUKOBIA and rifampicin is contraindicated. Although not studied, concomitant use of RUKOBIA and other strong CYP3A4 inducers is contraindicated. These include but are not limited to carbamazepine, phenytoin (anticonvulsants); mitotane (antineoplastic); enzalutamide (androgen receptor inhibitor); St. John's wort (*Hypericum perforatum*, herbal supplement).
HMG CO-A Reductase Inhibitors: Rosuvastatin Atorvastatin Pitavastatin Fluvastatin Simvastatin	Rosuvastatin ↑ AUC ↑ 69 % C_{max} ↑ 78 %	Co-administration of RUKOBIA increases rosuvastatin plasma concentrations caused by OATP1B1/3 and/or BCRP inhibition by temsavir. Use the lowest possible starting dose of rosuvastatin with careful monitoring. 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.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of temsavir or Concomitant Medicine	Clinical Comment
Hepatitis C Virus Direct-Acting Antivirals (HCV DAAs): Elbasvir/Grazoprevir	Grazoprevir ↑	This interaction has not been studied. Temsavir may increase grazoprevir plasma concentrations to a clinically relevant extent caused by OATP1B1/3 inhibition by temsavir. Co-administration of RUKOBIA 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 ↑	Although not studied, temsavir may increase plasma concentrations of other HCV DAAs with no clinically relevant impact. 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.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

The effect of RUKOBIA on human pregnancy is unknown.

Temsavir was shown to cross the placenta in an animal distribution study after dosing with radiolabelled fostemsavir and was found in foetal brain tissue.

RUKOBIA should not be used during pregnancy.

Breastfeeding:

Temsavir is likely to be secreted into breastmilk based on animal data, although this has not been confirmed in humans. Fostemsavir was associated with decreased pup survival during the peak lactation period in an animal study at exposures substantially higher than for the therapeutic dose. HIV-infected women should not take RUKOBIA when breastfeeding their infants.

Fertility:

There are no data on the effects of fostemsavir on human male or female fertility. Animal studies indicate no effects of RUKOBIA on male or female fertility at clinically relevant doses.

4.7 Effects on ability to drive or use machines:

There have been no studies to investigate the effect of RUKOBIA on driving performance or the ability to operate machinery. However, RUKOBIA causes dizziness and insomnia which can affect the ability to drive and operate machinery. 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.

4.8 Undesirable effects:

Clinical trial data:

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

The safety and tolerability of the recommended dose of RUKOBIA was evaluated in a Phase III, partially randomised, double-blind, placebo-controlled trial conducted in 371 heavily treatment-experienced adult subjects (*see Clinical Studies*). 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 (OBT). In the non-randomised Cohort, 99 subjects received open label fostemsavir, 600 mg twice daily, plus OBT from Day 1 onward.

Adverse 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 reactions listed, it is unclear whether they are related to RUKOBIA, 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 RUKOBIA

System	Frequency	Adverse Reactions
Immune system disorders	Common	Immune Reconstitution Inflammatory Syndrome[1] (*see section 4.4*)
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness, neuropathy peripheral[2], somnolence, dysgeusia
Cardiac disorders	Common	Electrocardiogram QT prolonged[3] (*see section 4.4*)
Gastrointestinal disorders	Very common	Diarrhoea, nausea, abdominal pain[4], vomiting
	Common	Dyspepsia
Hepatobiliary disorders	Common	Transaminases increased[5,6]
Skin and subcutaneous tissue disorders	Very common	Rash[7]
	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 RUKOBIA, which were mainly mild or moderate. These changes were rarely associated with musculoskeletal complaints and are not considered clinically relevant.

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 RUKOBIA and elevation in serum creatinine has not been established.

Increases in direct (conjugated) bilirubin have been observed following treatment with RUKOBIA. 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. *In vitro*, temsavir and its metabolites inhibit OATP1B1 and OATP1B3; two well-recognized transporters of direct and indirect (unconjugated) bilirubin (see Section 4.5). Fostemsavir may contribute to elevations in bilirubin when co-administered with other medicines known to cause hyperbilirubinemia, or when dosed in patients with liver disease or who otherwise have reduced activity of hepatic transport proteins, including patients with HIV infection.

Post-marketing data:

No data available.

Reporting of adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form', found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms and signs:

There is currently limited experience of overdosage with RUKOBIA.

Treatment:

There is no specific treatment for overdose with RUKOBIA. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As 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 poison centre, where available.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category A 20.2.8 Antiviral agents

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 viral entry into, and infection of, 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).

Antiviral Activity in Cell Culture:

Temsavir exhibited potent antiviral activity against eight of nine CCR5- and CXCR4-tropic laboratory strains of subtype B HIV-1, with EC_{50} values ranging from 0,4 to 58 nM. Only the CXCR4-tropic strain HIV-1 RF exhibited reduced susceptibility to temsavir (EC_{50} > 2 000 nM).

In one study, a total of 103 clinical isolates were examined for susceptibility to temsavir using PBMCs as the host cell. These viruses spanned multiple Group M subtypes, including A, B, B', C, D, F, CRF01_AE and G. In addition, 2 Group O viruses and 1 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 potent but variable activity regardless of tropism. However, all nine viruses examined from subtype CRF01_AE, both viruses examined from Group O and one HIV-2 virus all displayed reduced susceptibility to temsavir at the highest concentration tested.

In another study, 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 10 µM), while one sample exhibited an IC_{50} of ~222 nM. Of all isolates tested, 53,8 % and 80,1 % exhibited IC_{50}s < 1 nM, and < 10 nM, respectively, for all subtypes. Each of the subtypes displayed wide ranges of susceptibility to temsavir. For the subtype B viruses, IC_{50}s ranged from the low pM to > 10 µM. 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. These results demonstrate there is a large range of intrinsic susceptibility to temsavir in pre-treatment envelopes within the population.

Antiviral Activity in Combination with Other Antiviral Medicines:

No medicines 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.

Effect of Human Serum and Serum Proteins:

In vitro studies showed no significant serum effect. Infection of PM1 or MT-2 cells with laboratory strains HIV-1 LAI and HIV-1 NL4-3 demonstrated that the presence of 40 % human serum decreased the anti-HIV potency of temsavir by 1,5 - 2,1-fold.

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. Substitution M426L was associated with an 81-fold decrease in temsavir sensitivity for the recombinant virus, while a M434I or M475I change displayed a moderate effect on sensitivity to the inhibitor (11- and 4,8-fold decrease, respectively). Two other amino acid substitutions, L116P and A204D, located distal to the CD4 binding pocket of gp120, conferred high levels of resistance to temsavir in an 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. Treatment with fostemsavir is therefore unlikely to promote resistance to temsavir via generation of CD4 independent virus.

There was no evidence of cross-resistance to other ARVs including other HIV-1 entry inhibitors. Temsavir retained wild-type activity against viruses resistant to tenofovir, abacavir, zidovudine, lamivudine, rilpivirine, atazanavir, darunavir and raltegravir and all viruses resistant to ibalizumab and enfuvirtide retained full susceptibility to temsavir.

Although some CCR5-tropic, maraviroc-resistant viruses showed cross-resistance to temsavir, there was no absolute correlation. 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.

Resistance in vivo:

Results of the Phase III study 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.

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 c/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. However, increased baseline temsavir IC_{50} FC, or the presence of pre-defined gp160 substitutions, did not preclude subjects from achieving a response of > 1 log10 c/ml at Day 8. Indeed, 8 of 21 (38 %) subjects with IC_{50} FC > 100-fold did achieve a Day 8 response > 0,5 log10 c/ml and 7/21 (33 %) subjects achieved a > 1 log10 c/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 c/ml at Day 8, compared to -0,652 log_{10} c/ml change in viral load in subjects with pre-defined gp160 substitutions present. Baseline gp160 substitutions most associated with response < 0,5 log10 c/ml at Day 8 were S375H/M/N and M426L.

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 c/ml) through Week 96. These results demonstrate that response to fostemsavir, as determined by baseline virologic factors, is highly context dependent.

The percentage of randomised subjects who experienced protocol defined virologic failure (PDVF) was 11 % (31/272) through Week 24, 18 % (49/272) through Week 48, and 23 % (63/272) through Week 96. The criteria for PDVF were as follows: HIV-1 RNA confirmed, or last available prior to discontinuation, ≥ 400 c/ml at any time after prior confirmed suppression to < 400 c/ml, or confirmed, or last available, > 1 log10 c/ml increase in HIV-1 RNA at any time above nadir level where nadir is ≥ 40 c/ml (prior to Week 24); HIV-1 RNA confirmed, or last available, ≥ 400 c/ml (at or after Week 24). In the PDVF population through Week 96, 48 % (24/50) of evaluable randomised subjects had treatment-emergent gp160 genotypic substitutions of interest. Most frequently, there was emergence of M426L (32 %), S375N (26 %), M475I (12 %) and M434I (10 %).

Median increase in temsavir IC_{50} FC among randomised subjects meeting PDVF criteria was 1,67-fold; 37 % (19/51) of evaluable subjects had temsavir IC_{50} FC ≤ 10-fold and 49 % (25/51) had temsavir IC_{50} FC ≤ 100-fold at the time of virologic failure, indicating that a proportion of subjects likely retained phenotypic susceptibility to temsavir, despite meeting virologic failure criteria (temsavir IC_{50} FC is normalised to a 1nM reference virus and is therefore approximately equal to temsavir IC_{50} expressed in nM). Approximately 30 % (17/63) of randomised subjects who met PDVF were subsequently able to achieve virologic suppression to < 40 c/ml.

There were only two subjects with subtype AE virus at screening in the randomised cohort. One subject (IC_{50} FC > 4747-fold and gp160 substitutions at S375H and M475I at baseline) did not respond to fostemsavir at Day 8. A second subject (IC_{50} FC 298-fold and gp160 substitution at S375N at baseline) received placebo during functional monotherapy. Both subjects were virologically suppressed at Week 96, while receiving fostemsavir plus optimised background therapy.

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 1 200 mg once daily did not have a clinically meaningful effect on the QTc interval as the maximum mean time-matched (2-sided 90 % upper confidence bound) placebo-adjusted QTc change from baseline based on Fridericia's correction method (QTcF) was 4,3 (6,3) milliseconds (below the clinically important threshold of 10 milliseconds). However, fostemsavir administered at 2 400 mg twice daily for 7 days was associated with a clinically meaningful prolongation of the QTc interval as the maximum mean time-matched (2-sided 90 % upper confidence bound) for the placebo-adjusted change from baseline in QTcF interval was 11,2 (13,3) milliseconds. Steady-state administration of 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 section 4.4).

5.2 Pharmacokinetic properties:

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 and is generally not detectable in plasma following oral administration. The active moiety, temsavir, is readily absorbed with the median time to maximal plasma concentrations (T_{max}) at 2 hours post dose (fasted). Following oral administration, increases in plasma temsavir exposure (C_{max} and AUC) appeared dose proportional, or slightly greater than dose proportional, 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 3.

Table 3 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 medicines.
CV = Coefficient of Variation.

The absolute bioavailability of temsavir was 26,9 % following oral administration of a single 600 mg dose of fostemsavir.

Effect of Food:

Fostemsavir may be administered with or without 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) and is not considered clinically significant. Regardless of calorie and fat content, food had no impact on plasma temsavir C_{max}.

Distribution:

Temsavir is approximately 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. Ex vivo, the blood-to-plasma ratio (determined at 300, 1000, and 10 000 nanogram/ml) ranged from 0,785 to 0,963 [overall mean (SD) 0,869 ± 0,0599] with no apparent concentration dependence in the concentration range tested. Free fraction of temsavir in plasma was approximately 12 to 18 % in healthy subjects, 23 % in subjects with severe hepatic impairment, and 19 % in subjects with severe renal impairment and 12 % in HIV-1 infected patients.

Metabolism:

In vivo, temsavir is primarily metabolised via esterase hydrolysis (36,1% of administered dose) and secondarily by CYP3A4-mediated oxidative (21,2 % of administered dose) pathways. Other non-CYP3A4 metabolites account for 7,2 % of the administered dose. Glucuronidation is a minor metabolic pathway (< 1 % of administered dose).

Temsavir is extensively metabolized, accounting for the fact that only 3 % of the administered dose is recovered in human urine and faeces. Temsavir is biotransformed into two predominant circulating inactive metabolites, BMS-646915 (a product of hydrolysis) and BMS-930644 (a product of N-dealkylation). Medicines that are strong inducers of CYP3A are contraindicated with fostemsavir (see section 4.2 and Section 4.5).

Elimination:

Temsavir has a terminal half-life of approximately 11 hours. Plasma temsavir clearance 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 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.

Special patient populations:

Children:

The pharmacokinetics of temsavir have not been evaluated in children younger than 18 years (see section 4.4).

Elderly:

Population pharmacokinetic analysis of temsavir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on temsavir exposure. Pharmacokinetic data for temsavir in subjects aged 65 years and older are limited. Elderly patients may be more susceptible to drug-induced QT interval prolongation (see section 4.4).

Renal impairment:

No dosage adjustment of fostemsavir is required for patients with mild, moderate, or severe renal impairment and for patients with end stage renal disease (ESRD). 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 on haemodialysis (n = 6 per group). Classification of renal function was based on estimated glomerular filtration rate (eGFR), as follows: 60 ≤ eGFR ≤ 89 (mild), 30 ≤ eGFR < 60 (moderate), eGFR < 30 (severe, and ESRD on haemodialysis) ml/min/1,73 m^2. There was no effect of renal impairment on pharmacokinetic exposure parameters (C_{max} and AUCs) of temsavir (total and unbound) based on both eGFR and creatinine clearance (CLcr). 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.

Hepatic impairment:

No dosage adjustment of fostemsavir is necessary for patients with mild, moderate and severe 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 patients with mild to severe hepatic impairment, the increased exposure to both unbound and total C_{max} and AUC was in the range of 1,2- to 2,2-fold; however, the upper bounds of the 2-sided 90 % CI for the impact of hepatic impairment on plasma total and unbound temsavir C_{max} are lower than the C_{max} threshold established based on temsavir exposure-response (see section 5.1 Effects on Electrocardiogram).

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.

Clinical studies:

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.

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 (ARV) 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 medicines 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 (OBT) 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 medicines available at Screening, were treated with open-label fostemsavir, 600 mg twice daily, plus OBT from Day 1 onward. The use of an investigational medicine(s) as a component of the OBT was permitted in the non-randomised cohort.

Fifty two percent of subjects in the randomised cohort had one fully active medicine within their initial OBT, 42 % had two, and 6 % had zero. Within the Non-randomised Cohort, 81 % of subjects had no fully active medicines in their original OBT and 19 % had one, including 15 % (n=15) who received ibalizumab, which was an investigational medicine at the time of BRIGHTE study start-up.

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 4).

Table 4 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} c/ml and > 1 log_{10} c/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 c/ml achieved a median decline in viral load of 1,02 log_{10} c/ml at Day 8, compared with 0,00 log_{10} c/ml decline 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 5 for the randomised cohort.

Table 5 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%)
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.
* Includes subjects who never initiated OBT, were incorrectly assigned to the Randomised Cohort or had one or more active ARV medicines available at screening but did not use these as part of the initial OBT.

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 medicines 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.

5.3 Preclinical safety data:

Carcinogenesis/mutagenesis:

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. Fostemsavir was not carcinogenic in long term studies in the mouse and rat following oral gavage administration up to 26 and 100 weeks, respectively.

Reproductive Toxicology:

Fertility:

Oral administration of fostemsavir had no adverse effects on male or female fertility in rats at doses up to 300 mg/kg/day in males and 600 mg/kg/day in females (> 100 times the 600 mg twice daily human clinical exposure 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 > 85 times the 600 mg twice daily human clinical exposure based on AUC), with decreased motility and increased abnormal sperm (at > 95 times the 600 mg twice daily human clinical exposure based on AUC). These findings were not considered clinically relevant.

Pregnancy:

No foetal abnormalities were observed following oral administration of fostemsavir to pregnant rats during organogenesis at 600 mg/kg/day [> 100 times the predicted human exposure at the maximum recommended human dose (MRHD)]. No adverse effects were observed on pregnancy, delivery, or foetal and early offspring development when fostemsavir was administered at oral doses up to 300 mg/kg/day through pregnancy and lactation (> 100 times the human exposure at the MRHD). 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 (> 200 times the predicted 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 (> 30 times the predicted human exposure at the MRHD). Decreases in foetal body weights and embryonic deaths were evident at > 65 times the exposure at the MRHD. At doses equal to or greater than 250 mg/kg/day (>100 times the exposures at MRHD), oral administration of fostemsavir to pregnant rabbits resulted in abortions in the presence of severe maternal toxicity (deaths and inappetence, body weight loss).

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 foetal tissue.

Lactation:

In a pre- and postnatal development study in rats, lactational exposure at 300 mg/kg/day (corresponding to a plasma exposure multiple > 100 times that in humans at 600 mg twice daily based on AUC) was associated with reduced neonatal survival from post-natal days 7 to 14.

Animal toxicology and/or pharmacology:

Fostemsavir has been evaluated in repeat dose toxicity studies in rats (up to 26 weeks) and in dogs (up to 39 weeks). Principle findings were testicular toxicity (degeneration of seminiferous epithelium, decreases in sperm motility and sperm morphologic alterations), renal toxicity (decreases in urine pH, renal tubular dilatation, increase kidney weight and urine volume), adrenal toxicity (angiectasis, increased gland size and weight), and liver toxicity (hepatic canalicular bile pigment deposits and lipofuscin pigment deposits in Kupffer cells). These findings were observed in rats only (at systemic exposures ≥ 30 times the 600 mg twice daily human clinical exposure based on AUC), except liver toxicity reported in dogs (at exposure multiples ≥ 3). The majority of these effects were duration-dependent and reversible upon cessation of treatment.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core: Hydroxypropylcellulose, hypromellose, colloidal anhydrous silica, magnesium stearate.

Tablet coating: Polyvinyl alcohol, titanium dioxide (E171), macrogol 335, talc, iron oxide yellow (E172), iron oxide red (E172).

6.2 Incompatibilities:

No incompatibilities have been identified.

6.3 Shelf life:

36 months

6.4 Special precautions for storage:

Store at or below 30 ºC.

6.5 Nature and contents of container:

RUKOBIA tablets are supplied in opaque, white, 150 cc, high-density polyethylene (HDPE) bottles with polypropylene child resistant closures that include a polyethylene faced induction heat seal liner. Each bottle contains 60 film-coated tablets.

6.6 Special precautions for disposal:

There are no special requirements for use or handling of this product.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

54/20.2.8/0887

9. DATE OF FIRST AUTHORISATION:

23 August 2022

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