PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**RUKOBIA**

fostemsavir extended-release tablets

Extended Release Tablets, 600 mg fostemsavir (as fostemsavir tromethamine), oral

Antiretroviral Agent

ViiV Healthcare ULC
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Laval, Quebec
H7V 4A7

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RUKOBIA (fostemsavir extended release tablets) is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced (HTE) 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.

1.1 Pediatrics

Pediatrics (**< 18 years of age)**: The safety and efficacy of RUKOBIA have not been established in pediatric patients less than 18 years of age.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical trials of RUKOBIA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from adult patients < 65 years of age.

2 CONTRAINDICATIONS

- RUKOBIA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- RUKOBIA is contraindicated in combination with strong cytochrome P450 (CYP3A) inducers as significant decreases in temsavir (the active moiety of fostemsavir) plasma concentrations may occur which may result in loss of virologic response. These drugs include, but are not limited to (see 9 DRUG INTERACTIONS):
    - carbamazepine, phenytoin; anticonvulsants
    - mitotane; antineoplastic
    - enzalutamide; androgen receptor inhibitor
    - rifampin; antimycobacterial
    - St John's wort (*Hypericum perforatum*) (see 9 DRUG INTERACTIONS, Drug-herb Interactions)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

As with all antiretroviral drugs, therapy should be initiated by a healthcare professional experienced in the management of HIV infection.

4.2 Recommended Dose and Dosage Adjustment

Adults

The recommended dose of RUKOBIA in adults is one 600 mg tablet taken orally twice daily with or without food. Tablets should be swallowed whole, and not be split, crushed or chewed.

Pediatrics (< 18 years of age): Safety and efficacy of RUKOBIA have not been established in pediatric patients less than 18 years of age.

Geriatrics (≥ 65 years of age): Clinical studies of RUKOBIA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from adult patients < 65 years of age.

Renal Insufficiency

No dosage adjustment of RUKOBIA is required in patients with renal insufficiency or those on hemodialysis (see 10.3 Pharmacokinetics).

Hepatic Insufficiency

No dosage adjustment of RUKOBIA is required in patients with mild to severe hepatic insufficiency (Child-Pugh score A, B or C) (see 10.3 Pharmacokinetics).

4.5 Missed Dose

If the patient misses a dose of RUKOBIA, the patient should take RUKOBIA as soon as possible. The patient should not take a double dose to make up for the missing dose.

5 OVERDOSAGE

Symptoms and Signs

Experience with overdose of RUKOBIA is limited.

Treatment

There is no known specific treatment for overdose with RUKOBIA. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required, including monitoring of vital signs and ECG (QT interval), as well as observation of the clinical status of the patient. As fostemsavir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Extended-release tablet 600 mg fostemsavir (as fostemsavir tromethamine)	colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide

Each film-coated tablet of RUKOBIA contains 600 mg of fostemsavir (as 724.56 mg of fostemsavir tromethamine).

RUKOBIA extended-release tablets are beige, biconvex, oval shaped, film coated tablets, debossed with 'SV 1V7' on one side and other side plain.

RUKOBIA extended-release tablets are supplied in white 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.

7 WARNINGS AND PRECAUTIONS

General

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.

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.

Cardiovascular

QTc Prolongation with Higher than Recommended Dosages

A supratherapeutic dose of RUKOBIA (2,400 mg twice daily which is 4 times the recommended daily dose) has been shown to significantly prolong the QTc interval of the electrocardiogram (see 9.4 Drug-Drug Interactions and 10.2 Pharmacodynamics). RUKOBIA should be used with caution in patients with a history of QTc interval prolongation, when co-administered with a drug with a known risk of Torsade de Pointes or in patients with relevant pre-existing cardiac disease. Elderly patients may be more susceptible to drug-induced QT interval prolongation.

Hepatic/Biliary/Pancreatic

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. Elevations in hepatic transaminases were observed in a greater proportion of subjects with HBV and/or HCV co-infection compared with those with HIV mono-infection. Some of these elevations in transaminases were consistent with hepatitis B reactivation, particularly in the setting where anti-hepatitis therapy was withdrawn (see 8 ADVERSE REACTIONS). Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting RUKOBIA in patients co-infected with hepatitis B.

Immune

Immune Reconstitution Inflammatory Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

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.

Sexual Health

- **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 16 NON-CLINICAL TOXICOLOGY).

- **Reproduction**

  Antiretroviral Pregnancy Registry (APR): To monitor maternal-fetal outcomes of pregnant women with HIV exposed to RUKOBIA and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients:
  http://www.apregistry.com
  Telephone: (800) 258-4263
  Fax: (800) 800-1052

  Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

  The concomitant use of RUKOBIA and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of RUKOBIA and possible development of resistance due to reduced exposure of temsavir or possible prolongation of QTc interval from increased exposure to temsavir. Consider the potential for drug interactions prior to and during therapy with RUKOBIA, review concomitant medications during therapy with RUKOBIA, and monitor for the adverse reactions associated with the concomitant drugs (see 9 DRUG INTERACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

RUKOBIA has not been studied in pregnant women. RUKOBIA should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus).

No fetal 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 fetal 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 fetal abnormalities (cleft palate, open eyes, shortened snout, microstomia, misaligned mouth/jaw and protruding tongue) and reductions in fetal 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 fetal 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 fetal 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 fetal tissue.

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.

7.1.2 Breast-feeding

Where possible, HIV-1-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Based on animal studies, it is expected that temsavir could be present in breast milk. Where possible, HIV-1-infected mothers should be instructed not to breast-feed if they are receiving RUKOBIA.

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 (>100 times the human exposure at the MRHD).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Safety and efficacy of RUKOBIA have not been established in pediatric patients less than 18 years of age.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of RUKOBIA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from adult patients < 65 years of age. In general, caution should be exercised in administration of RUKOBIA in elderly patients reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see 10.3 Pharmacokinetics). Elderly patients may be more susceptible to drug-induced QT interval prolongation (see 7 WARNINGS AND PRECAUTIONS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse drug reactions are discussed in 7 WARNINGS AND PRECAUTIONS:

- Immune reconstitution inflammatory syndrome (see **Immune**)
- QTc prolongation (See **Cardiovascular**)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

The primary safety assessment of RUKOBIA is based on 96 weeks of data from a Phase III, partially-

randomized, double-blind, placebo-controlled trial (BRIGHTE) conducted in 371 heavily treatment-experienced adult subjects (see 14 CLINICAL TRIALS).

In the randomized cohort, 203 subjects received at least one dose of blinded RUKOBIA 600 mg twice daily and 69 subjects received placebo, in addition to their current failing regimen for 8 days of functional monotherapy. Beyond Day 8, all randomized subjects except one received open-label RUKOBIA 600 mg twice daily plus an optimized background therapy (OBT). In the non-randomized cohort, 99 subjects received open-label fostemsavir, 600 mg twice daily, plus OBT from Day 1 onward.

A total of 370 subjects (271 randomized and 99 non-randomized) received at least 1 dose of RUKOBIA 600 mg twice daily in the BRIGHTE trial. Overall, most (81%) of the adverse reactions reported with RUKOBIA were mild or moderate in severity. The proportion of subjects who discontinued treatment with RUKOBIA due to an adverse event was 7% at week 96 analysis (randomized: 5% and non-randomized: 12%). The most common adverse events leading to discontinuation were related to infections (3% of subjects receiving RUKOBIA). Serious drug reactions occurred in 3% of subjects and included 3 cases of severe immune reconstitution inflammatory syndrome.

Adverse reactions (all grades) reported in ≥2% of subjects in the Week 96 analysis are listed in **Table 2**. The most common adverse reactions (incidence ≥5%, all grades) were nausea and diarrhea.

Table 2 Adverse Reactions [a] (All Grades) Reported in ≥ 2% of Subjects Receiving RUKOBIA plus OBT in the BRIGHTE Trial (Week 96)

	Fostemsavir plus OBT (n=370)[b] n (%)
Gastrointestinal disorders	
Nausea	32 (9)
Diarrhea	18 (5)
Abdominal Pain[c]	8 (2)
Vomiting	8 (2)
Dyspepsia	8 (2)
General disorders and administration site conditions	
Fatigue	10 (3)
Immune system disorders	
Immune Reconstitution Inflammatory Syndrome[d]	7 (2)
Nervous system disorders	
Headache	11 (3)
Somnolence	7 (2)
Dizziness	6 (2)
Skin and subcutaneous tissue disorders	

	Fostemsavir plus OBT (n=370)[b] n (%)
Rash[e]	11 (3)

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events attributed to study drug by the investigator.
b. Of the 371 subjects enrolled, 1 subject in the randomized cohort who received placebo withdrew from the trial prior to receiving RUKOBIA in the open-label phase of the trial.
c. Includes pooled terms: abdominal discomfort, abdominal pain, and abdominal pain upper
d. Includes pooled terms: Central Nervous System Immune Reconstitution Inflammatory Response and Immune Reconstitution Inflammatory Syndrome.
e. Includes pooled terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular and rash pruritic

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions occurred in less than 2% of patients receiving RUKOBIA in the BRIGHTE trial. These events have been included based on assessment of potential causal relationship.

Cardiac Disorders: Electrocardiogram QT prolonged. All reports were asymptomatic.

General Disorders: Asthenia.

Hepatobiliary Disorders: Transaminases increased (includes pooled terms: ALT increased, AST increased, hepatic enzymes increased, and transaminases increased). Elevations in hepatic transaminases were generally asymptomatic, Grade 1 or 2 in intensity, and did not require interruption of treatment.

Investigations: Blood creatinine increased, blood creatine phosphokinase (CPK) increased. Elevations in creatinine and CPK were generally asymptomatic, Grade 1 or 2 in intensity, and did not require interruption of treatment. Changes in CPK were rarely associated with musculoskeletal complaints and were not considered clinically relevant.

Musculoskeletal Disorders: Myalgia.

Nervous System Disorders: Dysgeusia, neuropathy peripheral (includes pooled terms: neuropathy peripheral and peripheral sensory neuropathy).

Psychiatric Disorders: Insomnia.

Skin and Subcutaneous Tissue Disorders: Pruritus.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Selected laboratory abnormalities (Grades 3 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in ≥2% of subjects in the BRIGHTE trial are presented in **Table 3**.

Table 3 Selected Laboratory Abnormalities (Grades 3 to 4) Reported in ≥ 2% of Subjects Receiving RUKOBIA plus OBT in the BRIGHTE Trial (Week 96)

Laboratory Parameter Preferred Term	RUKOBIA plus OBT (n=370) n (%)
ALT (>5.0 x ULN)	15 (4)
AST (>5.0 x ULN)	12 (3)
Direct Bilirubin (≥2.6 x ULN)[a]	34 (9)
Bilirubin (≥2.6 x ULN)	13 (4)
Cholesterol (≥7.77 mmol/L)[a]	11 (4)
Creatinine (>1.8 x ULN or 1.5 x baseline)	79 (21)
Creatine kinase (≥10 x ULN)	9 (2)
Hyperglycemia (>13.89 mmol/L)	13 (4)
Lipase (>3.0 x ULN)	23 (6)
Triglycerides (>5.7 mmol/L)	18 (6)
Urate (>0.71 mmol/L)	13 (4)

ULN = Upper limit of normal.
[a] Grade 3 only (no Grade 4 values reported).

Changes in Serum Creatinine: 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.

Changes in Direct Bilirubin: Increases in direct (conjugated) bilirubin have been observed following treatment with RUKOBIA (**Table 3**). Cases of clinical significance were uncommon and were confounded by the presence of intercurrent serious comorbid events (e.g., sepsis, cholangiocarcinoma, or other complications of viral hepatitis co-infection). In the remaining cases, elevations in direct bilirubin (without clinical jaundice) were typically transient, occurred without increases in liver transaminases, and resolved on continued RUKOBIA. *In vitro*, temsavir and its metabolites inhibit organic anion transporting polypeptide (OATP)1B1 and OATP1B3, 2 well-recognized transporters of direct and indirect (unconjugated) bilirubin (see 9.4 Drug-Drug Interactions). RUKOBIA may contribute to elevations in bilirubin when co-administered with other drugs known to cause hyperbilirubinemia or in patients with liver disease or who otherwise have reduced activity of hepatic transport proteins, including patients with HIV-1 infection.

Changes in ALT and AST in Subjects with Hepatitis B and/or Hepatitis C Virus Co-infection: In the Phase III study 205888, 29 subjects with Hepatitis B and/or Hepatitis C co-infection at baseline had a higher incidence of post-baseline emergent Grade 3 and 4 elevations in ALT and AST (14% as compared with 3% (ALT) and 2% (AST) of subjects without viral hepatitis co-infection). Some of these elevations in

transaminases were consistent with hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn (see 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

RUKOBIA is contraindicated in combination with strong cytochrome P450 (CYP3A) inducers as significant decreases in temsavir (the active moiety of fostemsavir) plasma concentrations may occur which may result in loss of virologic response (see CONTRAINDICATIONS). Consider the potential for drug interactions prior to and during therapy with RUKOBIA, review concomitant medications during therapy with RUKOBIA, and monitor for the adverse reactions associated with the concomitant drugs (see 7 WARNINGS AND PRECAUTIONS).

9.4 Drug-Drug Interactions

Effect of Fostemsavir on the Pharmacokinetics of Other Agents

In vitro, temsavir inhibited renal OATP1B1 and OATP1B3 (IC_{50} = 32 and 16 micromolar, respectively). Additionally, temsavir and its 2 metabolites, BMS-646915 and BMS-930644, inhibited BCRP (IC_{50} = 12, 35, and 3.5 to 6.3 micromolar, respectively). Based on these data, temsavir is expected to affect the pharmacokinetics of drugs that are substrates of OATP1B1/3 or BCRP (e.g., rosuvastatin, atorvastatin, pitavastatin, simvastatin and fluvastatin). Co-administration of fostemsavir with elbasvir/grazoprevir is not recommended as increased grazoprevir concentrations may increase the risk of ALT elevations. Dose modification and/or careful titration of dose is recommended for certain statins.

When RUKOBIA 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 RUKOBIA.

Significant interactions are not expected when RUKOBIA is co-administered with substrates of cytochrome P_{450} (CYPs), uridine diphosphate glucuronosyl transferases (UGTs), 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 drug interaction data.

In vitro, temsavir was not a clinically relevant inhibitor of other transporters, major CYP enzymes, or UGTs (IC_{50} >40 micromolar). In addition, temsavir did not induce CYP enzymes *in vitro*.

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

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

Effect of Other Agents on the Pharmacokinetics of Temsavir

Temsavir is a substrate of P-glycoprotein (P-gp) and BCRP, but not of OATP1B1 or OATP1B3. Its biotransformation to 2 predominant 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.

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

When RUKOBIA was co-administered with rifampin, a strong CYP3A4 inducer, a significant reduction in temsavir plasma concentrations was observed. The use of RUKOBIA with other drugs that are strong inducers of CYP3A4 may also significantly decrease temsavir plasma concentrations and lead to loss of virologic response (see 2 CONTRAINDICATIONS).

RUKOBIA may be co-administered with moderate CYP3A inducers (e.g., efavirenz, etravirine, nevirapine, rifabutin) which reduced temsavir concentrations but with no clinically relevant impact.

Established or Potential Drug Interactions

Established and theoretical interactions with selected medicinal products are listed in

Table 4. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 Established or Potential Drug-Drug Interactions[a]

Concomitant Drug Class: Drug Name	**Effect on Concentration of Temsavir and/or Concomitant drug**	**Clinical Comment**
Androgen receptor inhibitor: Enzalutamide	Temsavir ↓	Co-administration is contraindicated.
Anticonvulsants: Carbamazepine Phenytoin	Temsavir ↓	
Antimycobacterial: Rifampin	Temsavir ↓	
Antineoplastic: Mitotane	Temsavir ↓	
Herbal product: St John's wort (*Hypericum perforatum*)	Temsavir ↓	

Concomitant Drug Class: Drug Name	Effect on Concentration of Temsavir and/or Concomitant drug	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 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 ↑	Although not studied, temsavir may increase plasma concentrations of other HCV DAAs. No dose adjustment is necessary.
Oral contraceptives: Ethinyl estradiol (EE)	EE ↑	**Ethinyl estradiol should not exceed 30 µg daily**. Caution is advised particularly in patients with additional risk factors for thromboembolic events
HMG CO-A Reductase Inhibitors: Rosuvastatin Atorvastatin Pitavastatin Fluvastatin Simvastatin	Rosuvastatin ↑ Atorvastatin ↑ Pitavastatin ↑ Fluvastatin ↑ Simvastatin ↑	Use the lowest possible starting dose for statins and monitor for statin associated adverse events.

Legend: ↑ = Increase, ↓ = Decrease
[a]This table is not all inclusive.

The effects of RUKOBIA on the exposure of co-administered drugs are shown in **Table 5** and the effects of co-administered drugs on the exposure of temsavir are shown in **Table 6**.

Table 5 Summary of Effect of Fostemsavir[a] on the Pharmacokinetics of Co-administered Drugs

Coadministered Drug(s) and Dose(s)		Dose of RUKOBIA	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drugs with/without RUKOBIA No Effect = 1.00		
				C_{max}	AUC	C_{τ}
Atazanavir +	300 mg once daily/	600 mg twice daily	18	1.03 (0.96, 1.10)	1.09 (1.03, 1.15)	1.19 (1.10, 1.30)
Ritonavir	100 mg once daily			1.02 (0.96, 1.09)	1.07 (1.03, 1.10)	1.22 (1.12, 1.32)
Darunavir +	600 mg twice daily/	600 mg twice daily	13	0.98 (0.93, 1.04)	0.94 (0.89, 1.00)	0.95 (0.87, 1.04)
Ritonavir	100 mg twice daily			1.00 (0.86, 1.16)	1.15 (0.99, 1.33)	1.19 (1.06, 1.35)
Darunavir +	600 mg twice daily/	600 mg twice daily	13	0.95 (0.90, 1.01)	0.94 (0.89, 0.99)	0.88 (0.77, 1.01)
Ritonavir +	100 mg twice daily/			1.14 (0.96, 1.35)	1.09 (0.98, 1.22)	1.07 (0.97, 1.17)
Etravirine	200 mg twice daily			1.18 (1.10, 1.27)	1.28 (1.20, 1.36)	1.28 (1.18, 1.39)
Etravirine	200 mg twice daily	600 mg twice daily	14	1.11 (1.04, 1.19)	1.11 (1.05, 1.17)	1.14 (1.08, 1.21)
Tenofovir disoproxil fumarate	300 mg once daily	600 mg twice daily	18	1.18 (1.12, 1.25)	1.19 (1.12, 1.25)	1.28 (1.20, 1.38)
Rosuvastatin	10-mg single dose	600 mg twice daily	18	1.78 (1.52, 2.09)	1.69 (1.44, 1.99)	NA
Ethinyl estradiol/	0.030 mg once daily/	600 mg twice daily	26	1.39 (1.28, 1.51)	1.40 (1.29, 1.51)	NA
Norethindrone	1.5 mg once daily			1.08 (1.01, 1.16)	1.08 (1.03, 1.14)	NA
Maraviroc	300 mg twice daily	600 mg twice daily	13	1.01 (0.84, 1.20)	1.25 (1.08, 1.44)	1.37 (1.26, 1.48)
Methadone	40 to 120 mg once daily	600 mg twice daily	16			
R(-) Methadone				1.15 (1.11, 1.20)	1.13 (1.07, 1.19)	1.09 (1.01, 1.17)
S(+) Methadone				1.15 (1.10, 1.19)	1.15 (1.09, 1.21)	1.10 (1.02, 1.19)
Total Methadone				1.15 (1.11, 1.19)	1.14 (1.09, 1.20)	1.10 (1.02, 1.18)
Buprenorphine/ Naloxone	8/2 to 24/6 mg once daily	600 mg twice daily	16			

Coadministered Drug(s) and Dose(s)		Dose of RUKOBIA	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drugs with/without RUKOBIA No Effect = 1.00		
				C_{max}	AUC	C_τ
Buprenorphine Norbuprenorph-ine				1.24 (1.06, 1.46) 1.24 (1.03, 1.51)	1.30 (1.17, 1.45) 1.39 (1.16, 1.67)	1.39 (1.18, 1.63) 1.36 (1.10, 1.69)

CI = Confidence Interval; n = Maximum number of subjects with data; NA = Not available.
AUC = AUC_τ for repeat-dose studies and $AUC_{(0-\infty)}$ for single-dose study.
[a] Temsavir is the active moiety.

Table 6 Summary of Effect of Co-administered Drugs on the Pharmacokinetics of Temsavir[a] Following Co-administration with Fostemsavir

Coadministered Drug(s) and Dose(s)		Dose of RUKOBIA	n	Geometric Mean Ratio (90% CI) of Temsavir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
				C_{max}	AUC	C_τ
Atazanavir + Ritonavir	300 mg once daily/ 100 mg once daily	600 mg twice daily	36	1.68 (1.58, 1.79)	1.54 (1.44, 1.65)	1.57 (1.28, 1.91)
Darunavir + Ritonavir	600 mg twice daily/ 100 mg twice daily	600 mg twice daily	14	1.52 (1.28, 1.82)	1.63 (1.42, 1.88)	1.88 (1.09, 3.22)
Darunavir + Ritonavir + Etravirine	600 mg twice daily/ 100 mg twice daily/ 200 mg twice daily	600 mg twice daily	18	1.53 (1.32, 1.77)	1.34 (1.17, 1.53)	1.33 (0.98, 1.81)
Etravirine	200 mg twice daily	600 mg twice daily	14	0.52 (0.45, 0.59)	0.50 (0.44, 0.57)	0.48 (0.32, 0.72)
Ritonavir	100 mg once daily	600 mg twice daily	18	1.53 (1.31, 1.79)	1.45 (1.29, 1.61)	1.44 (1.00, 2.08)
Raltegravir + Tenofovir disoproxil fumarate	400 mg twice daily/ 300 mg once daily	1,200 mg once daily	17	1.23 (0.92, 1.64)	1.07 (0.84, 1.34)	1.17 (0.59, 2.32)

Coadministered Drug(s) and Dose(s)		Dose of RUKOBIA	n	Geometric Mean Ratio (90% CI) of Temsavir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
				C_{max}	AUC	C_τ
Rifabutin + Ritonavir	150 mg once daily/ 100 mg once daily	600 mg twice daily	23	1.50 (1.38, 1.64)	1.66 (1.52, 1.81)	2.58 (1.95, 3.42)
Rifabutin	300 mg once daily	600 mg twice daily	22	0.73 (0.65, 0.83)	0.70 (0.64, 0.76)	0.59 (0.46, 0.77)
Rifampin	600 mg once daily	1,200-mg single dose	15	0.24 (0.21, 0.28)	0.18 (0.16, 0.2)	NA
Cobicistat	150 mg once daily	600 mg twice daily	16	1.71 (1.54, 1.90)	1.93 (1.75, 2.12)	2.36 (2.03, 2.75)
Darunavir + Cobicistat	800 mg once daily/ 150 mg once daily	600 mg twice daily	15	1.79 (1.62, 1.98)	1.97 (1.78, 2.18)	2.24 (1.75, 2.88)
Tenofovir disoproxil fumarate	300 mg once daily	600 mg twice daily	18	0.99 (0.86, 1.13)	1.00 (0.91, 1.11)	1.13 (0.77, 1.66)
Maraviroc	300 mg twice daily	600 mg twice daily	14	1.13 (0.96, 1.32)	1.10 (0.99, 1.23)	0.90 (0.69, 1.17)
Famotidine	40-mg single dose	600-mg single dose	24	1.01 (0.85, 1.21)	1.04 (0.87, 1.25)	0.90 (0.64, 1.28)

CI = Confidence Interval; n = Maximum number of subjects with data; NA = Not available.
AUC = AUC_τ for repeat-dose studies and $AUC_{(0-\infty)}$ for single-dose study.
$C_\tau = C_{12}$ for single-dose study.
[a]Temsavir is the active moiety.

Drugs 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 7 WARNINGS AND PRECAUTIONS and 10.2 Pharmacodynamics). RUKOBIA should be used with caution when co-administered with drugs with a known risk of Torsade de Pointes.

Drugs without Clinically Significant Interactions with RUKOBIA

Based on drug interaction study results, the following drugs can be co-administered with RUKOBIA without a dose adjustment: atazanavir/ritonavir, buprenorphine/naloxone, cobicistat, darunavir/cobicistat, darunavir/ritonavir with and without etravirine, etravirine, famotidine, maraviroc, methadone, norethindrone, raltegravir, ritonavir, rifabutin with and without ritonavir, tenofovir disoproxil fumarate.

9.5 Drug-Food Interactions

RUKOBIA may be taken without regard to food (see 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Co-administration of RUKOBIA with products containing St. John's wort may significantly decrease temsavir plasma concentrations, resulting in loss of therapeutic effect. Co-administration of RUKOBIA with products containing St. John's wort is contraindicated.

9.7 Drug-Laboratory Test Interactions

No Drug-Laboratory interactions have been identified.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Fostemsavir is a prodrug without significant biochemical or antiviral activity that is hydrolyzed to the active moiety, temsavir, an HIV-1 attachment inhibitor, 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, subsequent viral entry into, and infection of, host cells.

10.2 Pharmacodynamics

Effects on Electrocardiogram

In a randomized, placebo- and active-controlled, double-blind, cross-over thorough QT study, 60 healthy subjects received oral administration of placebo, RUKOBIA 1,200 mg (2 times the recommended dose) once daily, RUKOBIA 2,400 mg (4 times the recommended dose) twice daily, and moxifloxacin 400 mg (active control) in random sequence. RUKOBIA administered at 1,200 mg once daily did not have a clinically meaningful effect on the QTc interval as the maximum mean time-matched (2-sided 90% upper confidence bound) placebo-adjusted QTc change from baseline based on Fridericia's correction method (QTcF) was 4.3 (6.3) milliseconds (below the clinically important threshold of 10 milliseconds). However, RUKOBIA administered at 2,400 mg twice daily for 7 days was associated with a clinically meaningful prolongation of the QTc interval as the maximum mean time-matched (2-sided 90% upper confidence bound) for the placebo-adjusted change from baseline in QTcF interval was 11.2 (13.3) milliseconds. Steady-state administration of RUKOBIA 600 mg twice daily resulted in a mean temsavir C_{max} approximately 4.2-fold lower than the temsavir concentration predicted to increase QTcF interval 10 milliseconds (see 7 WARNINGS AND PRECAUTIONS).

10.3 Pharmacokinetics

The pharmacokinetic (PK) properties of temsavir following administration of RUKOBIA to healthy subjects are provided in **Table 7**. The multiple-dose PK parameters in HIV-1-infected subjects are provided in **Table 8**.

Table 7 Pharmacokinetic Properties of Temsavir

Absorption	
% Absolute bioavailability[a]	26.9
T_{max} (h)	2.0
Effect of standard meal (relative to fasting)[b]	AUC ratio = 1.10 (0.95, 1.26)
Effect of high-fat meal (relative to fasting)[b]	AUC ratio = 1.81 (1.54, 2.12)
Distribution	
% Bound to human plasma proteins	88.4 (primarily to HSA)
Source of protein-binding data	in vivo
Blood-to-plasma ratio	0.74
Volume of distribution (Vss, L)[c]	29.5
Elimination	
Major route of elimination	Metabolism
Clearance (CL and CL/F[d], L/h)	17.9 and 66.4
$t_{1/2}$ (h)	11
Metabolism	
Metabolic pathways[e]	Hydrolysis (esterases) [36.1% of oral dose] Oxidation (CYP3A4) [21.2% of oral dose] UGT [<1% of oral dose]
Excretion	
% of dose excreted in urine (unchanged drug)[f]	51
% of dose excreted in feces (unchanged drug)[f]	33

HSA = Human Serum Albumin; UGT = Uridine diphosphate glucuronosyl transferases.

[a] Dosing in absolute bioavailability study: single-dose administration of fostemsavir extended-release tablet 600 mg followed by single IV infusion of [13C] temsavir 100 mcg.

[b] Geometric mean ratio (fed/fasted) in PK parameters and (90% confidence interval). Multiple-dose administration of fostemsavir extended-release tablet 600 mg (bid) after a standard meal = ~423 kcal, 36% fat. Single-dose administration of fostemsavir extended-release tablet 600 mg after a high-calorie/high-fat meal = ~985 kcal, 60% fat, 28% carbohydrates, and 12% protein.

[c] Volume of distribution at steady state (Vss) following IV administration.

[d] Apparent clearance.

[e] In vitro studies have shown that temsavir is biotransformed into 2 predominant circulating inactive metabolites: BMS-646915 (via hydrolysis) and BMS-930644 (via N-dealkylation).

[f] Dosing in mass balance study: single-dose administration of [^{14}C] fostemsavir oral solution 300 mg containing 100 microCi (3.7 MBq) of total radioactivity.

Table 8 Multiple-Dose Pharmacokinetic Parameters of Temsavir

Parameter	Geometric Mean (CV%)[a]
C_{max} (ng/mL)	1770 (39.9)
AUC_{tau} (ng.h/mL)	12900 (46.4)
C_{trough} or C_{12} (ng/mL)	478 (81.5)

CV = Coefficient of Variation; C_{max} = Maximum concentration; AUC = Area under the time concentration curve; C_{12} = Concentration at 12 hours.

[a] Based on population PK analyses in HIV-1–infected, heavily treatment-experienced adult subjects receiving 600 mg of RUKOBIA twice daily with or without food in combination with other antiretroviral drugs.

Absorption: Fostemsavir is a prodrug that is metabolised to temsavir by alkaline phosphatases 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 a median T_{max} at 2 hours (after administration under fasting conditions). Temsavir is absorbed across the small intestine and the caecum/proximal ascending colon.

Following oral administration, increases in plasma temsavir exposure (C_{max} and AUC_{tau}) appeared dose proportional or slightly greater than dose proportional, over the range of 600 mg to 1,800 mg of RUKOBIA. The pharmacokinetics of temsavir following administration of RUKOBIA are similar between healthy and HIV-1–infected subjects.

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) and is not considered clinically significant. Regardless of calorie and fat content, food had no impact on plasma temsavir C_{max}. Relative to the fasted state, median T_{max} was delayed by 2 hours (after a standard meal) and by 4.5 hours after a high-fat meal. RUKOBIA may be administered with or without food.

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 metabolized 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 feces. Temsavir is biotransformed into two predominant circulating inactive metabolites, BMS-646915 (a product of hydrolysis) and BMS-930644 (a product of N-

dealkylation). Drugs that are strong inducers of CYP3A are contraindicated with fostemsavir (see 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS).

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 feces, 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 fecal excretion is from biliary excretion.

Special Populations and Conditions

- **Pediatrics:** RUKOBIA has not been studied in the pediatric population.
- **Geriatrics:** Population pharmacokinetic analyses indicated age had no clinically relevant effect on the pharmacokinetics of temsavir. Pharmacokinetic data in subjects aged 65 years and older are limited. Elderly patients may be more susceptible to drug-induced QT interval prolongation (see 7 WARNINGS AND PRECAUTIONS)
- **Gender:** Population pharmacokinetic analyses revealed that sex had no clinically relevant effect on the pharmacokinetics of temsavir.
- **Ethnic Origin:** Population pharmacokinetic analyses revealed that race had no clinically relevant effect on the pharmacokinetics of temsavir.
- **Hepatic Insufficiency:** 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 (ChildPugh Score A, n=6), moderate (Child-Pugh Score B, n=6), and severe (Child-Pugh Score C, n=6) hepatic impairment. In patients with mild to severe hepatic impairment, the increased exposure to both unbound and total C_{max} and AUC was in the range of 1.2- to 2.2-fold. However, the upper bounds of the 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 of an approximate 4.2-fold increase (7500 ng/ml) established based on temsavir exposure-response (see 10.2 PHARMACODYNAMICS, Effects on Electrocardiogram).
- **Renal Insufficiency:** 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). Based on creatinine clearance (CLcr), as follows: 60 ≤ CLcr ≤89 (mild), 30 ≤ CLcr <60 (moderate), CLcr <30 (severe, and ESRD on haemodialysis) mL/min, there was no clinically relevant effect of renal impairment on pharmacokinetic exposure parameters (C_{max} and AUCs) of temsavir (total and unbound). The mean fraction unbound (fu) TMR for the severe renal impairment group was approximately 58% higher compared with the normal renal function group. The regression model predicted average increases in plasma TMR (unbound fraction) C_{max} and AUC were ≤ 15% and for AUC ≤ 30% for the mild, moderate, and severe RI groups. C_{max} (bound and unbound) was lower than the C_{max} threshold of an approximately 4.2-fold increase (7500 ng/ml) established based on temsavir exposure-response. Temsavir was not readily cleared by hemodialysis, with approximately 12.3% of the administered dose removed during the 4-hour haemodialysis session. Hemodialysis 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 hemodialysis.

- **Hepatitis B or Hepatitis C Co-infection:** There are limited data for the use of temsavir in subjects with hepatitis B and/or hepatitis C co-infection.

11 STORAGE, STABILITY AND DISPOSAL

Store RUKOBIA at 15 °C to 25 °C.

Healthcare professionals should recommend that their patients return all unused medications to a pharmacy for proper disposal.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

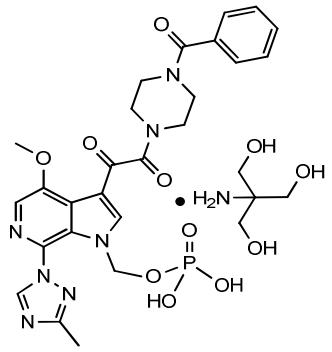
Drug Substance

Proper/Common name: fostemsavir tromethamine

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 and molecular mass: $C_{25}H_{26}N_7O_8P \bullet C_4H_{11}NO_3$
704.6 g/mol (583.5 as free acid)

Structural formula:



Physicochemical properties: Fostemsavir tromethamine is a white powder and is soluble to greater than 250 mg/mL in aqueous solutions with a pH greater than 3.7.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

HIV-1 infection in heavily treatment-experienced (HTE) adults with multidrug-resistant HIV-1 infection

The efficacy of RUKOBIA in HIV-1–infected, heavily treatment-experienced adult subjects is based on 96-week data from a Phase 3, partially-randomized, international, double-blind, placebo-controlled trial (BRIGHTE [205888]).

The BRIGHTE trial was conducted in 371 heavily treatment-experienced subjects with multi-class HIV-1 resistance. All subjects were required to have a viral load ≥400 copies/mL and ≤2 classes of antiretroviral medications remaining at baseline due to resistance, intolerability, contraindication, or other safety concerns. Subjects were enrolled in either a randomized or non-randomized cohort defined as follows:

- Within the randomized cohort (n = 272), subjects had 1, but no more than 2, fully active and available antiretroviral agent(s) at screening which could be combined as part of an efficacious background regimen. Randomized subjects received either blinded RUKOBIA 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, randomized subjects received open-label RUKOBIA 600 mg twice daily plus an investigator-selected optimized background therapy (OBT). This cohort provides primary evidence of efficacy of RUKOBIA.
- Within the non-randomized cohort (n = 99), subjects had no fully active and approved antiretroviral agents available at screening. Non-randomized subjects were treated with open-label RUKOBIA 600 mg twice daily plus OBT from Day 1 onward. The use of an investigational drug(s) as a component of the OBT was permitted in the non-randomized cohort.

In the randomized cohort, the baseline characteristics were well balanced between the placebo and fostemsavir group (see **Table 9**).

Table 9 Summary of Demographic and Baseline Characteristics in BRIGHTE trial-ITT-E Population

	Randomized Cohort			Non-Randomized Cohort FTR 600 mg BID N=99	TOTAL N=371
	Placebo[a] N=69	FTR 600 mg BID N=203	Total N=272		
Sex, n (%)					
Male	57 (83)	143 (70)	200 (74)	89 (90)	289 (78)
Age (yrs[b])					
Median	45.0	48.0	48.0	50.0	49.0
≥ 65, n (%)	1(1)	9(4)	10(4)	2(2)	12(3)
Race, n (%)					
White	48 (70)	137 (67)	185 (68)	74 (75)	259 (70)

	Randomized Cohort			Non-Randomized Cohort FTR 600 mg BID N=99	TOTAL N=371
	Placebo[a] N=69	FTR 600 mg BID N=203	Total N=272		
Baseline HIV-1 RNA (log10 c/mL)					
Median	4.6	4.7	4.7	4.3	4.6
Baseline CD4+ (cells/mm^3)					
Median	100.0	99.0	99.5	41.0	80.0
Baseline CD4+ (cells/mm^3), n (%)					
<20	17 (25)	55 (27)	72 (26)	40 (40)	112 (30)
<200	49(71)	150(73)	199(72)	79(79)	278(75)
AIDS History, n (%)[c]					
Yes	61 (88)	170 (84)	231 (85)	89 (90)	320 (86)
Number of Years Treated for HIV Infection, n (%)					
>15	40 (58)	142 (69)	182 (67)	80 (81)	262 (70)
Number of Prior ART Regimens (including current failing regimen) n (%)					
5 or more	57 (83)	169 (83)	226 (83)	90 (91)	316 (85)
Number fully active agents in their original OBT n (%)					
0	1 (1)	15 (7)	16 (6)	80 (81)	96 (26)
1	34 (49)	108 (53)	142 (52)	19 (19)[d]	161 (43)
2	34 (49)	80 (39)	114 (42)	0	114 (31)
Number with history of hepatitis B and/or C co-infection					
n (%)	6 (9)	15 (7)	21 (8)	8 (9)	29 (8)

a. Subjects randomised to the placebo group received fostemsavir 600 mg BID during the open-label phase.
b. Age is imputed when full date of birth is not provided.
c. History of AIDS = Yes if a subject has Nadir CD4+ count <200 cells/mm3, or if response to "Does subject have AIDS?" on Disease History CRF is Yes.
d. 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 randomized cohort, demonstrated superiority of RUKOBIA to placebo (0.79 vs. 0.17 $\log_{10}$ copies/mL decline, respectively; *P*<0.0001, Intent-to-Treat-Exposed [ITT-E] population) (**Table 10**).

Table 10 Plasma HIV-1 RNA Log10 (copies/mL) Change from Day 1 at Day 8 (Randomized Cohort) in BRIGHTE Trial – ITT-E Population

Randomized Treatment	n	Adjusted Mean[a] (95% CI)	Difference[b] (95% CI)	*P*-value[c]
Placebo	69	-0.166 (-0.326, -0.007)	-	-
RUKOBIA 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: RUKOBIA minus placebo.
[c] Mean value of viral load change from baseline (RUKOBIA = placebo).
[d] Two subjects who received RUKOBIA with 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 who received RUKOBIA had a reduction in viral load from baseline >0.5 log_{10} copies/mL and >1 log_{10} copies/mL, respectively, compared with 19% (13/69) and 10% (7/69) of subjects, respectively, in the placebo group.

By subgroup analysis, randomized subjects who received RUKOBIA with baseline HIV-1 RNA >1,000 copies/mL achieved a median decline in viral load of 1.015 log_{10} copies/mL at Day 8 compared with 0.00 log_{10} copies/mL in subjects treated with blinded placebo. Subjects with baseline HIV-1 RNA ≤1,000 copies/mL achieved a median decline in viral load of 0.14 log10 copies/mL at Day 8 compared with 0.06 log_{10} copies/mL in subjects treated with blinded placebo.

There was considerable variability in the number of antiretrovirals (fully active and otherwise) included in 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. Virologic outcomes by ITT-E Snapshot Analysis at Week 48 were consistent with those observed at Weeks 24 and 96.

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 11** for the randomized cohort.

Table 11 Virologic Outcomes (HIV-1 RNA <40 copies/mL) by Baseline Covariates at Weeks 24, 48, and 96 with RUKOBIA (600 mg Twice Daily) plus OBT (Randomized Cohort) in BRIGHTE Trial (ITT-E Population, Snapshot Algorithm)

	RUKOBIA 600 mg Twice Daily plus OBT		
	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 antiretroviral treatment 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			
Baseline plasma viral load (copies/mL)			
<100,000	60% (116/192)	61% (118/192)	65% (124/192)
≥100,000	35% (28/80)	35% (28/80)	49% (39/80)
Baseline CD4+ (cells/mm^3)			
<20	32% (23/72)	35% (25/72)	46% (33/72)
20 to <50	48% (12/25)	48% (12/25)	56% (14/25)
50 to <200	58% (59/102)	58% (59/102)	61% (62/102)
≥200	68% (50/73)	68% (50/73)	74% (54/73)
Number of fully active and available antiretroviral classes in initial OBT			
0[a]	31% (5/16)	31% (5/16)	19% (3/16)
1	56% (80/142)	58% (82/142)	65% (92/142)
2	52% (59/114)	52% (59/114)	60% (68/114)
Use of DTG and DRV[b] as a component of OBT			
DTG and DRV	58% (68/117)	51% (60/117)	64% (75/117)
With DTG, without DRV	54% (61/112)	60% (67/112)	63% (71/112)
Without DTG, with DRV	29% (5/17)	47% (8/17)	47% (8/17)
Without DTG/DRV	38% (10/26)	42% (11/26)	35% (9/26)

	RUKOBIA 600 mg Twice Daily plus OBT		
	Week 24 (n = 272)	**Week 48 (n = 272)**	**Week 96 (n = 272)**
Gender			
Male	52% (104/200)	51% (102/200)	59% (118/200)
Female	56% (40/72)	61% (44/72)	63% (45/72)
Race			
White	49% (90/185)	50% (92/185)	56% (103/185)
Black or African-American/Others	62% (54/87)	62% (54/87)	69% (60/87)
Age (years)			
<50	50% (81/162)	50% (81/162)	59% (96/162)
≥50	57% (63/110)	59% (65/110)	61% (67/110)

DTG = Dolutegravir, DRV = Darunavir

[a] Includes subjects who never initiated OBT, were incorrectly assigned to the randomized cohort, or had 1 or more active antiretroviral agents available at screening but did not use these as part of the initial OBT.

[b] Darunavir was coadministered with ritonavir or cobicistat.

In the randomized cohort, HIV-1 RNA <200 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 HIV-1 RNA <400 copies/mL was 75%, 70%, and 64%, respectively (ITT-E, Snapshot algorithm). Mean changes in CD4+ 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 subgroup analysis in the randomized cohort, subjects with the lowest baseline CD4+ cell counts (<20 cells/mm^3) had a similar increase in CD4+ count over time compared with subjects with higher baseline CD4+ cell count (>50, >100, >200 cells/mm^3).

In the nonrandomized cohort, HIV-1 RNA <40 copies/mL was achieved in 37% of subjects at Week 24, 38% at Week 48, and 37% at Week 96. At each of these respective 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/mm3 at Week 24, 64 cells/mm3 at Week 48, and 119 cells/mm3 at Week 96.

15 MICROBIOLOGY

Antiviral Activity In Cell Culture

Temsavir exhibited antiviral activity against 3 CCR5-tropic laboratory strains of subtype B HIV-1, with EC50 values ranging from 0.4 to 1.7 nM. The range of susceptibility to temsavir was broader for CXCR4-tropic laboratory strains with 2 strains having EC50 values of 0.7 and 2.2 nM and 3 strains having EC50 values of 14.8, 16.2, and >2,000 nM. Antiviral activity of temsavir against HIV-1 subtype B clinical isolates varied depending on tropism with median EC50 values against the CCR5-tropic viruses, CXCR4-tropic viruses, and dual/mixed viruses of 3.7 nM (n = 9; range: 0.3 to 345 nM), 40.9 nM (n = 4; range: 0.6 to >2,000 nM), and 0.8 nM (n = 2; range: 0.3 to 1.3), respectively, showing a broad range of EC50 values for temsavir across the different tropic strains.

Analysis of data from 1,337 clinical samples from the fostemsavir clinical development program (881 subtype B samples, 156 subtype C samples, 43 subtype A samples, 17 subtype A1 samples, 48 subtype

F1 samples, 29 subtype BF1 samples, 19 subtype BF samples, 5 CRF01_AE samples, and 139 other) showed temsavir susceptibility is highly variable across subtypes with a wide range in EC50 values from 0.018 nM to >5,000 nM. The majority of subtype B isolates (84%, 740/881) had EC50 values below 10 nM, with 6% of isolates having EC50 values >100 nM. Of all isolates from all subtypes tested, 9% exhibited EC50 values >100 nM. Subtypes BF, F1 and BF1 had higher proportions (21% to 38%) of isolates with EC50 values >100 nM, and all 5 of 5 subtype AE isolates had EC50 values >100 nM. From an additional panel of clinical isolates with non-B subtypes, temsavir EC50 values were greater than the upper limits of the concentrations tested (>1,800 nM) in all subtype E (AE; 3 of 3), Group O (2 of 2), and HIV-2 (1 of 1) isolates, and some subtype D (1 of 4) and subtype G (1 of 3) isolates.

Reduced Antiviral Activity Against Subtype AE

RUKOBIA is not recommended for treatment of infections due to HIV-1 Group M subtype CRF01_AE strains.

Temsavir showed reduced antiviral activity against 14 different subtype AE isolates in peripheral blood mononuclear cell (PBMC) assays and the Phenosense Entry assay indicating that subtype AE (or E) viruses are inherently less sensitive to temsavir. Genotyping of subtype AE viruses identified polymorphisms at amino acid positions S375H and M475I in gp120, which have been associated with reduced susceptibility to fostemsavir. Subtype AE is a predominant subtype in Southeast Asia, but it is not found in high frequencies elsewhere throughout the world.

There were 2 subjects with subtype AE virus at screening in the randomized cohort of the clinical trial. One subject (EC50 fold change >4,747-fold and gp120 substitutions at S375H and M475I at baseline) did not respond to RUKOBIA at Day 8. A second subject (EC50 fold change 298-fold and gp120 substitution at S375N at baseline) received placebo during functional monotherapy. Both subjects were virologically suppressed at Week 96 while receiving OBT (with dolutegravir) plus RUKOBIA.

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 nucleoside reverse transcriptase inhibitors (abacavir, didanosine, zalcitabine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, zidovudine), non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, delavirdine, rilpivirine), protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, darunavir), the gp41 fusion inhibitor enfuvirtide, the CCR5 co-receptor antagonist maraviroc, the CD4-directed post-attachment HIV-1 inhibitor ibalizumab, or integrase inhibitors (dolutegravir, 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- to 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. Selected viruses exhibited 18- to 159-fold decreased temsavir susceptibility and genotypic analysis identified the following emerging amino acid substitutions in gp120: L116P/Q, L175P, A204D, V255I, A281V, M426L, M434I, and M475I (S375 substitutions were identified based on in vivo data with a related attachment inhibitor). In general, most substitutions

mapped to the conserved regions (C1, C2, C4, and C5) of the gp120 envelope, confirming temsavir targets the viral envelope protein during infection.

Single-substitution recombinant viruses were engineered into the HIV-1 LAI viral background, and the resultant recombinants were examined against temsavir (L116P [>340-fold], A204D [>340-fold], S375M [47-fold], S375V [5.5-fold], S375Y [>10,000-fold], M426L [81-fold], M426V [3.3-fold], M434I [11-fold], M434T [15-fold], M475I [5-fold], M475L [17-fold], and M475V [9.5-fold]). Amino acid substitutions, L116P and A204D, located distal to the CD4 binding pocket of gp120, conferred substantial reduction in susceptibility 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 RUKOBIA.

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.

Cross-Resistance

Both the CD4-directed post-attachment inhibitor ibalizumab and the gp120-directed attachment inhibitor fostemsavir develop resistance in gp120. Five of 7 viruses resistant to ibalizumab retained susceptibility to temsavir while the other 2 viruses had reduced susceptibility to both temsavir (>1,400-fold decreased susceptibility) and ibalizumab. Resistance to the CCR5 coreceptor antagonist maraviroc can also develop in the gp120 envelope. Some CCR5-tropic maraviroc-resistant viruses showed reduced susceptibility to temsavir. Viruses resistant to the gp41 fusion inhibitor enfuvirtide retained susceptibility to temsavir. Temsavir retained wild-type activity against viruses resistant to the INSTI raltegravir; the NNRTI rilpivirine; the NRTIs abacavir, lamivudine, tenofovir, zidovudine; and the PIs atazanavir and darunavir.

Additionally, ibalizumab, maraviroc, enfuvirtide, the INSTI raltegravir, NNRTIs (efavirenz, rilpivirine), NRTIs (abacavir, tenofovir), and PIs (atazanavir, darunavir) retained activity against site-directed mutants with reduced temsavir susceptibility (S375M, M426L, or M426L plus M475I) or against clinical envelopes that had decreased baseline susceptibility to temsavir.

Day 8 Response by Genotype and Phenotype

The effect of the gp120 resistance-associated polymorphisms (RAPs) on response to fostemsavir functional monotherapy at Day 8 was assessed in an as-treated analysis by censoring the subjects who had a >0.4 log10 decline in HIV-1 RNA from screening to baseline or <400 copies/mL at screening (n = 47 subjects were censored).

The presence of gp120 RAPs at key sites S375, M426, M434, or M475 was associated with a lower overall decline in HIV-1 RNA and fewer subjects achieving >0.5 log10 decline in HIV-1 RNA compared with subjects with no changes at these sites (**Table 12**). However, the presence of the gp120 RAPs did not preclude some subjects from achieving a response of >0.5 log10 copies/mL at Day 8. Baseline gp120 RAPs most associated with decreased response of <0.5 log10 copies/mL at Day 8 were S375M, M426L, and M475V (**Table 12**). There was no difference in response rates and median decline in viral load for subjects with more than one gp120 RAP.

Table 12 Outcome of Randomized Fostemsavir Cohort by Presence of Screening gp120 RAPs (As-Treated Analysis[a])

Envelope RAPs	Response Rate at Day 8 (>0.5 log10 decline) n = 151	Median Log10 Decline in Viral Load: Baseline to Day 8 n = 151
Overall	107/151 (71%)	1.05
No gp120 RAPs (at predefined sites)	70/83 (84%)	1.11
Predefined gp120 RAPs:		
S375I/M/N/T, M426L, M434I, or M475I/V	37/68 (54%)	0.66
S375M	1/5 (20%)	0.32
M426L	6/17 (35%)	0.19
M434I	3/6 (50%)	0.66
M475V	0/1 (0%)	0
1 gp120 RAP	38/62 (61%)	1.03
2 or 3 gp120 RAPs	18/26 (69%)	1.09

[a] Removed subjects who had <400 copies/mL at screening or >0.4 log_{10} decline from screening to baseline.

The fold change in susceptibility to temsavir for subject isolates at screening was highly variable ranging from 0.06 to 6,651.

The effect of screening fostemsavir phenotype on response of >0.5 log_{10} decline at Day 8 was assessed in the as-treated analysis. The majority of these subjects (55%, 83/151) had a screening temsavir EC_{50} fold change normalized to a reference virus of <2-fold. The response rate for fostemsavir phenotypes ≤2 was 80% (66/83) (**Table 13**). Response rates for fostemsavir phenotypic fold changes of >2 to 200 were moderately decreased to 69% (29/42). Phenotypic fold changes of >200 resulted in lower response rates to fostemsavir (29%, 5/17). Five subjects, despite having >200-fold decreased fostemsavir susceptibility and the presence of screening gp120 RAPs, had over 1 log_{10} declines in HIV-1 RNA at Day 8. Lack of resistance to background drugs or higher fostemsavir concentrations do not explain the >1 log_{10} response of these 5 subjects.

Table 13 Response Rate of Randomized Fostemsavir Cohort (>0.5 Log_{10} Decline Day 8) by Screening Phenotype

Fostemsavir Phenotypic Fold Change	Response Rate at Day 8 (>0.5 log_{10} decline) As-Treated Analysis[a] n = 151
Not Reported	9
0 -2	66/83 (80%)
>2 -10	17/25 (68%)
10 -200 (Range 11 -104)	12/17 (71%)
>200 (Range 234 -6,651)	5/17 (29%)

[a] Removed subjects who had <400 copies/mL at screening or >0.4 log_{10} decline from screening to baseline.

Resistance In Vivo

The percentage of subjects who experienced virologic failure through the Week 96 analysis was 25% (69/272) in the randomized cohort (including 25% [51/203] among subjects who received blinded fostemsavir functional monotherapy and 26% [18/69] among subjects who received blinded placebo during the 8-day double-blind period) (**Table 14**). Virologic failure = confirmed ≥400 copies/mL after prior confirmed suppression to <400 copies/ml, ≥400 copies/ml at last available prior to discontinuation, or >1 log10 copies/mL increase in HIV-1 RNA at any time above nadir level (≥40 copies/ml). Overall, 51% (27/53) of evaluable subjects with virologic failure in the randomized cohorts had treatment-emergent gp120 genotypic substitutions at 4 key sites (S375, M426, M434, and M475) (**Table 14)**.

The median temsavir EC50 fold change at failure in randomized evaluable subject isolates with emergent gp120 substitutions at positions 375, 426, 434, or 475 (n = 26) was 1,755-fold. In randomized evaluable subject isolates with no emergent gp120 substitutions at those positions (n = 27), the median temsavir EC50 fold change at failure was 3.6-fold.

Thirty percent (21/69) of the virologic failures in the randomized groups combined had genotypic or phenotypic resistance to at least one drug in the OBT at screening, and 48% (31/64) of the virologic failures with post-baseline data had emergent resistance to at least one drug in the OBT.

Rates of virologic failure were higher in the nonrandomized cohort at 51% (50/99) (**Table 14)**. While the proportion of virologic failures with gp120 RAPs at screening was similar between subjects in the randomized and nonrandomized cohorts, the proportion of subjects with emergent gp120 resistance-associated substitutions at the time of failure was higher among nonrandomized subjects (**Table 14)**.The median temsavir EC50 fold change at failure in nonrandomized evaluable subject isolates with emergent substitutions at positions 375, 426, 434, or 475 (n = 33) was 4,216-fold and was 767-fold among failure subject isolates without emergent resistance associated substitutions (n = 12). Consistent with the nonrandomized group of subjects having fewer antiretroviral options, 90% (45/50) of the virologic failures in this group had genotypic or phenotypic resistance to at least one drug in the OBT at screening, and 55% (27/49) of the virologic failures with post-baseline data in the nonrandomized group had emergent resistance to at least one drug in the OBT.

Table 14 Virologic Failures in BRIGHTE Trial

	Randomized Cohort Total	**Nonrandomized Cohort Total**
Number of virologic failures	69/272 (25%)	50/99 (51%)
With gp120 RAPs at screening (of those with genotypic data)	42/68 (62%)	26/48 (54%)
Virologic failures with post-baseline data	53	45
With emergent gp120 RAS	27/53 (51%)	33/45 (73%)
S375N	18/53 (34%)	21/45 (47%)
M426L/I	17/53 (32%)	23/45 (51%)
M434I/L	5/53 (9%)	5/45 (11%)
M475I/L/V	8/53 (15%)	5/45 (11%)

RAPs = Resistance-associated polymorphisms; RAS = Resistance-associated substitutions.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

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.

Carcinogenicity

In a 2-year carcinogenicity study conducted in rats and a 26-week carcinogenicity study conducted in transgenic mice, fostemsavir produced no statistically significant increases in tumors over controls. The maximum daily exposures in rats were approximately 5 times (males) and 16 times (females) greater than those in humans at the MRHD.

Mutagenesis

Fostemsavir was not genotoxic in the bacterial reverse mutation assay (Ames test in *Salmonella* and E. coli), a chromosome aberration test in human lymphocytes, and rat bone marrow micronucleus test.

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]RUKOBIA

fostemsavir extended-release tablets

Read this carefully before you start taking **RUKOBIA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RUKOBIA**.

What is RUKOBIA used for?

- RUKOBIA is used to treat HIV (human immunodeficiency virus) infection in adults who have had difficulty in controlling their HIV with many other antiretroviral medicines.
- It is used in patients who have HIV that is resistant to many antiretroviral medicines.
- RUKOBIA is used in combination with other antiretroviral medicines.

How does RUKOBIA work?

RUKOBIA belongs to a group of anti-retroviral medicines called attachment inhibitors (AIs). It works by binding to the virus and then blocking HIV from attaching to and infecting your blood cells.

RUKOBIA helps to reduce the amount of virus in your body and keep it at a low level. This helps maintain the number of CD4+ cell count in your blood. CD4+ cells are a type of white blood cells that are important in helping your body to fight infection. RUKOBIA does not cure HIV infection.

What are the ingredients in RUKOBIA?

Medicinal ingredients: 600 mg fostemsavir (as fostemsavir tromethamine).

Non-medicinal ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

RUKOBIA comes in the following dosage forms:

As an extended-release tablet containing 600 mg fostemsavir.

Do not use RUKOBIA if:

- You are allergic to fostemsavir or to any ingredient in RUKOBIA (listed above).
- You are taking any of these medicines:
  - carbamazepine, or phenytoin, known as anticonvulsants used to treat epilepsy and prevent seizures.
  - rifampin used to treat some bacterial infections such as tuberculosis.
  - mitotane used to treat several types of cancer.
  - enzalutamide used to treat prostate cancer.

- products that contain St John's wort (*Hypericum perforatum*) which is a herbal product used to treat depression.

These medicines are not recommended with RUKOBIA:

- elbasvir/grazoprevir used to treat hepatitis C infection.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RUKOBIA. Talk about any health conditions or problems you may have, including if you:

- Have or have had a heart problem, including a heart rhythm problem called QTc prolongation (irregular heartbeat).
- Have or have had liver problems including hepatitis B or C infection. Your healthcare professional may need to do tests to check your liver enzymes before and during treatment with RUKOBIA.

Other warnings you should know about:

Pregnancy:

Tell your doctor if you are pregnant or planning to become pregnant. You should not take RUKOBIA if you are pregnant or planning on becoming pregnant. It is not known if RUKOBIA can harm your unborn baby. Tell your doctor if you become pregnant while you are taking RUKOBIA.

Pregnancy Registry:

There is a pregnancy registry for women who take antiretroviral medicines while they are pregnant. The purpose of this registry is to collect information about the health of you and your baby. If you do become pregnant while taking RUKOBIA, talk to your doctor about taking part in this registry.

Breastfeeding:

You should not breastfeed if you are taking RUKOBIA. This is because RUKOBIA may pass into breast milk. You should also not breastfeed a baby if you are infected with HIV. This is because you can pass HIV to your baby. If you breastfeed a baby they can get HIV from you.

HIV Transmission:

RUKOBIA will not stop you from passing HIV to others, although this risk is lower if you take your HIV medicine as instructed by your healthcare professional. Always practice safe sex. Use condoms when you have oral or penetrative sex. Never re-use or share needles or other injection equipment. Ask your doctor if you have any questions about safe sex or how to prevent passing HIV to other people.

Immune Reconstitution Inflammatory Syndrome (disorder involving changes to your immune system) and Autoimmune Disorders:

Changes in your immune system can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Autoimmune disorders (when the immune system attacks healthy body tissue), may also occur after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), or polymyositis (which affects the muscles). Autoimmune disorders may occur many months after the start of treatment. See "Serious side effects and what to do about them".

QTc prolongation (Heart rhythm problem):

RUKOBIA may cause a heart rhythm problem called QTc prolongation. QTc prolongation causes an irregular heartbeat. If you are elderly, you may be at a greater risk for developing this heart problem with RUKOBIA. See "Serious side effects and what to do about them".

Changes in liver function:

Tell your doctor if you have hepatitis B or C infection. You are more likely to have negative changes to liver function test results while you are taking Rukobia. Your doctor will check your liver enzymes before and during your treatment with Rukobia. If you stop your hepatitis B treatment your hepatitis B infection may become active again. Always take all hepatitis B or C medicines prescribed to you while you are receiving RUKOBIA. See "Serious side effects and what to do about them".

Other complications:

Patients receiving RUKOBIA may develop complications of HIV, including infection. While taking Rukobia, you should remain under the close supervision of a doctor who is experienced in the treatment of HIV.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RUKOBIA:

- Medicines used to treat heart conditions such as amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, or sotalol.
- Medicines known as statins such as rosuvastatin, atorvastatin, pitavastatin, simvastatin or Fluvastatin, used to lower cholesterol levels.
- Ethinyl estradiol, used for birth control or hormone replacement therapy.

How to take RUKOBIA:

- Always take RUKOBIA exactly as your doctor has told you to.
- Swallow RUKOBIA tablets whole.
- Take with or without food.
- Do not break, crush or chew RUKOBIA tablets before swallowing.
- RUKOBIA tablets may have a slight odor like vinegar. This is normal.
- Check with your healthcare professional if you're not sure how to take RUKOBIA.

Usual dose:

The usual dose of RUKOBIA is one tablet taken twice a day.

Overdose:

If you think you, or a person you are caring for, have taken too much RUKOBIA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take RUKOBIA as soon as you remember. Never take a double dose to make up for a

missed dose.

What are possible side effects from using RUKOBIA?

These are not all the possible side effects you may have when taking RUKOBIA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of RUKOBIA include:

- nausea
- diarrhea
- headache
- rash
- dizziness
- abdominal pain
- vomiting
- feeling sleepy
- feeling weak
- tingling, numbness, weakness in hands and/or feet
- indigestion
- lack of energy
- difficulty sleeping
- muscle ache or pain
- itching
- taste disturbance
- changes in laboratory results that could mean muscle injury
- changes in laboratory results that could mean kidney injury

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Immune Reconstitution Inflammatory Syndrome and Autoimmune Disorders: fever, redness, rash or swelling, fatigue, joint or muscle pain , numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, chest pain or rapid heart rate, yellowing of the eyes and skin.		X	
FREQUENCY NOT KNOWN			
QTc prolongation (Heart rhythm problems): dizziness, feeling lightheaded, changes in heartbeat,		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
fainting (loss of consciousness).			
Changes in liver function: yellowing of the skin and the whites of the eyes, dark or tea coloured urine, pale coloured stools/ bowel movements, nausea, vomiting, loss of appetite, pain, aching or tenderness on right side below the rib, bilirubin increase (substance produced by liver), increase of liver enzymes (transaminases).		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store RUKOBIA at 15 °C to 25 °C.

Keep out of reach and sight of children.

If you want more information about RUKOBIA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.viivhealthcare.ca, or by calling 1-877-393-8448.

This leaflet was prepared by ViiV Healthcare ULC

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