Efficacy and Safety of Fostemsavir Plus Optimized Background Therapy in Heavily Treatment-Experienced Adults With HIV-1: Week 240 Results of the Phase 3 BRIGHTE Study

P061

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Key Takeaways

- **Efficacy and safety of fostemsavir + optimized background therapy (OBT) in heavily treatment-experienced (HTE) participants were evaluated through 240 weeks in the phase 3 BRIGHTE study**
- **Through ~5 years of treatment with fostemsavir-based regimens, durable virologic responses, clinically meaningful improvements in CD4+ T-cell counts, and a favorable safety and tolerability profile were observed in HTE participants with multidrug-resistant HIV-1**

Introduction

- Fostemsavir is approved for the treatment of multidrug-resistant HIV-1 in HTE adults who are otherwise unable to form a suppressive antiretroviral (ARV) regimen because of resistance, prior intolerance, or other safety concerns[1-3]
- Fostemsavir is the prodrug of temsavir, a first-in-class attachment inhibitor that binds to the HIV-1 envelope gp120, preventing attachment and entry into host T cells and other immune cells[4]
- In the ongoing phase 3 BRIGHTE study, fostemsavir + OBT demonstrated durable virologic suppression through 96 weeks in HTE adults with HIV-1[4-6]
- The BRIGHTE study was designed to continue beyond the Week 96 endpoint until participants could access fostemsavir through other means
  - This study period extended into the COVID-19 pandemic[7]

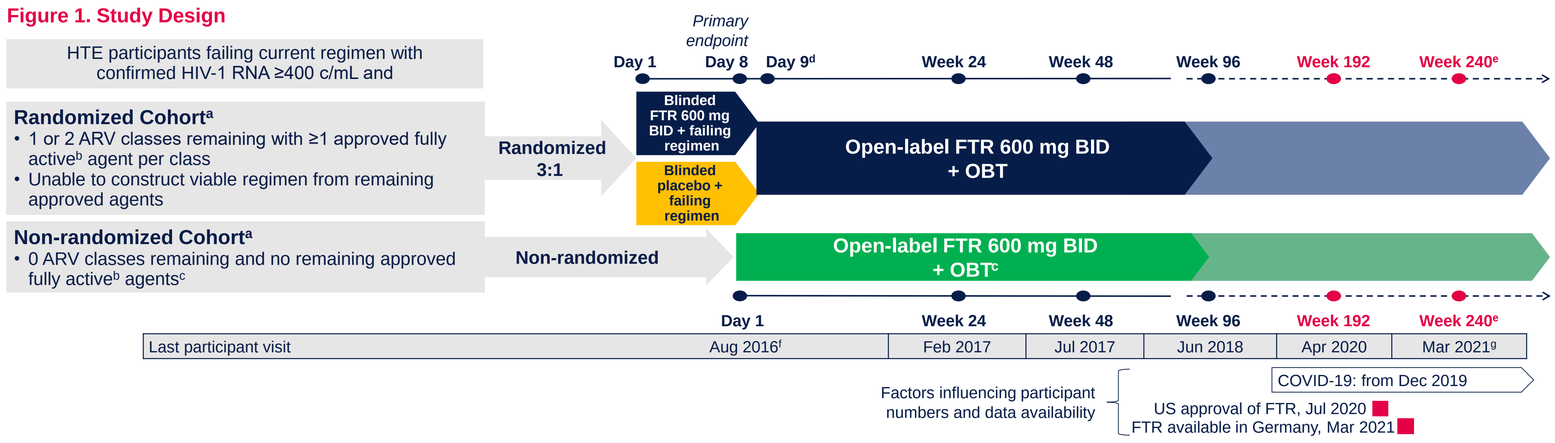
Objective

- The Week 240 interim analysis was conducted to evaluate the efficacy and safety of fostemsavir + OBT beyond Week 96 in BRIGHTE participants who remained in the study

Methods

- BRIGHTE is an ongoing phase 3 study evaluating twice-daily (BID) fostemsavir 600 mg + OBT in HTE adults failing ARV therapy with limited treatment options (Figure 1)

Figure 1. Study Design



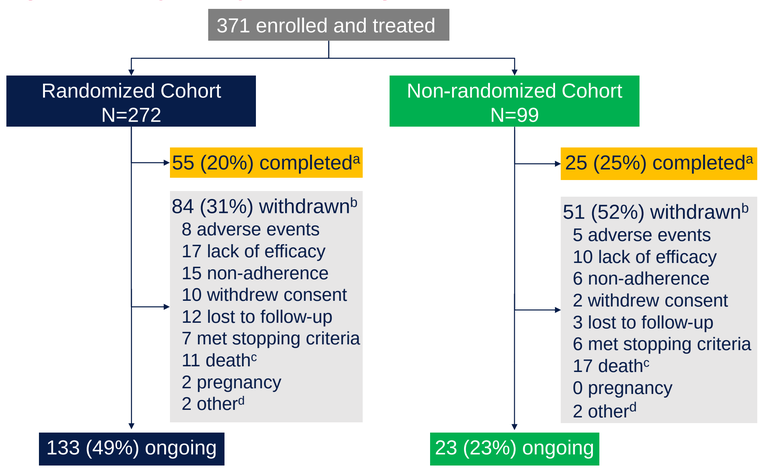
[a]There were no screening temsavir susceptibility criteria. [b]Fully active is based on susceptibility (current or historical resistance measures) and availability (the participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the ARV). [c]Use of investigational agents as part of OBT was permitted in the Non-randomized Cohort only. [d]Subsequent time points were measured from the start of open-label FTR 600 mg BID + OBT. [e]The study is expected to be conducted until participants can access FTR through other means (eg, marketing approval). [f]Last study participant first dose. [g]Database lock June 2021.

Results

Study Participants

- Of 371 participants enrolled, 49% (133/272) in the Randomized Cohort and 23% (23/99) in the Non-randomized Cohort were ongoing at the Week 240 data cutoff (June 24, 2021; Figure 2)
  - 80 (22%) participants completed the study and transitioned to commercially available fostemsavir before the Week 240 data cutoff
  - 135 (36%) participants discontinued/withdrew
    - 17 discontinuations occurred since the onset of the COVID-19 pandemic, 1 of which was considered related to COVID-19 (led to inability to comply with the protocol and attend visits)

Figure 2. Participant Disposition Through the Week 240 Database Lock



[a]80 participants completed the study by the time of the Week 240 database lock. [b]Primary reasons listed. Each participant may have only 1 primary reason. [c]A total of 35 participants died. Death was recorded as the reason for withdrawal in 28/35 cases. [d]Other reasons for discontinuation were investigator decision, HIV resistance, investigator discretion due to rapid progression of the participant's malignancy, and participant developed transportation obstacles preventing ongoing participation.

- Most participants had advanced HIV disease (Table 1)

Table 1. Baseline Disease Characteristics

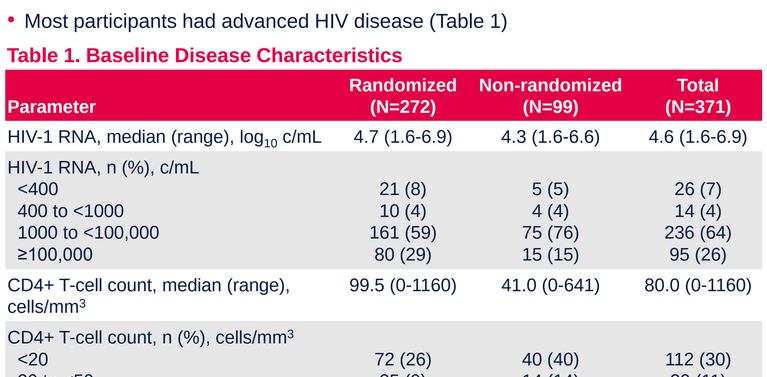
Parameter	Randomized (N=272)	Non-randomized (N=99)	Total (N=371)
HIV-1 RNA, median (range), log_{10} c/mL	4.7 (1.6-6.9)	4.3 (1.6-6.6)	4.6 (1.6-6.9)
HIV-1 RNA, n (%), c/mL			
<400	21 (8)	5 (5)	26 (7)
400 to <1000	10 (4)	4 (4)	14 (4)
1000 to <100,000	161 (59)	75 (76)	236 (64)
≥100,000	80 (29)	15 (15)	95 (26)
CD4+ T-cell count, median (range), cells/mm^3	99.5 (0-1160)	41.0 (0-641)	80.0 (0-1160)
CD4+ T-cell count, n (%), cells/mm^3			
<20	72 (26)	40 (40)	112 (30)
20 to <50	25 (9)	14 (14)	39 (11)
50 to <200	102 (38)	25 (25)	127 (34)
200 to <500	58 (21)	18 (18)	76 (20)
≥500	15 (6)	2 (2)	17 (5)
AIDS history, n (%)[a]	231 (85)	89 (90)	320 (86)

[a]History of AIDS = yes if participant had nadir CD4+ T-cell count <200 cells/mm^3 or if response to "Does participant have AIDS?" on disease history CRF was yes.

Virologic Response

- In the Randomized Cohort, virologic response rates (HIV-1 RNA <40 c/mL) generally remained consistent through Week 240 (Figure 3)
  - Reduced virologic response rates by Snapshot at Week 192 and beyond were partially confounded by missing data due to COVID-19: at Week 240, 19 (7%) participants in the Randomized Cohort and 5 (5%) in the Non-randomized Cohort were counted as virologic failures for this reason (Table 2)

Figure 3. HIV-1 RNA <40 c/mL Through Week 240 by Snapshot Analysis (ITT-E) and Observed Analysis



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.

- By observed analysis at Weeks 96, 192, and 240
  - HIV-1 RNA was <200 c/mL for 187/214 (87%), 181/195 (93%), and 151/164 (92%) participants, respectively, in the Randomized Cohort and 43/66 (65%), 40/50 (80%), and 27/35 (77%) participants, respectively, in the Non-randomized Cohort
  - HIV-1 RNA was <400 c/mL for 189/214 (88%), 182/195 (93%), and 155/164 (95%) participants, respectively, in the Randomized Cohort and 45/66 (68%), 40/50 (80%), and 28/35 (80%) participants, respectively, in the Non-randomized Cohort

Table 2. Virologic Outcomes and Protocol-Defined Virologic Failure Through Week 240 by Snapshot Analysis (ITT-E)

	Randomized Cohort			Non-randomized Cohort		
Outcome, n (%)	Week 96	Week 192[a]	Week 240[b]	Week 96	Week 192[a]	Week 240[b]
Number of participants	**272**	**272**	**267**	**99**	**99**	**92**
HIV-1 RNA <40 c/mL	**164 (60)**	**145 (53)**	**120 (45)**	**37 (37)**	**32 (32)**	**20 (22)**
HIV-1 RNA ≥40 c/mL	**80 (29)**	**90 (33)**	**89 (33)**	**43 (43)**	**43 (43)**	**43 (47)**
Data in window not <40 c/mL	32 (12)	27 (10)	20 (7)	15 (15)	5 (5)	5 (5)
D/C for lack of efficacy	9 (3)	12 (4)	14 (5)	3 (3)	6 (6)	6 (7)
D/C for other reason while not <40 c/mL	17 (6)	21 (8)	24 (9)	6 (6)	10 (10)	10 (11)
Change in background ART	22 (8)	30 (11)	31 (12)[c]	19 (19)	22 (22)	22 (24)[d]
No virologic data	**28 (10)**	**37 (14)**	**58 (22)**	**19 (19)**	**24 (24)**	**29 (32)**
D/C study due to AE or death	15 (6)	16 (6)	17 (6)	14 (14)	18 (8)	18 (20)
D/C study for other reasons	8 (3)	15 (6)	19 (7)	4 (4)	4 (4)	4 (4)
Missing data during window but on study						
Not COVID-19 related	5 (2)	2 (<1)	3 (1)	1 (1)	0	2 (2)
COVID-19 related	—	4 (1)	19 (7)	—	2 (2)	5 (5)
Protocol-defined virologic failure[e]	63 (23)	75 (28)	80 (29)	49 (49)	52 (53)	53 (54)

D/C, discontinuation. [a]Week 192 was the last study time point that included all participants from the original ITT-E population (no participants had completed the study). [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. [e]Protocol-defined virologic failure was defined as the following: before Week 24, confirmed HIV-1 RNA ≥400 c/mL after confirmed suppression to <400 c/mL or confirmed >1 log_{10} c/mL increase in HIV-1 RNA above nadir where nadir is ≥40 c/mL; at or after Week 24, confirmed HIV-1 RNA ≥400 c/mL.

Immunologic Response

- CD4+ T-cell counts increased steadily from baseline through Week 240 (Figures 4-6)
  - In the Randomized Cohort between baseline and Week 240, 73/94 (78%) participants had a change in CD4+ T-cell count from <200 to ≥200 cells/mm^3, and 22/33 (67%) had a change from <20 to ≥200 cells/mm^3
  - Participants with HIV-1 RNA ≥40 c/mL at Week 240 experienced CD4+ T-cell count recovery similar to those with HIV-1 RNA <40 c/mL
- Mean CD4+/CD8+ ratio also increased steadily from baseline (0.2) to Week 240 (0.6) in the Randomized Cohort (Figure 7)

Figure 4. Change in CD4+ T-Cell Count From Baseline to Week 240 (Observed Analysis)

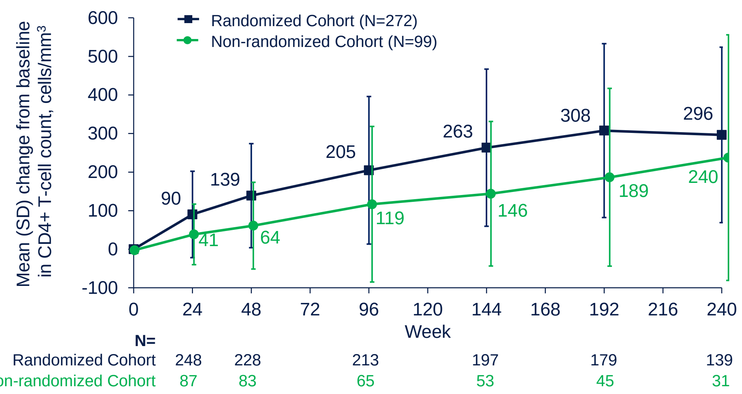


Figure 5. Change in CD4+ T-Cell Count From Baseline to Week 240 by Baseline CD4+ T-Cell Count (Randomized Cohort, Observed Analysis)

Figure 6. Change in CD4+ T-Cell Count From Baseline to Week 240 by Virologic Response at the Same Time Point (Randomized Cohort, Observed Analysis)

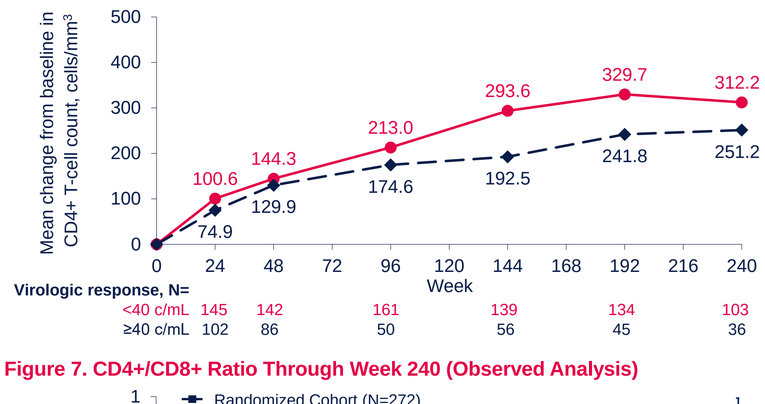
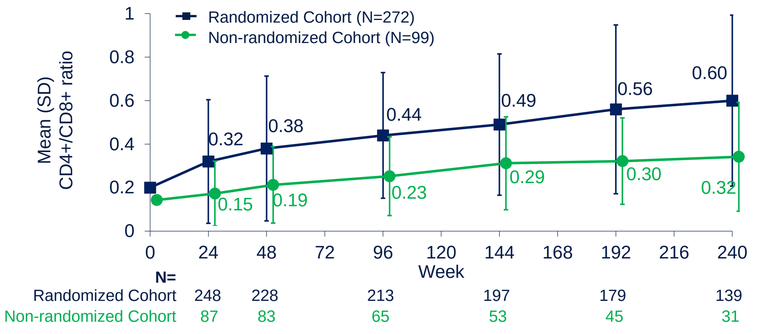


Figure 7. CD4+/CD8+ Ratio Through Week 240 (Observed Analysis)



Safety

- The safety profile was consistent with earlier findings across both cohorts (Table 3)
- Through the Week 240 data cutoff, 6 participants became pregnant
  - 3 pregnancies led to normal births of healthy infants with no complications
  - 2 pregnancies had complications (1 fetal growth restriction and 1 premature birth) but led to otherwise normal births of infants with no congenital abnormalities
  - 1 pregnancy ended in an elective abortion
- During the study, 25/371 participants were diagnosed with 28 COVID-19 and COVID-19–related events[7]
  - All cases resolved without reported sequelae, and there were no COVID-19–related deaths or reports of post–COVID-19 syndrome[7]

Table 3. Cumulative Summary of Safety

	Randomized Cohort (N=272)		Non-randomized Cohort (N=99)		Total (N=371)	
Parameter, n (%)	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)

D/C, discontinuation. [a]Drug-related grade 2-4 AEs occurring in ≥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 ≥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.

Conclusions

- HTE participants with multidrug-resistant HIV-1 treated for ~5 years with fostemsavir-based regimens experienced durable virologic responses and clinically meaningful improvements in CD4+ T-cell count and CD4+/CD8+ ratio
- The safety and tolerability profile of fostemsavir-based ARV regimens in these participants remained consistent with previous observations, and no new trends have emerged
- Rates of virologic suppression (by Snapshot analysis) were consistent through Week 192. Beyond Week 192, results were confounded by missing data related to inability to attend study visit(s) because of the COVID-19 pandemic
- Notably, in the Randomized Cohort at Week 240, of the 60% of participants who remained in the study with available efficacy data, >80% had HIV-1 RNA <40 c/mL
- Despite the history of advanced HIV disease of the participants, there were no COVID-19–associated deaths during the study

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