ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rukobia 600 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains fostemsavir tromethamine equivalent to 600 mg fostemsavir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Beige, biconvex, oval tablets approximately 19 mm in length, 10 mm in width, and 8 mm in thickness and debossed with 'SV 1V7' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rukobia, in combination with other antiretrovirals, is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Rukobia should be prescribed by physicians experienced in the management of HIV infection.

Posology

The recommended dose is 600 mg of fostemsavir twice daily.

Missed doses
If the patient misses a dose of fostemsavir, the patient should take the missed dose as soon as the patient remembers, unless it is almost time for the next dose. In this case, the missed dose should be skipped and the next dose should be taken according to the regular schedule. The patient should not take a double dose to make up for the forgotten dose.

Elderly
No dosage adjustment is required (see sections 4.4 and 5.2).

Renal impairment
No dosage adjustment is required for patients with renal impairment or 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

The safety and efficacy of fostemsavir in children and adolescents aged less than 18 years have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

Method of administration

Oral use.
Fostemsavir can be taken with or without food (see section 5.2). The prolonged-release tablet should be swallowed whole with water, and not chewed, crushed or split.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with strong CYP3A inducers including, but not limited to: carbamazepine, phenytoin, mitotane, enzalutamide, rifampicin and St John's wort (see section 4.5).

4.4 Special warnings and precautions for use

Immune reconstitution inflammatory 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* (formerly *P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, 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

A supratherapeutic dose (at a C_{max} approximately 4.2-fold the therapeutic dose) of fostemsavir has been shown to significantly prolong the QTc interval of the electrocardiogram (see section 5.1). Fostemsavir should be used with caution in patients with a history of QT interval prolongation, when co-administered with a medicine with a known risk of Torsade de Pointes (e.g. amiodarone, disopyramide, ibutilide, procainamide, quinidine, or sotalol) or in patients with relevant pre-existing cardiac disease. Elderly patients may be more susceptible to drug-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. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Opportunistic infections

Patients should be advised that fostemsavir or any other antiretroviral therapy does not cure HIV infection and that they 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.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, biphosphonates, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Restricted range of antiviral activity

In vitro data indicate that the antiviral activity of temsavir is restricted to HIV-1 Group M strains. Rukobia should not be used to treat infections due to HIV-1 strains other than those of Group M (see section 5.1).

Within HIV-1 group M, there is considerably reduced antiviral activity against CRF01_AE virus. Available data indicate that this subtype has a natural occurring resistance to temsavir (see section 5.1). It is recommended that Rukobia is not used to treat infections due to HIV-1 Group M subtype CRF01_AE strains.

Interactions with other medicinal products

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

When fostemsavir is co-administered with tenofovir alafenamide (TAF), temsavir is expected to increase plasma concentrations of TAF via inhibition of OATP1B1/3 and/or BCRP. The recommended dose of TAF is 10 mg when co-administered with fostemsavir (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medical products on the pharmacokinetics of temsavir

Temsavir is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not of organic anion transporters OATP1B1 or OATP1B3. Its biotransformation to two circulating metabolites, BMS-646915 and BMS-930644, is mediated by unidentified esterases (36.1%) and by cytochrome P_{450} (CYP)3A4 enzyme (21.2%), respectively.

When fostemsavir was co-administered with the strong CYP3A inducer rifampicin, a significant reduction in temsavir plasma concentrations was observed. Significant decreases in temsavir plasma concentrations may also occur when fostemsavir is co-administered with other strong CYP3A inducers, and may result in loss of virologic response (see section 4.3).

Fostemsavir 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 drug interaction studies with cobicistat and ritonavir.

Effect of temsavir on the pharmacokinetics of other medicinal products

In vitro, temsavir inhibited OATP1B1 and OATP1B3 (IC_{50} = 32 and 16 µM, respectively). Additionally, temsavir and its two metabolites (BMS-646915 and BMS-930644) inhibited 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 active substances 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.

Interaction table

Selected drug interactions are presented in Table 1. Recommendations are based on either drug interaction studies or predicted interactions based on the expected magnitude of the interaction and potential for serious adverse events or loss of efficacy. (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).

Table 1: Interactions

Concomitant medicinal product by therapeutic area	**Effect on concentration of temsavir or concomitant medicinal product**	**Recommendation concerning co-administration**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor		
Efavirenz (EFV)	Temsavir ↓ (induction of CYP3A enzymes)[1]	This interaction has not been studied. Efavirenz is expected to decrease temsavir plasma concentrations. No dose adjustment is necessary.
Etravirine (ETR) without boosted protease inhibitors	Temsavir ↓ AUC ↓ 50% C_{max} ↓ 48% Cτ ↓ 52% (induction of CYP3A enzymes)[1] ETR ↔	Etravirine decreased temsavir plasma concentrations. No dose adjustment of either medicinal product is necessary.
Nevirapine (NVP)	Temsavir ↓ (induction of CYP3A enzymes)[1]	This interaction has not been studied. Nevirapine is expected to decrease temsavir plasma concentrations. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor		
Tenofovir disoproxil (TDF)	Temsavir ↔ AUC ↔ C_{max} ↓ 1% Cτ ↑ 13% Tenofovir ↑ AUC ↑ 19% C_{max} ↑ 18% Cτ ↑ 28%	No dose adjustment of either medicinal product is necessary.

Tenofovir alafenamide (TAF)	TAF ↑ (inhibition of OATP1B1/3 and/or BCRP)	This interaction has not been studied. Temsavir is expected to increase tenofovir alafenamide plasma concentrations. The recommended dose of TAF is 10 mg when co-administered with fostemsavir.
Protease Inhibitor		
Atazanavir (ATV)/ritonavir (RTV)	Temsavir ↑ AUC ↑ 54% C_{max} ↑ 68% Cτ ↑ 57% (inhibition of CYP3A enzymes and P-gp)[1] ATV ↔ RTV ↔	Atazanavir/ritonavir increased temsavir concentrations. No dose adjustment of either medicinal product is necessary.
Darunavir (DRV)/cobicistat	Temsavir ↑ AUC ↑ 97% C_{max} ↑ 79% Cτ ↑ 124% (inhibition of CYP3A enzymes, P-gp and/or BCRP)[1]	Darunavir/cobicistat increased temsavir plasma concentrations. No dose adjustment is necessary.
Darunavir (DRV)/ritonavir	Temsavir ↑ AUC ↑ 63% C_{max} ↑ 52% Cτ ↑ 88% (inhibition of CYP3A enzymes and P-gp)[1] DRV ↔ AUC ↓ 6% C_{max} ↓ 2% Cτ ↓ 5% RTV ↔ AUC ↑ 15% C_{max} ↔ Cτ ↑ 19%	Darunavir/ritonavir increased temsavir plasma concentrations. No dose adjustment is necessary for any medicinal product when co-administered.
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 ↔	Darunavir/ritonavir co-administered with etravirine increased temsavir plasma concentrations. No dose adjustment is necessary for any medicinal product when co-administered.

	AUC ↑ 28% C_{max} ↑ 18% Cτ ↑ 28%	
Pharmacokinetic Enhancer		
Cobicistat (COBI)	Temsavir ↑ AUC ↑ 93% C_{max} ↑ 71% Cτ ↑ 136% (inhibition of CYP3A enzymes, P-gp and/or BCRP)[1]	Cobicistat increased temsavir plasma concentrations. No dose adjustment is necessary.
Ritonavir	Temsavir ↑ AUC ↑ 45% C_{max} ↑ 53% Cτ ↑ 44% (inhibition of CYP3A and P-gp)[1] RTV ↔	Ritonavir increased temsavir plasma concentrations. No dose adjustment of either medicinal product is necessary.
Others		
Maraviroc (MVC)	Temsavir ↔ C_{max} ↑ 13% AUC ↑ 10% Cτ ↓ 10% MVC ↔ AUC ↑ 25% C_{max} ↑ 1% Cτ ↑ 37%	No dose adjustment of either medicinal product is necessary.
Raltegravir (RAL)	Temsavir ↔* RAL ↔*	No dose adjustment of either medicinal product is necessary.
Other medicinal products		
Buprenorphine/naloxone	Buprenorphine ↔ AUC ↑ 30% C_{max} ↑ 24% Norbuprenorphine ↔ AUC ↑ 39% C_{max} ↑ 24%	No dose adjustment necessary.
Methadone	Methadone ↔ R-Methadone AUC ↑ 13% C_{max} ↑ 15% S-Methadone AUC ↑ 15% C_{max} ↑ 15%	No dose adjustment necessary.
H_2-Receptor Antagonists: Famotidine	Temsavir ↔ AUC ↑ 4% C_{max} ↑ 1% Cτ ↓ 10%	No dose adjustment is necessary when combined with medicinal products that increase gastric pH.

Oral contraceptives: Ethinyl estradiol (EE) Norethindrone acetate (NE)	EE ↑ AUC ↑ 39% C_{max} ↑ 40% (inhibition of CYP enzymes and/or BCRP)[1] NE ↔ AUC ↑ 8% C_{max} ↑ 8%	EE should not exceed 30 µg daily. Caution is advised, particularly in patients with additional risk factors for thromboembolic events (see section 4.4). No dose adjustment is necessary
Rifabutin	Temsavir ↓ AUC ↓ 30% C_{max} ↓ 27% Cτ ↓ 41% (induction of CYP3A enzymes)[1]	Rifabutin decreased temsavir plasma concentrations. No dose adjustment is necessary.
Rifabutin + Ritonavir	Temsavir ↑ AUC ↑ 66% C_{max} ↑ 50% Cτ ↑ 158%	Rifabutin co-administered with ritonavir increased temsavir plasma concentrations. No dose adjustment is necessary.
Rifampicin	Temsavir ↓ AUC ↓ 82% C_{max} ↓ 76% (induction of CYP3A enzymes)	Rifampicin co-administration may lead to loss of virologic response to fostemsavir due to significant decreases in temsavir plasma concentrations caused by strong CYP3A4 induction. Therefore, the concomitant use of fostemsavir and rifampicin is contraindicated. Although not studied, concomitant use of fostemsavir and other strong CYP3A4 inducers is contraindicated (see section 4.3).
HMG CO-A Reductase Inhibitors: Rosuvastatin Atorvastatin Pitavastatin Fluvastatin Simvastatin Pravastatin	Rosuvastatin ↑ AUC ↑ 69% C_{max} ↑ 78% (inhibition of OATP1B1/3 and/or BCRP) Pravastatin ↑	Coadministration of fostemsavir increases rosuvastatin plasma concentrations caused by OATP1B1/3 and/or BCRP inhibition by temsavir. Therefore 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 reactions. 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 required.

Hepatitis C virus Direct-Acting Antivirals (HCV DAAs): Elbasvir/Grazoprevir	Grazoprevir ↑ (inhibition of OATP1B1/3)	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.

[1]Potential mechanism(s) of drug interactions

QT prolonging medicinal products

There is no information available on the potential for a pharmacodynamic interaction between fostemsavir and medicinal products that prolong the QTc interval of the ECG. However, based on a study of healthy subjects, in which a supratherapeutic dose of fostemsavir prolonged the QTc interval, fostemsavir should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of fostemsavir in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposure levels of temsavir in the range of the recommended human dose (RHD) (see section 5.3). In pregnant rats fostemsavir and/or its metabolites cross the placenta and are distributed to all foetal tissues.

As a precautionary measure, it is preferable to avoid the use of Rukobia during pregnancy.

Breast-feeding

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

It is unknown whether fostemsavir/temsavir are excreted in human milk. Available toxicokinetic data in lactating rats have shown excretion of fostemsavir/temsavir in milk (see section 5.3).

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 section 5.3).

4.7 Effects on ability to drive and use machines

Fostemsavir has a minor influence on the ability to drive and use machines. Patients should be informed that headache, dizziness and somnolence have been reported during treatment with fostemsavir (see section 4.8). The clinical status of the patient and the adverse reaction profile of fostemsavir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reaction was immune reconstitution inflammatory syndrome (see section 4.4). The most commonly seen adverse reactions were diarrhoea (24%), headache (17%), nausea (15%), rash (12%), abdominal pain (12%), and vomiting (11%).

Tabulated list of adverse reactions

The adverse reactions identified in clinical trials are listed in Table 2 by body system, organ class and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 2: Tabulated list of adverse reactions

System Organ Class	Frequency[1]	Adverse Reactions
Immune system disorders	Common	Immune reconstitution inflammatory syndrome[2] (see section 4.4)
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness, somnolence, dysgeusia
Cardiac disorders	Common	Electrocardiogram QT prolonged (see section 4.4)
Gastrointestinal disorders	Very common	Diarrhoea, nausea, abdominal pain[3], vomiting
	Common	Dyspepsia, flatulence
Hepatobiliary disorders	Common	Transaminases increased[4]
Skin and subcutaneous tissue disorders	Very common	Rash[5]
	Common	Pruritus[6]
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Blood creatinine increased, blood creatine phosphokinase increased

[1] Calculated based on safety data from 570 subjects (n=370 from phase III [BRIGHTE] study at 144 weeks, and n=200 from phase IIb study with mean duration 174 weeks).
[2]Includes central nervous system immune reconstitution inflammatory response and immune reconstitution inflammatory syndrome.
[3]Includes abdominal discomfort, abdominal pain and abdominal pain upper.
[4]Includes increases in ALT, AST, hepatic enzymes and transaminases.
[5]Includes rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic and rash vesicular.
[6]Includes pruritus and pruritus generalised.

Description of selected adverse reactions

Changes in laboratory chemistries
Increases in creatine phosphokinase (CPK) were observed following treatment with fostemsavir, which were mainly mild or moderate. These changes were rarely associated with musculoskeletal complaints 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 medicinal products known to cause increases in creatinine. A causal association between fostemsavir and elevation in serum creatinine has not been established.

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

Increases in direct (conjugated) bilirubin have been observed following treatment with fostemsavir. Cases of clinical significance were uncommon and were confounded by the presence of intercurrent serious comorbid events not related to dosing with study medication (e.g. sepsis, cholangiocarcinoma or other complications of viral hepatitis co-infection). In the remaining reports, elevations in direct bilirubin (without clinical jaundice) were typically transient, occurred without increases in liver transaminases and resolved on continued fostemsavir.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for overdose with fostemsavir. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and given appropriate symptomatic treatment. Standard supportive measures should be applied as required, including monitoring of vital signs as well as observation of the clinical status of the patient. 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 poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AX29.

Mechanism of action

Fostemsavir is a prodrug without significant antiviral activity that is hydrolysed to the active moiety, temsavir, upon cleavage of a phosphonooxymethyl group *in vivo* (see section 5.2). 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 receptor, thereby preventing viral entry into, and infection of, host cells.

Pharmacodynamic effects

Antiviral activity in cell culture
Temsavir exhibited variable activity across HIV-1 subtypes. Temsavir IC_{50} value ranged from 0.01 to >2000 nM against clinical isolates of subtypes A, B, B', C, D, F, G and CRF01_AE in PBMCs. Temsavir was not active against HIV-2. Due to high frequencies of polymorphism S375H (98%) and S375M/M426L/M434I (100%) temsavir is not active against Group O and Group N (see section 4.4).

Against a panel of 1337 clinical isolates tested with the PhenoSense Entry assay, the mean IC_{50} value was 1.73 nM (range 0.018 to >5000 nM). Isolates tested included subtype B (n=881), C (n=156), F1 (n=48), A (n=43), BF1 (n=29), BF (n=19), A1 (n=17) and CRF01_AE (n=5). Subtype CRF01_AE was associated with higher IC_{50} values (5/5 isolates with temsavir IC_{50} values >100 nM). CRF01_AE is considered naturally resistant to temsavir on the basis of available data, due to the presence of polymorphisms at positions S375H and M475I (see below).

Antiviral activity in combination with other antiviral agents
When tested with temsavir *in vitro*, no antagonism was seen with abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil, zidovudine, efavirenz, nevirapine, atazanavir, indinavir, lopinavir, ritonavir, saquinavir, enfuvirtide, maraviroc, ibalizumab, delavirdine, rilpivirine, darunavir, dolutegravir or raltegravir. In addition, antivirals without inherent anti-HIV activity (entecavir, ribavirin) have no apparent effect on temsavir activity.

Resistance in vitro
Serial passage of lab-strains LAI, NL_{4-3}, or Bal, in increasing concentrations of temsavir (TMR) over 14 to 49 days resulted in gp120 substitutions at L116, A204, M426, M434 and M475. Phenotypes of recombinant LAI viruses containing TMR-selected substitutions were investigated. Additionally, phenotypes of viruses with substitutions at position S375 that were identified in pre-treatment samples in fostemsavir clinical studies were evaluated. The phenotypes of those considered clinically relevant are tabulated below (Table 3).

Table 3: Phenotypes of recombinant LAI viruses containing clinically relevant gp120 substitutions

Substitutions	**Fold-change vs wild type EC_{50}**	**Frequency in 2018 LANL database %**
Wild type	1	-
S375H	48	10.71
S375I	17	1.32
S375M	47	1.17
S375N	1	1.96
S375T	1	8.86
S375V	5.5	-
S375Y	>10000	0.04
M426L	81	5.33
M426V	3.3	0.31
M434I	11	10.19
M434T	15	0.55
M475I	4.8	8.84
M475L	17	0.09
M475V	9.5	0.12

Note: The phenotype of substitutions at L116 and A204 have been excluded from the table as they are not considered clinically relevant.

Temsavir remained active against laboratory derived CD4-independent viruses.

Cross-Resistance
There was no evidence of cross-resistance to representative agents from other antiretroviral (ARV) classes. Temsavir retained wild-type activity against viruses resistant to the INSTI raltegravir; the NNRTIs rilpivirine and efavirenz; the NRTIs abacavir, lamivudine, tenofovir, zidovudine and the PIs atazanavir and darunavir. Additionally, abacavir, tenofovir, efavirenz, rilpivirine, atazanavir, darunavir and raltegravir retained activity against site-directed mutant viruses with reduced temsavir susceptibility (S375M, M426L, or M426L plus M475I).

No cross-resistance was observed between temsavir and maraviroc or enfuvirtide. Temsavir was active against viruses with resistance to enfuvirtide. Some CCR5-tropic, maraviroc-resistant, viruses showed reduced susceptibility to temsavir, however, there was no absolute correlation between maraviroc resistance and reduced sensitivity to temsavir. Maraviroc and enfuvirtide retained activity against clinical envelopes from the Phase IIa study (206267) that had reduced susceptibility to temsavir and contained S375H, M426L, or M426L plus M475I substitutions.

Temsavir was active against several ibalizumab-resistant viruses. Ibalizumab retained activity against site-directed mutant viruses that had reduced susceptibility to temsavir (S375M, M426L, or M426L plus M475I). HIV-1 gp120 E202 was identified as a rare treatment-emergent substitution in BRIGHTE that can reduce susceptibility to temsavir, and, depending on the sequence context of the envelope, may also result in reduced susceptibility to ibalizumab.

Virologic response at Day 8 by genotype and phenotype in BRIGHTE
The effect of the gp120 resistance-associated polymorphisms (RAPs) on response to fostemsavir functional monotherapy at Day 8 was assessed in the Phase III study (BRIGHTE [205888]) in heavily treatment-experienced adult subjects. 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 log_{10} decline in HIV-1 RNA compared with subjects with no changes at these sites (Table 4).

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 ITT-E population (Table 5). While there does appear to be a trend toward reduced clinical response at higher TMR IC_{50} values, this baseline variable fails to reliably predict efficacy outcomes in the intended use population.

Table 4: Virologic Response Category at Day 8 (Randomised Cohort) by presence of gp120 resistance-associated polymorphisms (RAPs) at baseline – ITT-E Population

		Randomised Cohort FTR 600 mg BID (N=203) n (%)			
		Response Category[a]			**Missing[b]**
	n	**>1.0 log_{10}**	**>0.5 to ≤1.0 log_{10}**	**≤0.5 log_{10}**	
n	203	93	38	64	8
Sequenced	194				
No gp120 RAPs (at pre-defined sites)	106	54 (51)	25 (24)	24 (23)	3 (3)
Pre-defined gp120 RAPs (S375H/I/M/N/T, M426L, M434I, M475I)	88	36 (41)	12 (14)	37 (42)	3 (3)
S375 S375H/I/M/N/T S375H S375M S375N	 64 1 5 22	 29 (45) 0 1 (20) 10 (45)	 9 (14) 0 0 3 (14)	 23 (36) 1 (100) 4 (80) 8 (36)	 3 (5) 0 0 1 (5)
M426L	22	7 (32)	3 (14)	12 (55)	0
M434I	9	5 (56)	0	4 (44)	0
M475I	1	0	0	1 (100)	0
1 gp120 RAP	80	31 (39)	12 (15)	34 (43)	3 (4)
2 gp120 RAPs	8	5 (63)	0	3 (38)	0

a. Change in HIV-1 RNA (log10 c/mL) from Day 1 at Day 8, n (%)
b. Subjects with Day 8 Virologic Response Category unevaluable due to missing Day 1 or Day 8 HIV-1 RNA, n (%)
Note: S375Y was not included in the list of substitutions pre-defined for analysis in the phase III study, although. it was subsequently identified as a novel polymorphism and shown to substantially decrease TMR susceptibility in a LAI envelope *in vitro.*
RAPs = Resistance-associated polymorphisms

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

Baseline Temsavir IC_{50} Fold Change Category	**Virologic Response at Day 8 (>0.5 log_{10} decline in HIV-1 RNA from Day 1 to Day 8) n=203**
IC_{50} FC value not reported	5/9 (56%)
0-3	96/138 (70%)
>3-10	11/13 (85%)
>10-200	12/23 (52%)
>200	7/20 (35%)

Antiviral activity against subtype AE
Within HIV-1 Group M, temsavir showed considerably reduced antiviral activity against subtype AE isolates. Rukobia is not recommended to be used to treat infections due to HIV-1 Group M subtype CRF01_AE strains. 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 frequently elsewhere.

Two subjects in the Randomised Cohort had subtype AE virus at screening. One subject (EC_{50} fold change >4,747-fold and gp120 substitutions at S375H and M475I at baseline) did not respond to fostemsavir at Day 8. The second subject (EC_{50} fold change 298-fold and gp120 substitution at S375N at baseline) received placebo during functional monotherapy. Both subjects had HIV RNA <40 copies/mL at Week 96 while receiving fostemsavir plus OBT that included dolutegravir.

Emergence of Resistance in vivo
The percentage of subjects who experienced virologic failure through the Week 96 analysis was 25% (69/272) in the randomised cohort (Table 6). Overall, 50% (26/52) of the viruses of evaluable subjects with virologic failure in the Randomised Cohort had treatment-emergent gp120 genotypic substitutions at 4 key sites (S375, M426, M434, and M475).

The median temsavir EC_{50} fold change at failure in randomised evaluable subject isolates with emergent gp120 substitutions at positions 375, 426, 434, or 475 (n = 26) was 1,755-fold compared to 3-fold for isolates with no emergent gp120 substitutions at these positions (n = 26).

Of the 25 evaluable subjects in the Randomised Cohort with virologic failure and emergent substitutions S375N and M426L and (less frequently) S375H/M, M434I and M475I, 88% (22/25) had temsavir IC_{50} FC Ratio > 3-fold (FC Ratio is temsavir IC_{50} FC on-treatment compared to baseline).

Overall, 21/69 (30%) of the virus isolates of patients with virologic failure in the Randomised Cohort had genotypic or phenotypic resistance to at least one drug in the OBT at screening and in 48% (31/64) of the virologic failures with post-baseline data the virus isolates had emergent resistance to at least one drug in the OBT.

In the Non-randomised Cohort virologic failures were observed in 51% (50/99) through Week 96 (Table 6). While the proportion of viruses with gp120 resistance-associated substitutions at screening was similar between patients in the Randomised and Non-randomised Cohorts, the proportion of virus isolates with emergent gp120 resistance-associated substitutions at the time of failure was higher among Non-randomised patients (75% vs. 50%). The median temsavir EC_{50} fold change at failure in Non-randomised evaluable subject isolates with emergent substitutions at positions 375, 426, 434, or 475 (n = 33) was 4,216-fold and compared to 402-fold for isolates without substitutions at these positions (n = 11).

Of the 32 evaluable virologic failures in the Non-randomised Cohort with emergent substitutions S375N and M426L and (less frequently) S375H/M, M434I and M475I, 91% (29/32) had temsavir IC_{50} FC Ratio > 3-fold.

Overall, 45/50 (90%) of the viruses of patients with virologic failure in the Non-randomised Cohort had genotypic or phenotypic resistance to at least one drug in the OBT at screening and in 55% (27/49) of the virologic failures with post-baseline data the virus isolates had emergent resistance to at least one drug in the OBT.

Table 6: Virologic Failures in BRIGHTE Trial

	Randomised Cohort Total	**Non-randomised Cohort Total**
Number of virologic failures	69/272 (25%)	50/99 (51%)
Virologic failures with available gp120 data at baseline	68/272 (25%)	48/99 (48%)
With baseline EN RAPs	42/68 (62%)	26/48 (54%)
Virologic failures with post-baseline gp120 data	52	44
With Any Emergent EN RAS[a]	26/52 (50%)	33/44 (75%)
With emergent EN RAS[b]	25/52 (48%)	32/44 (73%)
S375H	1/52 (2%)	2/44 (5%)
S375M	1/52 (2%)	3/44 (7%)
S375N	13/52 (25%)	17/44 (39%)
M426L	17/52 (33%)	21/44 (48%)
M434I	5/52 (10%)	4/44 (9%)
M475I	6/52 (12%)	5/44 (11%)
With EN RAS and with temsavir IC_{50} fold change ratio >3-fold[b,c]	22/52 (42%)	29/44 (66%)
Without EN RAS and with temsavir IC_{50} fold change ratio >3-fold[c]	3/52 (6%)	2/44 (5%)

EN RAPs = Envelope resistance-associated polymorphisms; EN RAS = Envelope resistance-associated substitutions.

a. Substitutions at positions: S375, M426, M434, M475.
b. Substitutions: S375H, S375M, S375N, M426L, M434I, M475I.
c. Temsavir IC_{50} fold change ratio >3-fold is outside of the usual variability observed in the PhenoSense Entry assay.

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 1 200 mg once daily, fostemsavir 2 400 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).

Clinical efficacy

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

BRIGHTE (205888), 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 ARVs which could be combined as part of an efficacious background regimen. 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). The Randomised Cohort provides primary evidence of efficacy of fostemsavir.

Within the Non-randomised Cohort, 99 subjects with no fully active, approved ARVs available at Screening, were treated with open-label fostemsavir, 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.

Table 7: Summary of Demographic and Baseline Characteristics in BRIGHTE trial-ITT-E Population

	Randomised Cohort			Non-Randomised 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)
Baseline HIV-1 RNA (log_{10} 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/mm^3, 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 Randomised Cohort, demonstrated superiority of fostemsavir to placebo (0.79 vs. 0.17 log_{10} decline, respectively; p<0.0001, Intent To Treat-Exposed [ITT-E] population) (Table 8).

Table 8: 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.

Median change in HIV-1 RNA log_{10} c/mL from Day 1 to Day 8 of FTR functional monotherapy was similar in subjects with subtype B and non-B subtype virus (F1, BF1 and C). There was a reduced median response at Day 8 observed in subtypes A1 (n=2) and AE (n=1) but sample size was limited (Table 9).

Table 9: HIV-1 RNA ($log1_0$ c/mL) Change from Day 1 at Day 8 by HIV subtype at Baseline

Randomised Cohort FTR 600 mg BID (N=203)								
	Plasma HIV-1 RNA (log_{10} copies/mL) Change from Day 1 at Day 8							
HIV subtype at Baseline	**n**	**Mean**	**SD**	**Median**	**Q1**	**Q3**	**Min.**	**Max.**
n	199[a]	-0.815	0.7164	-0.877	-1.324	-0.317	-2.70	1.25
B	159[a]	-0.836	0.7173	-0.923	-1.360	-0.321	-2.70	1.25
F1	14	-0.770	0.6478	-0.760	-1.287	-0.417	-1.61	0.28
BF1	10	-0.780	0.5515	-0.873	-1.074	-0.284	-1.75	-0.01
C	6	-0.888	0.6861	-0.823	-1.155	-0.558	-2.02	0.05
A1	2	-0.095	0.3155	-0.095	-0.318	0.128	-0.32	0.13
AE	1	0.473		0.473	0.473	0.473	0.47	0.47
Other[b]	7	-0.787	1.0674	-1.082	-1.529	-0.034	-2.11	1.16

Note: FTR Monotherapy refers to functional monotherapy where FTR is given on a background of failing ARV therapy.
a. Number of subjects with both Day 1 and Day 8 data available
a. Other includes (n): Non-analysable/Not reported (1), G (2); Recombinant virus/Mixtures (4).

Virologic outcomes by ITT-E Snapshot Analysis at Weeks 24, 48 and 96 are shown in Tables 10 and 11 for the Randomised and Non-randomised Cohorts, respectively.

Table 10: 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%)
Response by DTG as a component of OBT			
DTG	129/229 (56%)	127/229(55%)	146/229 (64%)
DTG (once daily)	35/58 (60%)	34/58 (59%)	40/58 (69%)
DTG (twice daily)	94/171 (55%)	93/171 (54%)	106/171 (62%)
No DTG	15/43 (35%)	19/43 (44%)	17/43 (40%)
Response by DTG and DRV as a component of OBT			
DTG and DRV	68/117 (58%)	60/117 (51%)	75/117 (64%)
With DTG, without DRV	61/112 (54%)	67/112 (60%)	71/112 (63%)
Without DTG, with DRV	5/17 (29%)	8/17 (47%)	8/17 (47%)
Without DTG, without DRV	10/26 (38%)	11/26 (42%)	9/26 (35%)
Gender			
Male	104 / 200 (52%)	102 / 200 (51%)	118 / 200 (59%)
Female	40 / 72 (56%)	44 / 72 (61%)	45 / 72 (63%)
Race			
White	90 / 185 (49%)	92 / 185 (50%)	103 / 185 (56%)
Black or African-American/Others	54 / 87 (62%)	54 / 87 (62%)	60 / 87 (69%)
Age (years)			
<50	81 / 162 (50%)	81 / 162 (50%)	96 / 162 (59%)
≥50	63 / 110 (57%)	65 / 110 (59%)	67 / 110 (61%)

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

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).

Table 11: Virologic Outcomes (HIV-1 RNA <40 copies/mL) at Weeks 24, 48 and 96 with Fostemsavir (600 mg twice daily) plus Optimised Background Treatment (Non-Randomised Cohort) in BRIGHTE trial (ITT-E Population, Snapshot Algorithm)

	Fostemsavir 600 mg twice daily		
	Week 24 (N = 99)	**Week 48 (N = 99)**	**Week 96 (N = 99)**
HIV-1 RNA <40 copies/mL	37%	38%	37%
HIV-1 RNA ≥40 copies/mL	55%	53%	43%
Data in window not <40 copies/mL	44%	33%	15%
Discontinued for lack of efficacy	0%	2%	3%
Discontinued for other reasons while not suppressed	2%	3%	6%
Change in ART regimen	8%	14%	19%
No virologic data	8%	9%	19%
Reasons			
Discontinued study/study drug due to adverse event or death	4%	7%	14%
Discontinued study/study drug for other reasons	0%	2%	4%
Missing data during window but on study	4%	0%	1%

In the Non-randomised Cohort (subjects with no fully active and approved ARVs available at Screening), 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%, at Weeks 24, 48 and 96, 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Rukobia in one or more subsets of the paediatric population in HIV infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of temsavir following administration of fostemsavir are similar between healthy and HIV-1 infected subjects. In HIV-1 infected subjects, the between-subject variability (%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 oral central 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 prodrug that is metabolised 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). Temsavir is absorbed across the small intestine and caecum/proximal ascending colon.

Pharmacokinetic parameters following multiple oral doses of fostemsavir 600 mg twice daily in HIV-1 infected, adult subjects are shown in Table 12.

Table 12: Multiple-Dose Pharmacokinetic Parameters of Temsavir following oral administration of Fostemsavir 600 mg twice daily

Pharmacokinetic Parameters	**Geometric Mean (CV%)[a]**
C_{max} (μg/mL)	1.77 (39.9)
AUC (μg*hr/mL)	12.90 (46.4)
C_{12} (μg/mL)	0.478 (81.5)

a. Based on population pharmacokinetic analyses with or without food, in combination with other antiretroviral drugs.
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

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. 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.

Biotransformation

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 metabolised, 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).

Interactions

Significant interactions are not expected when fostemsavir is co-administered with substrates of CYPs, uridine diphosphate glucuronosyl transferases (UGTs), P-gp, multidrug resistance protein (MRP)2, bile salt export pump (BSEP), sodium taurocholate co-transporting polypeptide (NTCP), OAT1, OAT3, organic cation transporters (OCT)1, and OCT2 based on *in vitro* and clinical drug interaction data. Based on *in vitro* data, temsavir and its two metabolites (BMS-646915 and BMS-930644) inhibited multidrug and toxin extrusion protein (MATE)1/2K; this interaction is unlikely to be of clinical significance.

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 administration was 66.4 L/hr. After oral administration of a single 300 mg dose of ^{14}C-labelled 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 the faecal excretion is from biliary excretion.

Linearity/non-linearity

Following single and repeat administration of fostemsavir ER tablets, increases in plasma temsavir exposure (C_{max} and AUC) appeared dose proportional, or slightly greater than dose proportional, in HIV-1 infected subjects.

Special patient populations

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

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 greater than 65 years old are limited. Elderly patients may be more susceptible to drug-induced QT interval prolongation (see section 4.4).

Renal impairment
The effect of renal impairment on the exposure of temsavir after a single 600 mg dose of fostemsavir was evaluated in an open-label study in 30 adult subjects with normal renal function, mild, moderate, and severe renal impairment, and subjects with ESRD on haemodialysis (n=6 per group). Based on creatinine clearance (CLcr), as follows: $60 \leq$ CLcr ≤ 89 (mild), $30 \leq$ 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 $\leq$15% and for AUC $\leq$30% for the mild, moderate, and severe RI groups. C_{max} (bound and unbound) was lower than the C_{max} threshold of an approximate 4.2-fold increase (7500 ng/ml) established based on temsavir exposure-response. 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
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. 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 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.

5.3 Preclinical safety data

Carcinogenesis and 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 toxicity

In rats, male fertility was not affected at TMR exposures up to 125 times the human exposure at the RHD despite testicular and epididymal toxicity. Female fertility and early pregnancy were also not adversely affected at exposures up to 186 times the human exposure at the RHD. While embryofetal exposure was demonstrated in a separate distribution study in pregnant rats with oral administration of ^{14}C-FTR, no effects on embryofetal development were noted in this species at exposures up to 200 times the human exposure at the RHD. In rabbits embryofetal development was also not affected at exposures up to 30 times the human exposure at the RHD. Prenatal and postnatal development including the attainment of puberty and learning memory in offspring was not influenced in rats at exposures up to 50 times the human exposure at the RHD. At maternal exposures that are up to 130 times the human AUC at the RHD, reduced postnatal viability probably due to an increased lactational exposure to TMR was noted in the offspring. TMR is present in the milk of lactating rats and in the blood of the rat pups exposed through lactation.

Repeated dose toxicity

Fostemsavir has been evaluated in repeat dose toxicity studies in rats (up to 26 weeks) and in dogs (up to 39 weeks). Cardiovascular telemetry studies indicated that both FTR and TMR minimally prolonged the QT interval in dogs (approximately 8 to 18 msec) at plasma concentrations of TMR >2x RHD C_{max}. 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

Poly(vinyl alcohol)
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White high density polyethylene (HDPE) bottles with polypropylene child resistant closures that include a polyethylene faced induction heat seal liner. Each pack consists of one or three bottles, each containing 60 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1518/001
EU/1/20/1518/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 February 2021
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana, 90
San Polo di Torrile
Parma, 43056
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rukobia 600 mg prolonged-release tablets
fostemsavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains fostemsavir tromethamine equivalent to 600 mg fostemsavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet
60 prolonged-release tablets

180 (3 bottles of 60) prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1518/001
EU/1/20/1518/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rukobia

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Rukobia 600 mg prolonged-release tablets
fostemsavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains fostemsavir tromethamine equivalent to 600 mg fostemsavir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1518/001
EU/1/20/1518/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rukobia 600 mg prolonged-release tablets
fostemsavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rukobia is and what it is used for

Rukobia contains fostemsavir and is a type of HIV medicine (anti-retroviral) known as an *attachment inhibitor* (AI). It works by attaching to the virus and then blocking it from entering your blood cells.

Rukobia is used with other anti-retroviral medicines (*combination therapy*), to treat HIV infection in adults with limited treatment options (other anti-retroviral medicines are not sufficiently effective or are not suitable).

Rukobia does not cure HIV infection; it reduces the amount of virus in your body and keeps it at a low level. Given HIV reduces the number of CD4 cells in your body, keeping HIV at a low level also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cell that are important in helping your body fight infection.

2. What you need to know before you take Rukobia

Do not take Rukobia

- if you are **allergic to fostemsavir** or to any of the other ingredients of this medicine (listed in Section 6)
- if you are taking any of these medicines:
    - **carbamazepine**, or **phenytoin** (used to treat **epilepsy** and prevent seizures (fits))
    - **mitotane** (to treat several types of **cancer**)
    - **enzalutamide** (to treat **prostate cancer**)
    - **rifampicin** (to treat some **bacterial infections** such as **tuberculosis**)

- medicines that contain **St John's wort (***Hypericum perforatum***)** (a herbal product for **depression**).

➔ **If you think any of these apply to you, do not take Rukobia** until you have checked with your doctor.

Warnings and precautions
Conditions you need to look out for
Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:

- infections and inflammation
- joint pain, stiffness and bone problems

You need to know about important signs and symptoms to look out for while you are taking Rukobia.

➔ See Section 4 of this leaflet.

Before you take Rukobia your doctor needs to know

- if you have or had a **heart problem,** or if you notice any unusual changes in your heart beat (such as beating too fast or too slow). Rukobia can affect heart rhythm.

- if you have or had **liver disease,** including hepatitis B or hepatitis C.

➔ **Talk to your doctor** if this applies to you. You may need extra check-ups, including blood tests, while you are taking your medicines.

You will need regular blood tests
For as long as you are taking Rukobia, your doctor will arrange regular blood tests to measure the amount of HIV in your blood, and to check for side effects. There is more information about these side effects in **Section 4** of this leaflet.

Stay in regular contact with your doctor
Rukobia helps to control your condition, but it is not a cure for HIV infection. You need to keep taking it every day to stop your illness from getting worse. Because Rukobia does not cure HIV infection, you may still develop other infections and illnesses linked to HIV infection.

➔ **Keep in touch with your doctor, and do not stop taking Rukobia** without your doctor's advice.

Children and adolescents
Rukobia is not recommended for people aged under 18 years because it has not been studied in this age group.

Other medicines and Rukobia
Tell your doctor or pharmacist if you are taking any other medicines, if you have taken any recently, or if you start taking new ones.

Rukobia must not be taken with some other medicines

Do not take Rukobia if you are taking any of these medicines:

- **carbamazepine**, or **phenytoin**, to treat **epilepsy** and prevent seizures

- **mitotane**, to treat several types of **cancer**

- **enzalutamide**, to treat **prostate cancer**

- **rifampicin**, to treat **some bacterial infections** such as **tuberculosis**
- products that contain **St John's wort** (*Hypericum perforatum*) (an herbal product for **depression**).

This medicine is not recommended with Rukobia:

- elbasvir/grazoprevir, to treat **hepatitis C infection.**

➔ **Tell your doctor or pharmacist** if you are being treated with this medicine.

Some medicines can affect how Rukobia works

Or they can make it more likely that you will have side effects. Rukobia can also affect how some other medicines work.

Tell your doctor if you are taking any of the medicines in the following list:

- amiodarone, disopyramide, ibutilide, procainamide, quinidine, or sotalol, used to treat **heart conditions**
- **statins** (atorvastatin, fluvastatin, pitavastatin, rosuvastatin or simvastatin), used to **lower cholesterol levels**
- ethinyl estradiol, used for **birth control**
- tenofovir alafenamide, used as an **antiviral.**

➔ **Tell your doctor or pharmacist** if you are taking any of these. Your doctor may decide to adjust your dose or that you need extra check-ups.

Pregnancy
If you are **pregnant**, or **think you could be**, or if you are **planning to have a baby, do not take Rukobia** without checking with your doctor. **Your doctor** will discuss with you the benefit and the risk to your baby of taking Rukobia while you're pregnant.

Breast-feeding

Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

It is not known whether the ingredients of Rukobia can pass into breast milk and harm your baby.
If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

Driving and using machines
Rukobia can make you dizzy and have other side effects that make you less alert.
Do not drive or use machines unless you are sure you are not affected.

3. How to take Rukobia

Always take Rukobia exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

- **The usual dose** of Rukobia is one 600 mg tablet, twice a day.
- **Rukobia should be swallowed whole,** with some liquid. **Do not chew, crush or split the tablets** — if you do, there is a danger the medicine may be released into your body too quickly.

- You can take Rukobia **with or without food**.

If you take more Rukobia than you should

If you take too many tablets of Rukobia **contact your doctor or pharmacist**. If possible, show them the Rukobia pack.

If you forget to take Rukobia

Take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and go back to your regular schedule. **Do not take a double dose** to make up for a missed dose. If you are not sure what to do, **ask your doctor or pharmacist.**

If you stop taking Rukobia

Do not stop Rukobia without checking with your doctor.

To control your HIV infection and to stop your illness getting worse, take Rukobia for as long as your doctor recommends. Do not stop unless your doctor asks you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, but not everybody gets them, **so it is very important to talk to your doctor about any changes in your health.**

Symptoms of infection and inflammation are common (may affect up to 1 in 10 people)

People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections *(opportunistic infections)*. When they start treatment, the immune system becomes stronger, so the body starts to fight infections.

Symptoms of infection and inflammation may develop, caused by either:
- old, hidden infections flaring up again as the body fights them
- the immune system mistakenly attacking healthy body tissue (*autoimmune disorders*).

The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection.

Symptoms may include:
- **muscle weakness** and/or **pain**
- **joint pain** or **swelling**
- **weakness** that starts in the hands and feet and moves up towards the trunk of the body
- **palpitations** or **tremor**
- **excessive restlessness** and **movement** (*hyperactivity*).

If you get any symptoms of infection and inflammation or if you notice any of the symptoms above:

➔ **Tell your doctor immediately**. Do not take other medicines for the infection without checking with your doctor.

Very common side effects (may affect **more than 1 in 10 people**)**:**

- feeling sick (*nausea*)
- diarrhoea
- being sick (*vomiting*)
- stomach pain (*abdominal pain*)
- headache
- rash.

➔ **Talk to your doctor** if you get any side effects.

Common side effects (may affect **up to 1 in 10 people**):

- indigestion (*dyspepsia*)
- lack of energy (*fatigue*)
- disturbance in heart rhythm seen in ECG test (*prolonged QT interval*)
- muscle pain (*myalgia*)
- feeling drowsy (*somnolence*)
- dizziness
- taste disturbance (*dysgeusia*)
- wind
- difficulty sleeping *(insomnia)*
- itching (*pruritus*).

➔ **Talk to your doctor** if you get any side effects.

Some side effects may only be seen in your blood tests and may not appear immediately after you start taking Rukobia.

Common side effects that may show up in blood tests are:

- increase in enzymes produced in the muscles (creatine phosphokinase, an indicator of muscle damage)
- increase in creatinine, an indicator of how well your kidneys are working
- increase in enzymes produced in the liver (transaminases, an indicator of liver damage).

Other side effects that may show up in blood tests

Other side effects have occurred in some people but their exact frequency is unknown:

- increase in bilirubin (a substance produced by the liver) in the blood.

Joint pain, stiffness and bone problems

Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:

- stiffness in the joints
- aches and pains in the joints (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:

→ **Tell your doctor**.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Rukobia

Keep out of the sight and reach of children.

Do not take Rukobia after the expiry date shown on the pack which is stated after EXP on the carton and bottle.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines in wastewater or household waste. Ask your pharmacist how to throw away medicines no longer required. This will help protect the environment.

6. Contents of the pack and other information

What Rukobia contains

- The active substance is fostemsavir. Each tablet contains fostemsavir tromethamine equivalent to 600 mg fostemsavir.
- The other ingredients are hydroxypropylcellulose, hypromellose, colloidal anhydrous silica, magnesium stearate, poly(vinyl alcohol), titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172), iron oxide red (E172).

What Rukobia looks like and contents of the pack

Rukobia 600 mg prolonged-release tablets are beige, oval, biconvex tablets, approximately 19 mm in length, 10 mm in width, and 8 mm in thickness, and marked with the code ‘SV 1V7’ on one side.

Each pack consists of one or three bottles, each containing 60 prolonged-release tablets.

Not all pack sizes may be available in your country.

Marketing Authorisation Holder

ViiV Healthcare BV

Van Asch van Wijckstraat 55H
3811 LP Amersfoort
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Manufacturer
GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana, 90
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This leaflet was last revised in {**MM/YYYY**}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.