

Use of Rukobia in Heavily Treatment-Experienced Patients with Multidrug-Resistant HIV-1: BRIGHTE Study

Summary

- BRIGHTE is an ongoing, phase 3 study evaluating *Rukobia* (fostemsavir [FTR]) in heavily treatment-experienced (HTE) adults with multi-drug resistant HIV-1.¹ At day 8, the mean decrease in HIV-1 RNA was 0.79 log₁₀ copies/mL (superior to placebo).
 - In the randomized cohort, virologic response (HIV-1 RNA <40 copies/mL) occurred in 53% of patients at Week 24, 54% of patients at Week 48, 60% of patients at Week 96, and 45% of patients at Week 240.^{1,2} The mean increase in CD4+ T-cell count was 296 cells/μL at Week 240.²
 - Grade 2-4 drug-related adverse events (AEs) and AEs leading to the discontinuation of FTR occurred in 24% and 8% of patients, respectively.²
 - Click [here](#) to display an infographic summarizing Week 96 results for the BRIGHTE study.
- Important safety information is found in the attached Prescribing Information.

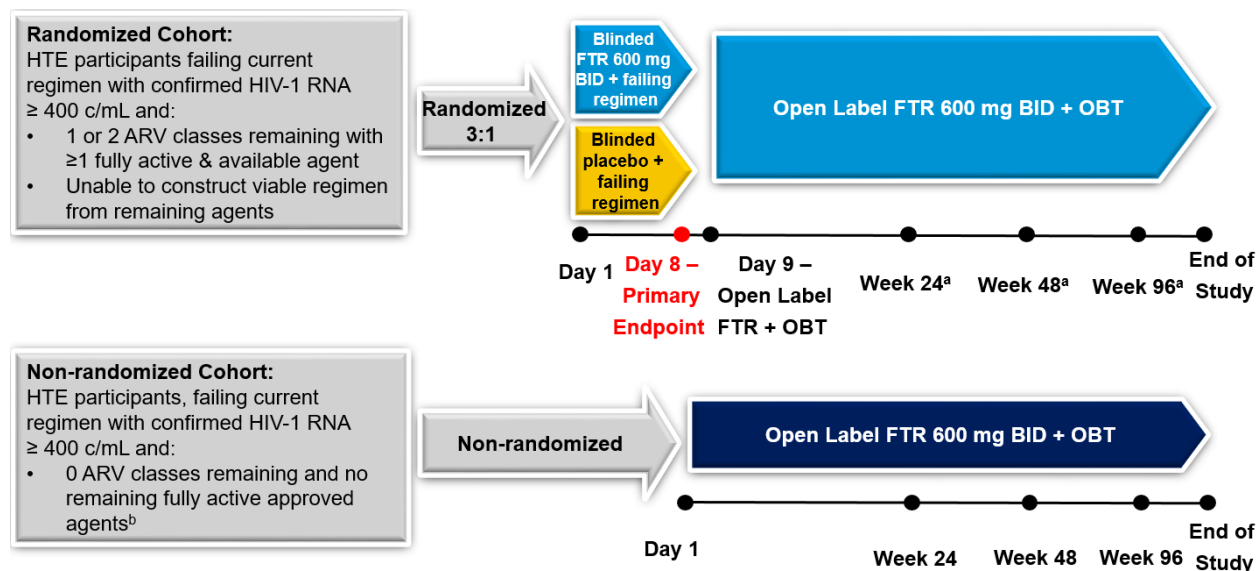
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STUDY DESIGN

BRIGHTE is an ongoing, partially-randomized, placebo-controlled, double-blind, phase 3 trial designed to evaluate the efficacy and safety of FTR in HTE patients with multi-drug resistant HIV-1.¹ Patients were failing their current regimen (HIV-1 RNA ≥ 400 copies/mL) and enrolled into 1 of 2 cohorts, according to their remaining treatment options. At baseline, those with ≥ 1 antiretroviral (ARV) drug in at least 1 but no greater than 2 ARV classes were randomized (Day 1 to Day 8) to add either FTR 600 mg twice daily or placebo to their failing regimen (randomized cohort). Patients with no fully active, approved ARV options received open-label FTR and optimized background therapy (OBT) on Day 1 (non-randomized cohort).

Figure 1. BRIGHTE Study Schematic³



^a Measured from start of open-label FTR 600 mg BID + OBT; ^b Use of investigational agents as part of OBT was permitted.

ARV = antiretroviral; BID = twice daily; c/mL = copies/mL; FTR = fostemsavir; HTE = heavily treatment-experienced; OBT = optimized background therapy.

The primary endpoint was the mean change in log₁₀ level of HIV-1 RNA from Day 1 to Day 8 in the randomized cohort.¹ Patient demographics and disease characteristics at baseline were similar between the FTR and placebo arms during the blinded phase. Within the randomized cohort, 85% of patients had a history of AIDS and 73% had a baseline CD4+ T-cell count < 200 cells/mm³. Patients in the non-randomized cohort were older and had more severe immunosuppression at baseline.

Table 1. Select Characteristics of Patients at Baseline, BRIGHT Study^{1,3}

Characteristic	Randomized Cohort			Non-randomized Cohort
	Placebo (N = 69)	Fostemsavir (N = 203)	Total (N = 272)	Fostemsavir (N = 99)
Age				
Median (range) – yr	45 (19–66)	48 (18–73)	48 (18–73)	50 (17–72)
< 50 yr – n (%)	46 (67)	116 (57)	162 (60)	44 (44)
Male sex – n (%)	57 (83)	143 (70)	200 (74)	89 (90)
Race or ethnic group – n (%)				
White	47 (68)	137 (67)	184 (68)	73 (74)
Black	18 (26)	42 (21)	60 (22)	23 (23)
Hispanic	18 (26)	61 (30)	79 (29)	28 (28)
HIV-1 RNA Level				
Median (IQR) – log ₁₀ copies/mL	4.5 (3.6-5.2)	4.7 (4.0-5.1)	4.7 (3.9-5.1)	4.3 (3.6-4.8)
Distribution – n (%)				
< 400 c/mL ^a	7 (10)	14 (7)	21 (8)	5 (5)
400 to <1000 c/mL	3 (4)	7 (3)	10 (4)	4 (4)
1000 to <100,000 c/mL	35 (51)	126 (62)	161 (59)	75 (76)
≥ 100,000 c/mL	24 (35)	56 (28)	80 (29)	15 (15)
CD4+ T-cell Count				
Median (IQR) – cells/mm ³	100 (23-244)	99 (15-203)	99 (15-203)	41 (6-161)
Distribution – n (%)				
< 20 cells/mm ³	17 (25)	55 (27)	72 (26)	40 (40)
20 to < 50 cells/mm ³	6 (9)	19 (9)	25 (9)	14 (14)
50 to < 200 cells/mm ³	26 (38)	76 (37)	102 (38)	25 (25)
200 to < 500 cells/mm ³	16 (23)	42 (21)	58 (21)	18 (18)
≥ 500 cells/mm ³	4 (6)	11 (5)	15 (6)	2 (2)
History of AIDS diagnosis	61 (88)	170 (84)	231 (85)	89 (90)
Fully Active ARV drugs in Initial OBT – n (%)				
0	1 (1)	15 (7)	16 (6) ^b	80 (81)
1	34 (49)	108 (53)	142 (52)	19 (19) ^c
2	34 (49)	80 (39)	114 (42)	0

^a HIV-1 RNA > 400 c/mL for all patients at time of screening; ^b Patients who d/c from trial during double-blind period but before OBT initiation, had fully active ARVs but did not receive as part of OBT, or were incorrectly assigned to randomized cohort; ^c 15 patients received investigational ibalizumab, 4 patients classified as protocol violation due to receipt of approved ARV.

ARV = antiretroviral; c/mL = copies/mL; IQR = interquartile range; OBT = optimized background therapy; Yr = year.

EFFICACY RESULTS

Primary Endpoint

At Day 8, the mean reduction from baseline in HIV-1 RNA level was 0.79 log₁₀ copies/mL in the FTR group and 0.17 log₁₀ copies/mL in the placebo group (difference -0.63; 95% CI -0.81 to -0.44; P < 0.001).¹ Among the 241 patients who had a baseline HIV-1 RNA level of >1000 copies/mL, the mean reduction from baseline was 0.86 log₁₀ copies/mL in the FTR group and 0.20 copies/mL in the placebo group (median declines of 1.02 log₁₀ copies/mL and 0.00 log₁₀ copies/mL, respectively).⁴ There was no effect on between-group differences in the HIV-1 RNA level on the basis of age, sex, race, or geographic region.¹

Virologic Response

In the randomized cohort, the rate of virologic response (HIV-1 RNA < 40 copies/mL) using the FDA snapshot algorithm was 53% at Week 24, 54% at Week 48, 60% at Week 96, and 45% at Week 240.^{1,2} In the non-randomized cohort, virologic response at Week 24, Week 48, Week 96, and Week 240 was 37%, 38%, 37%, and 22%, respectively.

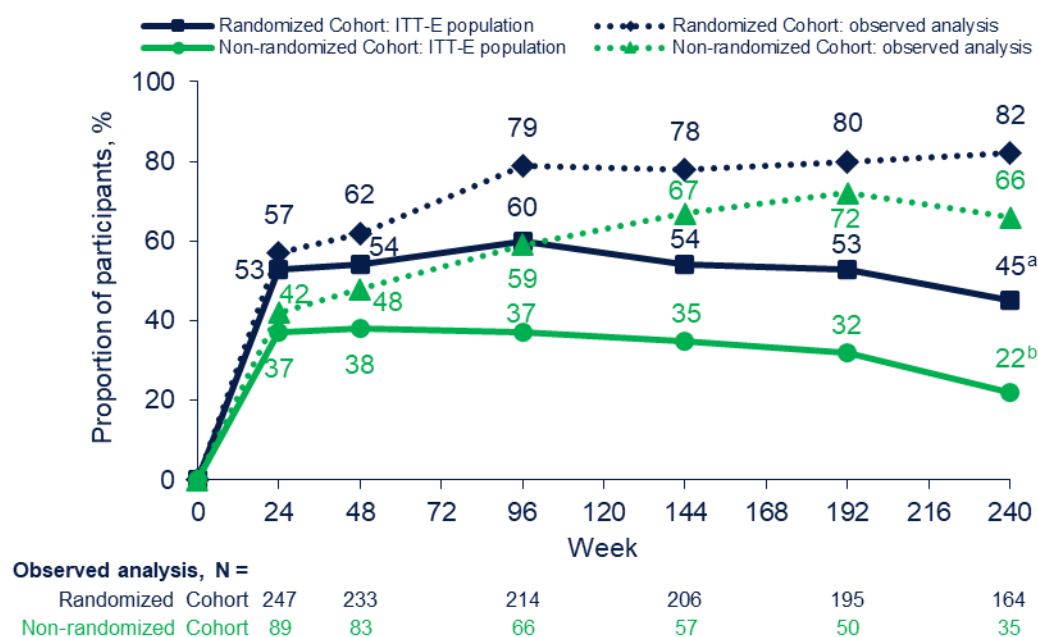
Table 2. Virologic Response at Week 96 and Week 240, Snapshot Analysis (ITT-E), BRIGHT E Study²

Response, n (%)	Randomized Cohort		Non-randomized Cohort	
	Week 96	Week 240 ^b	Week 96	Week 240 ^b
Number of Participants	272	267	99	92
HIV-1 RNA < 40 c/mL	164 (60)	120 (45)	37 (37)	20 (22)
HIV-1 RNA ≥ 40 c/mL	80 (29)	89 (33)	43 (43)	43 (47)
Data in window not below threshold	32 (12)	20 (7)	15 (15)	5 (5)
D/C for lack of efficacy	9 (3)	14 (5)	3 (3)	6 (7)
D/C for other reason while not below threshold	17 (6)	24 (9)	6 (6)	10 (11)
Change in ART ^a	22 (8)	31 (12) ^c	19 (19)	22 (24) ^d
No Virologic Data	28 (10)	58 (22)	19 (19)	29 (32)
D/C study due to AE or death	15 (6)	17 (6)	14 (14)	18 (20)
D/C study for other reasons	8 (3)	19 (7)	4 (4)	4 (4)
Missing data during window				
Not COVID-19 related	5 (2)	3 (1)	1 (1)	2 (2)
COVID-19 related	--	19 (7)	--	5 (5)

^a Change in ART for efficacy reasons were considered virologic failures in this analysis. ^b At Week 240, 12 participants had completed the study by transitioning to locally approved fostemsavir (the first fostemsavir approval was in the US in July 2020). ^c Week 240 HIV-1 RNA was <40 c/mL for 17 of these 31 participants. ^d Week 240 HIV-1 RNA was <40 c/mL for 4 of these 22 participants.

AE = adverse event; ART = antiretroviral; c/mL = copies/mL; D/C = discontinuation; ITT-E = intent-to-treat exposed population.

Figure 1. Virologic Response through Week 240, Snapshot Analysis (ITT-E) and Observed Analysis²

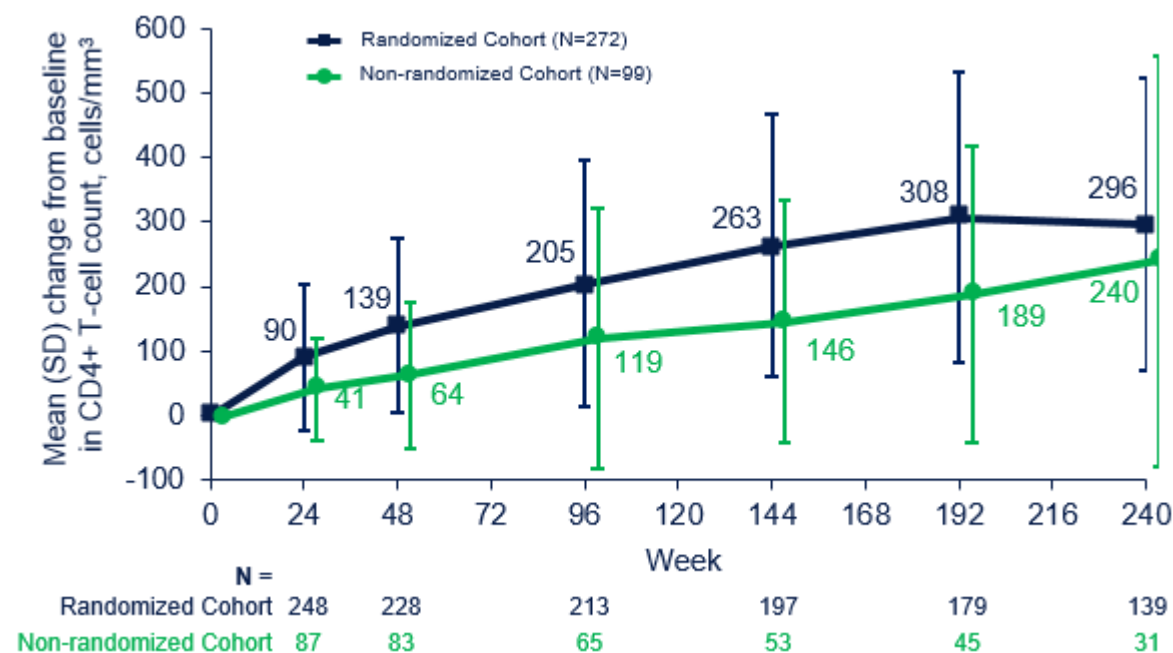


ITT-E participants without an HIV-1 RNA value at the relevant time point or those who changed OBT due to lack of efficacy up to each time point counted as failures. a ITT-E population, N=267. b ITT-E population, N=92.

CD4 Recovery

CD4+ T-cell counts increased steadily over time, reaching a mean increase of 296 cells/mm³ at Week 240 in the randomized cohort.² CD4+:CD8+ T-cell ratio increased from 0.20 at baseline to 0.6 at Week 240 in the randomized cohort.

Figure 2. CD4+ T-Cell Response through Week 240²



VIROLOGY

Drug resistance was assessed as a secondary endpoint (randomized cohort) or exploratory endpoint (non-randomized cohort) through phenotypic and genotypic resistance testing among patients identified as meeting protocol-defined virologic failure (PDVF).⁴ Before Week 24, PDVF was defined as

HIV-1 RNA ≥ 400 copies/mL (confirmed or last available) after prior confirmed suppression to < 400 copies/mL or ≥ 1.0 log₁₀ increase in HIV-1 RNA above nadir (≥ 40 copies/mL).¹ During or after Week 24, PDVF was a confirmed or last available HIV-1 RNA level ≥ 400 copies/mL. Through Week 240, 80 of 267 patients (29%) in the randomized cohort and 53 of 92 patients (54%) in the non-randomized cohort met PDVF criteria.²

Genotypic substitutions to gp120 of interest occurred in 24 of 50 (48%) PDVF patients with available sequencing in the randomized cohort and 33 of 44 (75%) in the non-randomized cohort.⁴ Of the gp120 positions identified as potentially influencing HIV-1 susceptibility to temsavir (S375H/I/M/N/T, M426L/P, M434I/K, and M475I), M426L, M426M/L, and S375N were the most frequent.^{3,4} Despite the potential for reduced susceptibility in vitro, the presence of these substitutions did not prevent patients in the randomized cohort from achieving a reduction in HIV-1 RNA > 1 log₁₀ copies/mL at Day 8 and did not impact durability of response (HIV-1 RNA < 40 copies/mL) through Week 96.⁵ Rates of PDVF at Week 96 were comparable regardless of baseline gp120 polymorphisms of interest (22% of patients without and 25% with gp120 polymorphisms experienced PDVF).⁶ Emergent gp120 substitutions of interest correlated with a greater median increase in temsavir IC₅₀ fold-change from baseline.

SAFETY RESULTS

During the double-blind period of the randomized cohort, the frequency of drug-related AEs was similar for both groups (FTR 20%, placebo 19%), with most Grade 1 or 2 in severity.⁴ Through 240 weeks, the most common drug-related AEs ($\geq 2\%$ in either cohort) were nausea (11% randomized, 6% non-randomized), diarrhea (4% randomized, 6% non-randomized), headache (4% randomized, 1% non-randomized), fatigue (2% randomized, 5% non-randomized), dyspepsia (3% randomized, 0% non-randomized), vomiting (2% randomized, 3% non-randomized), somnolence (2% randomized, 1% non-randomized), dizziness (1% randomized, 2% non-randomized), and immune reconstitution inflammatory syndrome (2% randomized, 1% non-randomized).⁴ Most serious AEs were due to infections or complications associated with advanced AIDS. Serious AEs, AEs leading to discontinuation from the study, and deaths were more common in the non-randomized cohort.

Table 3. Safety Summary through Week 240, BRIGHT Study²

Parameter, n (%)	Randomized Cohort (N=272)		Non-randomized Cohort (N=99)		Total (N=371)	
	Week 96	Week 240	Week 96	Week 240	Week 96	Week 240
Any AE	249 (92)	259 (95)	98 (99)	98 (99)	347 (94)	357 (96)
Any grade 2-4 AE	216 (79)	242 (89)	87 (88)	94 (95)	303 (82)	336 (91)
Drug-related grade 2-4 AEs ^a	57 (21)	65 (24)	22 (22)	23 (23)	79 (21)	88 (24)
Any grade 3-4 AE	78 (29)	110 (40)	49 (49)	60 (61)	127 (34)	170 (46)
Any SAE ^b	92 (34)	122 (45)	48 (48)	55 (56)	140 (38)	177 (48)
Drug-related SAEs ^c	9 (3)	10 (4)	3 (3)	3 (3)	12 (3)	13 (4)
Any AE leading to D/C ^d	14 (5)	17 (6)	12 (12)	13 (13)	26 (7)	30 (8)
Any CDC class C event	23 (8)	25 (9)	15 (15)	19 (19)	38 (10)	44 (12)
Deaths ^e	12 (4)	15 (6)	17 (17)	20 (20)	29 (8)	35 (9)

a Drug-related grade 2-4 AEs occurring in $\geq 2\%$ of participants were nausea (n=17), diarrhea (n=8), headache (n=7), and immune reconstitution inflammatory syndrome (IRIS, n=7); all except 3 cases of nausea were reported before the Week 96 data cutoff. b SAEs occurring in $\geq 2\%$ of participants were pneumonia (n=25), cellulitis (n=10), acute myocardial infarction (n=8), acute kidney injury (n=8, all with identified reversible causes not related to study drug), COVID-19 (n=7), sepsis (n=6), and coronary artery disease (n=6). c Drug-related SAEs (16 events in 13 participants) included IRIS (n=3); nephrolithiasis (n=2); and 1 each of acute kidney injury, hyperglycemia, hyperkalemia, loss of consciousness, myocarditis, hepatocellular cytolysis, rhabdomyolysis, fetal growth restriction, disorientation, and rash through the Week 96 data cutoff and supraventricular tachycardia (n=1) after the Week 96 data cutoff. d The most common AEs leading to discontinuation were related to infections (n=12); 4 participants discontinued because of an AE after the Week 96 cutoff (1 each for pneumonia, cytomegaloviral pneumonia, polyneuropathy, and rash). e Of the 35 deaths, 6 occurred since Week 96; 12 deaths were AIDS related (5 since Week 96), 12 were acute infections (1 since Week 96), 6 were non-AIDS-related malignancies, and the remaining 5 were related to other conditions. Six deaths occurred after the participant withdrew from the study. One death occurred on the day of study withdrawal for AEs.

AE = adverse event; D/C = discontinuation; SAE = serious adverse event.

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This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.



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3. Lataillade M, Lalezari J, Aberg J, et al. Week 96 safety and efficacy of the novel HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced participants infected with multi-drug resistant HIV-1 (BRIGHT study). Presented at the 10th International AIDS Society Conference on HIV Science, July 21-24, 2019, Mexico City, Mexico. Presentation MOAB0102.
4. Data on File. Study 205888 (NCT02362503). ViiV Healthcare Study Register. Study entry at: <https://www.viiv-studyregister.com/en/study/?id=205888>.
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