Sustained Improvements in Biomarkers Observed With Fostemsavir in Heavily Treatment-Experienced Adults With Multidrug-Resistant HIV-1 From the Phase 3 BRIGHTE Study Through Week 240

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**Presenting on behalf of the authors.*

Key Takeaways

- **The phase 3 BRIGHTE study evaluated the safety and efficacy of fostemsavir (FTR) + optimized background therapy (OBT) in heavily treatment-experienced (HTE) adults with multidrug-resistant HIV-1; through Week 240, BRIGHTE participants experienced durable virologic responses and clinically meaningful improvements in CD4+ T-cell count and CD4+/CD8+ ratio**
- **In an exploratory analysis at Week 240, BRIGHTE participants treated with FTR + OBT demonstrated decreases in biomarkers of coagulopathy (D-dimer), immune activation (soluble CD14 [sCD14]), and inflammation (soluble CD163 [sCD163]), which have been linked to increased risk of mortality and non–AIDS-related comorbidities in people with HIV-1**

Introduction

- People with multidrug-resistant HIV-1 demonstrate elevated levels of inflammation and immune activation, even when virologically suppressed,[1] which are associated with an increased risk of adverse health outcomes[2]
- HIV-1 gp120 contributes to persistent immunologic dysfunction by mediating cytokine bursts in monocytes and exposing uninfected bystander CD4+ T cells to antibody-dependent cellular cytotoxicity[3,4]; temsavir inhibits these activities in vitro, suggesting that it could help improve immunologic outcomes in addition to inhibiting viral replication[4]
- FTR 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[5]
- FTR is approved for the treatment of multidrug-resistant HIV-1 in HTE adults who are otherwise unable to form a suppressive antiretroviral (ARV) regimen due to resistance, prior intolerance, or other safety concerns[6]
- In a phase 2b study, early and sustained decreases in sCD14 concentrations were observed among participants treated with FTR and a backbone of raltegravir (RAL) + tenofovir disoproxil fumarate (TDF) compared with a ritonavir-boosted atazanavir + RAL + TDF reference group, with greater decreases observed with higher FTR doses[7]
- In the phase 3 BRIGHTE study, HTE adults with multidrug-resistant HIV-1 who completed 240 weeks of treatment with FTR + OBT had durable virologic responses and clinically meaningful increases in CD4+ T-cell count and CD4+/CD8+ ratio[8]
- In this analysis, we assessed changes in immunologic parameters and biomarkers of coagulopathy, inflammation, and immune activation with use of FTR-based regimens in participants from BRIGHTE through Week 240

Methods

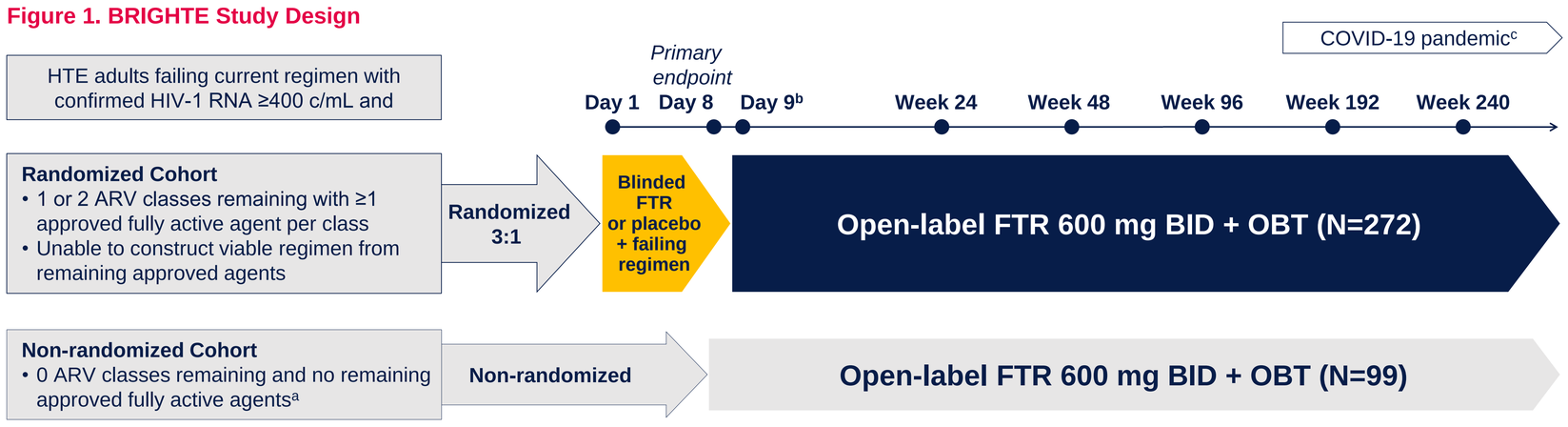
Study Design

- BRIGHTE included HTE adults (aged ≥18 years) with HIV-1 who were failing their current ARV regimen (confirmed HIV-1 RNA ≥400 c/mL) and had ≤2 fully active and available ARV classes remaining (Figure 1)
  - Fully active was based on susceptibility (current or historical resistance measures) and availability (the participant was tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the ARV)
- Participants with 1 to 2 fully active ARVs remaining were randomly assigned (3:1) to receive FTR 600 mg twice daily or placebo + current failing regimen (Randomized Cohort) for 8 days followed by open-label FTR + OBT for all participants
- Participants with no fully active and available ARVs remaining received open-label FTR + OBT starting on Day 1 (Non-randomized Cohort); samples for biomarker analysis were not collected from the Non-randomized Cohort

Analysis

- CD4+/CD8+ ratio and serum or plasma concentrations of D-dimer, sCD14, and sCD163 were monitored among all participants in the Randomized Cohort from baseline through Week 240 as exploratory outcomes
- Participant serum or plasma samples were sent to centralized locations for testing: ICON Laboratory Services (Farmingdale, NY) for D-dimer and sCD14 and Myriad RBM (Austin, TX) for sCD163
- Results were summarized using descriptive statistics and reported as mean change from baseline

Figure 1. BRIGHTE Study Design



[a]Use of investigational agents as part of OBT was permitted in the Non-randomized Cohort only. [b]Subsequent time points were measured from the start of open-label FTR 600 mg twice daily + OBT. [c]The COVID-19 pandemic impacted study participation during Weeks 192 and 240.

Results

Study Population

- At the Week 240 data cutoff, 133/272 (49%) participants in the Randomized Cohort were ongoing in the study; 55 had completed the study and transitioned to commercially available FTR, 5 of whom did so before their Week 240 visit
- In the Randomized Cohort (N=272), 26% of participants were female, 68% identified as White, and median (range) age was 48 (18-73) years (Table)
- Median (range) baseline HIV-1 RNA was 4.66 (1.59-6.91) $\log_{10}$ c/mL, and median (range) baseline CD4+ T-cell count was 100 (0-1160) cells/mm^3

Table. Demographics and Baseline Characteristics in the Randomized Cohort

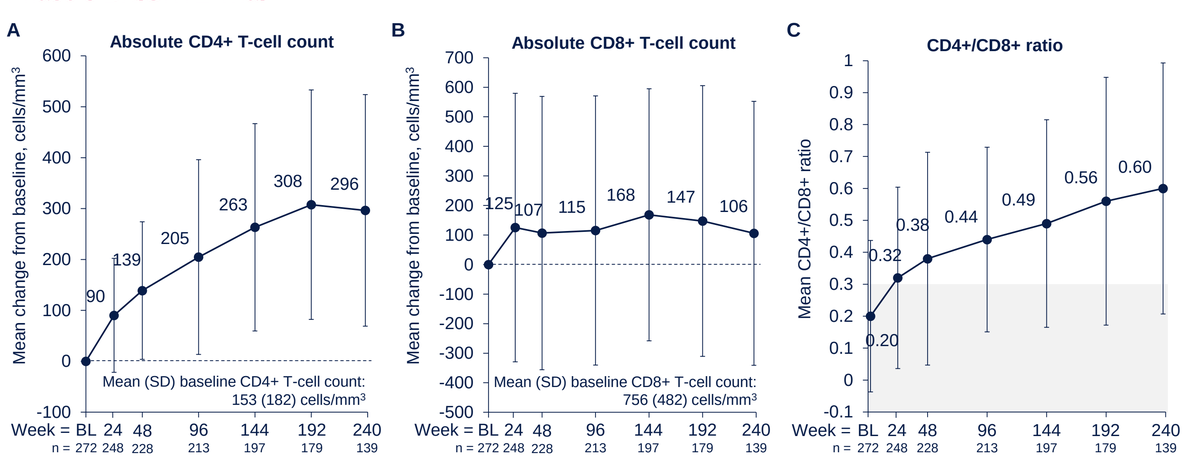
Characteristic	Randomized Cohort (N=272)[a]
Age, n (%), y	
<35	61 (22)
35 to <50	100 (37)
≥50	111 (41)
Sex, n (%)	
Male	201 (74)
Female	71 (26)
Race, n (%)	
Black or African American	60 (22)
White	185 (68)
Other races[b]	27 (10)
Geographic region, n (%)[c]	
North America	108 (40)
South America	105 (39)
Europe	51 (19)
Baseline HIV-1 RNA, n (%), c/mL	
<1000	31 (11)
1000 to <10,000	44 (16)
10,000 to <100,000	117 (43)
≥100,000	80 (29)
Baseline CD4+ T-cell count, n (%), cells/mm^3	
<20	72 (26)
20 to <50	25 (9)
50 to <100	39 (14)
100 to <200	63 (23)
≥200	73 (27)
No. of fully active ARVs in initial OBT, n (%)	
0	15 (6)[d]
1	142 (52)
2	115 (42)
D-dimer, mean (SD), mg/L FEU	0.488 (0.379)
sCD14, mean (SD), µg/L	2502.5 (1034.6)
sCD163, mean (SD), µg/L	545.2 (212.5)

FEU, fibrinogen-equivalent units. [a]N=267 at Week 240 after 5 participants completed the study before their Week 240 visit. [b]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, individuals of multiple races, and individuals of other races. [c]Subgroup categories with few participants not shown. [d]Includes participants who discontinued the study during the blinded period and never started OBT, not treated with a fully active ARV in initial OBT despite having a fully active ARV available at screening, and inadvertently assigned to the Randomized Cohort despite having no fully active ARV available at screening.

Immunologic Responses

- From baseline to Week 240, CD4+ T-cell count increased by 296 cells/mm^3 on average (SD, 228), and CD8+ T-cell count increased by 106 cells/mm^3 on average (SD, 447; Figure 2A-B)
- Additionally, mean CD4+/CD8+ ratio improved steadily at each time point assessed, increasing from 0.20 (SD, 0.24) at baseline to 0.60 (SD, 0.39) at Week 240 (Figure 2C)

Figure 2. (A) Mean Change From Baseline in Absolute CD4+ T-cell Count, (B) Mean Change From Baseline in Absolute CD8+ T-cell Count, and (C) Mean CD4+/CD8+ Ratio Through Week 240 of the Phase 3 BRIGHTE Trial

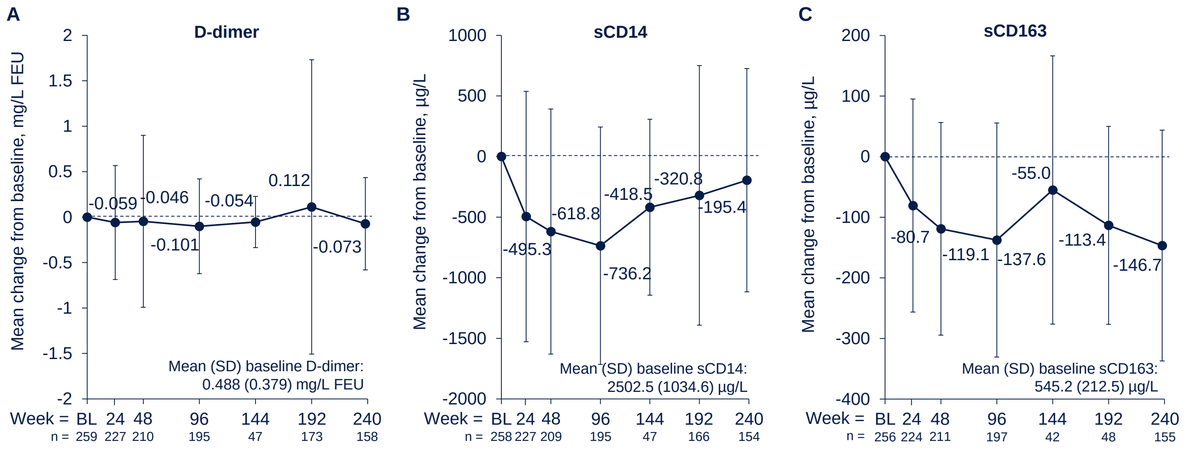


Error bars represent SD. In panels A and B, the dashed line represents no change from baseline. In panel C, the shaded region represents CD4+/CD8+ ratio <0.3, which is associated with a significantly higher risk of progression to severe non–AIDS-defining events or death. BL, baseline.

Biomarkers

- D-dimer, sCD14, and sCD163 decreased from baseline at Week 240 (Figure 3)
- Mean (SD) change from baseline in D-dimer was −0.073 (0.508) mg/L fibrinogen-equivalent units (FEU; baseline, 0.488 [0.379] mg/L FEU), change in sCD14 was −195.4 (920.7) µg/L (baseline, 2502.5 [1034.6] µg/L), and change in sCD163 was −146.7 (190.5) µg/L (baseline, 545.2 [212.5] µg/L)

Figure 3. Mean Change From Baseline in (A) D-dimer, (B) sCD14, and (C) sCD163 Concentrations Through Week 240 of the Phase 3 BRIGHTE Trial



Error bars represent SD. The dashed line represents no change from baseline. BL, baseline; FEU, fibrinogen-equivalent units; s, soluble.

Conclusions

- Through ~5 years of treatment with FTR + OBT, HTE adults with multidrug-resistant HIV-1 had decreased levels of D-dimer, sCD14, and sCD163, which have been independently associated with higher likelihood of mortality and morbidity in individuals with HIV[9-12]
- Participants in the Randomized Cohort receiving FTR + OBT also had clinically meaningful improvements in CD4+ T-cell count and CD4+/CD8+ ratio[13,14]
- Durable virologic suppression in HTE adults treated with FTR + OBT resulted in sustained improvement in immune activation and inflammation
  - The unique mechanism of action of temsavir targeting gp120 may favorably impact the persistent inflammatory milieu of HIV, although further studies are required

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