U.S. FOOD & DRUG ADMINISTRATION

RUKOBIA: New Drug Approved for HIV-1

Today, the U.S. Food and Drug Administration approved RUKOBIA (fostemsavir), a human immunodeficiency virus type 1 (HIV-1) gp120-directed attachment inhibitor, in combination with other antiretroviral(s), for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

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

Rukobia is contraindicated in patients:

- with previous hypersensitivity to fostemsavir or any of the components of Rukobia.
- coadministered strong cytochrome P450 (CYP)3A 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:
  - Androgen receptor inhibitor: Enzalutamide
  - Anticonvulsants: Carbamazepine, phenytoin
  - Antimycobacterial: Rifampin
  - Antineoplastic: Mitotane
  - Herbal product: St John’s wort (Hypericum perforatum)

The safety and efficacy of Rukobia, taken twice daily by mouth, were evaluated in a Phase 3, partially-randomized, international, double-blind, placebo-controlled trial clinical trial of 371 heavily treatment-experienced adult participants with HIV-1 infection.

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 nonrandomized 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 OBT. This cohort provides primary evidence of efficacy of RUKOBIA.
- Within the nonrandomized cohort (n = 99), subjects had no fully active and approved antiretroviral agent(s) available at screening. Nonrandomized 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 nonrandomized cohort.

Overall, the majority of subjects were male (78%), white (70%), and the median age was 49 years (range: 17 to 73 years). At baseline, the median HIV-1 RNA was 4.6 log10 copies/mL and the median CD4+ cell count was 80 cells/mm3 (100 and 41 cells/mm3 for randomized and nonrandomized subjects, respectively). Seventy-five percent (75%) of all treated subjects had a CD4+ cell count <200 cells/mm3 at baseline (with 30% <20 cells/mm3). Overall, 86% had a history of Acquired Immune Deficiency Syndrome (AIDS) and 8%had a history of hepatitis B and/or C virus co-infection at baseline. Seventy one percent (71%) of subjects had been treated for HIV for >15 years; 85% had been exposed to ≥5 different HIV treatment regimens upon entry into the trial.

Fifty-two percent (52%) of subjects in the randomized cohort had 1 fully active agent within their initial failing background regimen, 42% had 2, and 6% had no fully active agent. Within the nonrandomized cohort, 81%of subjects had no fully active agent(s) in their original regimen and 19% had 1 fully active agent, including 15% (n = 15) who received ibalizumab, which was an investigational agent at the time of the BRIGHTE trial start-up.

ADVERSE REACTIONS:

The most common adverse reaction (>5%) was nausea (10%).

Adverse reactions in the nonrandomized cohort were similar to those observed in the randomized cohort. The most common adverse reactions reported in nonrandomized subjects were fatigue (7%), nausea (6%), and diarrhea (6%).

The product labeling includes the following WARNINGS AND PRECAUTIONS

- Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including RUKOBIA. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia
[PCP], or tuberculosis), which may necessitate further evaluation and treatment.

- Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) 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.

- QTc Prolongation with Higher than Recommended Dosages

RUKOBIA at 2,400 mg twice daily, 4 times the recommended daily dose, has been shown to significantly prolong the QTc interval of the electrocardiogram. RUKOBIA should be used with caution in patients with a history of QTc interval prolongation, when coadministered 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.

- Elevations in Hepatic Transaminases in 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. 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.

- 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

- Possible prolongation of QTc interval from increased exposure to temsavir

Steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations are included in labeling. 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.

Efficacy results

Randomized Cohort

The primary efficacy endpoint was the adjusted mean decline in HIV-1 RNA from Day 1 to Day 8 with RUKOBIA versus placebo in the randomized cohort. The results of the primary endpoint analysis demonstrated superiority of RUKOBIA compared with placebo, as shown in Table 11.

Table 11. Plasma HIV-1 RNA Log_{10} (copies/mL) Change from Day 1 to Day 8 (Randomized Cohort) in BRIGHTE Trial – ITT-E Population

	RUKOBIA 600 mg Twice Daily (n = 201[a])	**Placebo (n = 69)**
Adjusted Mean[b] (95% CI)	-0.791 (-0.885, -0.698)	-0.166 (-0.326, -0.007)
Difference[c] (95% CI)	-0.625 (-0.810, -0.441)[d]	-

[a] Two subjects who received RUKOBIA with missing Day 1 HIV-1 RNA values were not included in the analysis.
[b] Mean adjusted by Day 1 log_{10} HIV-1 RNA.
[c] Difference: RUKOBIA minus placebo.
[d] *P*-value <0.0001 for the adjusted and unadjusted mean difference of viral load change from baseline for RUKOBIA compared with placebo.

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 log10 copies/mL and >1 log10 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 mean decline in viral load of 0.86 log10 copies/mL at Day 8 compared with 0.20 log10 copies/mL in subjects treated with blinded placebo. Subjects with baseline HIV-1 RNA ≤1,000 copies/mL achieved a mean decline in viral load of 0.22 log10 copies/mL at Day 8 compared with a mean increase of 0.10 log10 copies/mL in subjects treated with blinded placebo.

Virologic outcomes by ITT-E Snapshot Analysis at Weeks 24 and 96 in the BRIGHTE trial are shown in Table 12 and Table 13 for the randomized cohort. 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 Week 24.

Table 12. Virologic Outcomes (HIV-1 RNA <40 copies/mL) at Weeks 24 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 96** **(n = 272)**
HIV-1 RNA <40 copies/mL	53%	60%
HIV-1 RNA ≥40 copies/mL	40%	30%
Data in window not <40 copies/mL	32%	12%
Discontinued for lack of efficacy	<1%	4%
Discontinued for other reasons while not suppressed	1%	6%
Change in antiretroviral treatment regimen	6%	8%
No virologic data	7%	10%
Reasons:		
Discontinued study/study drug due to adverse event or death	4%	6%
Discontinued study/study drug for other reasons	2%	3%
Missing data during window but on study	1%	2%

Table 13. Virologic Outcomes (HIV-1 RNA <40 copies/mL) by Baseline Covariates at Weeks 24 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 96 (n = 272)**
Baseline plasma viral load (copies/mL)		
<100,000	60% (116/192)	65% (124/192)
≥100,000	35% (28/80)	49% (39/80)
Baseline CD4+ (cells/mm^3)		
<20	32% (23/72)	46% (33/72)
20 to <50	48% (12/25)	56% (14/25)
50 to <200	58% (59/102)	61% (62/102)
≥200	68% (50/73)	74% (54/73)
Number of fully active and available antiretroviral classes in initial background regimen		
0[a]	31% (5/16)	19% (3/16)
1	56% (80/142)	65% (92/142)
2	52% (59/114)	60% (68/114)
Use of DTG and DRV[b] as a component of OBT		
DTG and DRV	58% (68/117)	64% (75/117)
With DTG, without DRV	54% (61/112)	63% (71/112)
Without DTG, with DRV	29% (5/17)	47% (8/17)
Without DTG/DRV	38% (10/26)	35% (9/26)
Gender		
Male	52% (104/200)	59% (118/200)
Female	56% (40/72)	63% (45/72)
Race		
White	49% (90/185)	56% (103/185)
Black or African-American/Others	62% (54/87)	69% (60/87)
Age (years)		
<50	50% (81/162)	59% (96/162)
≥50	57% (63/110)	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% and 64% of subjects at Weeks 24 and 96, respectively (ITT-E, Snapshot algorithm). Mean changes in CD4+ cell count from baseline increased over time: 90 cells/mm3 at Week 24 and 205 cells/mm3 at Week 96. Based on a sub-analysis in the randomized cohort, subjects with the lowest baseline CD4+ cell counts (<20 cells/mm3) had a similar increase in CD4+ cell count over time compared with subjects with higher baseline CD4+ cell count (>200 to <500 cells/mm3).

Nonrandomized Cohort

In the nonrandomized cohort, HIV-1 RNA <40 copies/mL was achieved in 37% of subjects at Weeks 24 and 96. At these timepoints, the proportion of subjects with HIV-1 RNA <200 copies/mL was 42% and 39%, respectively (ITT-E, Snapshot algorithm). Mean changes in CD4+ cell count from baseline increased over time: 41 cells/mm3 at Week 24 and 119 cells/mm3 at Week 96.

The following is a summary of additional analyses in section 12.4 Microbiology

Reduced Antiviral Activity against Subtype AE

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.

Response at Day 8 by Genotype

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 8). 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 8). There was no difference in response rates and median decline in viral load for subjects with more than one gp120 RAP.

Table 8. Outcome of Randomized Fostemsavir Cohort by Presence of Screening gp120 RAPs (As-Treated Analysis[a])

Envelope RAPs	Response Rate at Day 8 (>0.5 log_{10} decline) n = 151	Median Log_{10} 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.

Response at Day 8 by Phenotype

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 log10 decline at Day 8 was assessed in the as-treated analysis. The majority of these subjects (55%, 83/151) had a screening temsavir EC50 fold change normalized to a reference virus of <2-fold. The response rate for fostemsavir phenotypes ≤2 was 80% (66/83) (Table 9). 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 log10 declines in HIV-1 RNA at Day 8. Lack of resistance to background drugs or higher fostemsavir concentrations do not explain the >1 log10 response of these 5 subjects.

Table 9. 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 Clinical Subjects

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 10). 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 10).

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 10). 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 10). 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 10. 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.

The label will soon be available at Drugs@FDA or DailyMed.

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