LONG-TERM INFLAMMATION BIOMARKER CHANGES WITH FOSTEMSAVIR IN HEAVILY TREATMENT-EXPERIENCED ADULTS WITH HIV-1: EXPLORATORY ANALYSES OF THE PHASE 3 BRIGHTE STUDY

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Introduction

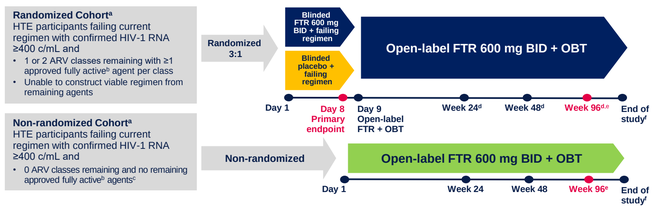
- Fostemsavir is approved for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced (HTE) adults who are otherwise unable to form a suppressive antiretroviral (ARV) regimen due to resistance, prior intolerance, or other safety concerns[1,2]
- Fostemsavir is the prodrug 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[3]
- The gp120 envelope glycoprotein induces pro-inflammatory cytokine production by immune cells, likely contributing to the persistent chronic inflammation associated with HIV-1 infection, even among virologically suppressed individuals[4,5]
- In the phase 3 BRIGHTE study, fostemsavir plus optimized background therapy (OBT) demonstrated durable rates of virologic suppression and continuous clinically meaningful increases in CD4+ T-cell count through 96 weeks in HTE adults with HIV-1 infection[3,6,7]
- This analysis evaluates long-term changes in immunologic responses and inflammation biomarkers with fostemsavir-based regimens through 96 weeks in BRIGHTE

Methods

Study Design

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

Figure 1. BRIGHTE 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]Measured from the start of open-label FTR 600 mg BID + OBT. [e]The Week 96 database lock was August 14, 2018. [f]The study is expected to be conducted until participants can access FTR through other means (eg, marketing approval).

Analysis

- CD4+ T-cell counts, CD4+/CD8+ ratios, and inflammation biomarkers (D-dimer, soluble [s] CD14, sCD163) were evaluated in the Randomized Cohort at baseline and through Week 96
- Post hoc inflammation biomarker subgroup analyses were performed based on demographics (age, sex, race, and geographic region), baseline disease characteristics (HIV-1 RNA and CD4+ T-cell count, number of fully active agents in initial OBT), and clinical outcomes (virologic suppression and CD4+ T-cell recovery)

Results

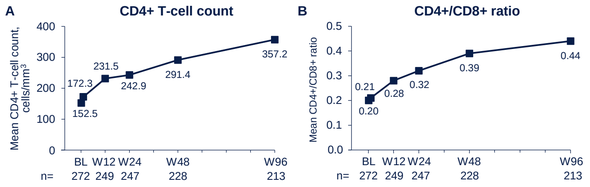
Baseline Characteristics

- Among participants in the Randomized Cohort (N=272), 26% were female, 68% were White, and median (range) age was 48 (18-73) years
- 29% of participants had baseline HIV-1 RNA ≥100,000 c/mL; median (range) baseline CD4+ T-cell count was 99.5 (0-1160) cells/mm^3

Immunologic Responses

- In the Randomized Cohort, sustained increases from baseline in mean CD4+ T-cell counts were observed through Week 96 (Figure 2A)
- Mean CD4+/CD8+ ratios were low at baseline (0.20) and increased over time (0.44 at Week 96; Figure 2B)

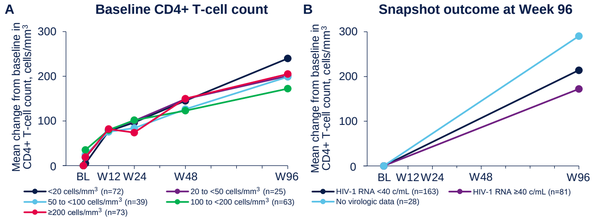
Figure 2. Mean (A) CD4+ T-cell Count and (B) CD4+/CD8+ Ratio Through Week 96 (Randomized Cohort)



BL, baseline; W, week.

- Increases from baseline in mean CD4+ T-cell counts were observed at Week 96 regardless of baseline CD4+ T-cell count and virologic outcome at Week 96, including among participants who were not virologically suppressed (Figure 3)

Figure 3. Mean Change From Baseline in CD4+ T-cell Count by (A) Baseline CD4+ T-cell Count and (B) Snapshot Outcome at Week 96 (Randomized Cohort)



BL, baseline; W, week.

Inflammation Biomarkers

- Steady decreases in the inflammation biomarkers D-dimer, sCD14, and sCD163 were seen through Week 96 by observed analysis (Figure 4)
- At Week 96, mean sCD14 and sCD163 levels were decreased from baseline across all subgroups evaluated, including demographics and baseline disease characteristics
- Among participants with the lowest baseline CD4+ T-cell counts (<20 cells/mm^3; n=72), each inflammation biomarker decreased from baseline at Week 96, with mean (SD) decreases of −0.168 (0.366) mg/L FEU for D-dimer, −1229.6 (1224.4) µg/L for sCD14, and −95.5 (187.5) µg/L for sCD163
- By observed analysis at Week 96, median D-dimer, sCD14, and sCD163 levels were generally decreased from baseline across subgroups stratified by 96-week viral load, including among most subgroups consisting of participants who were not virologically suppressed (Figure 5)
  - Increases from baseline at Week 96 were observed in D-dimer and sCD14 among participants with HIV-1 RNA between 10,000 and <100,000 c/mL and in sCD163 among those with HIV-1 RNA ≥100,000 c/mL
- By observed analysis at Week 96, median levels of each inflammation biomarker were decreased from baseline across most subgroups stratified by 96-week CD4+ T-cell count (Figure 6)
  - Through Week 96, median increases from baseline were observed among participants with CD4+ T-cell counts <20 cells/mm^3 for sCD163 and among those with CD4+ T-cell counts 20 to <50 cells/mm^3 for D-dimer, sCD14, and sCD163

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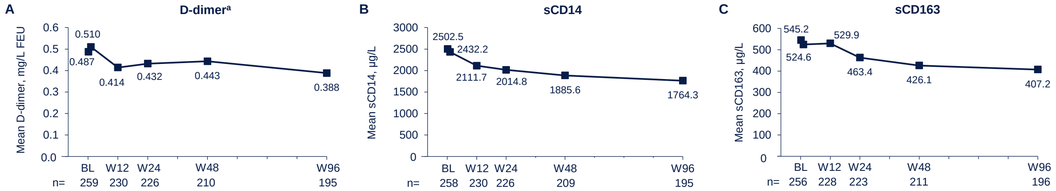
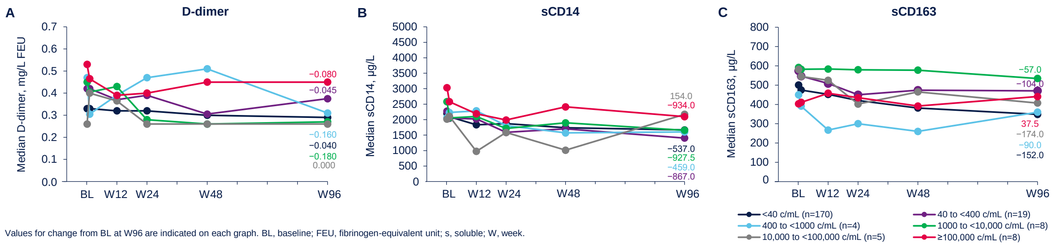
References: 1. Rukobia [prescribing information]. ViiV Healthcare; 2020. **2.** Rukobia [summary of product characteristics]. ViiV Healthcare; 2021. **3.** Kozal et al. *N Engl J Med*. 2020;382:1232-1243. **4.** Levast et al. *PLoS One*. 2017;12:e0174550. **5.** Deeks et al. *Immunity*. 2013;39:633-645. **6.** Lataillade et al. *Lancet HIV*. 2020;7:e740-e751. **7.** Ackerman et al. *AIDS*. 2021;35:1061-1072. **8.** Burdo et al. *J Infect Dis*. 2011;204:154-163. **9.** Freiberg et al. *PLoS One*. 2016;11:e0152588. **10.** Grund et al. *PLoS One*. 2016;11:e0155100. **11.** Sandler et al. *J Infect Dis*. 2011;203:780-790.

Figure 4. Mean (A) D-dimer (mg/L FEU), (B) sCD14 (µg/L), and (C) sCD163 (µg/L) Through Week 96 (Randomized Cohort)



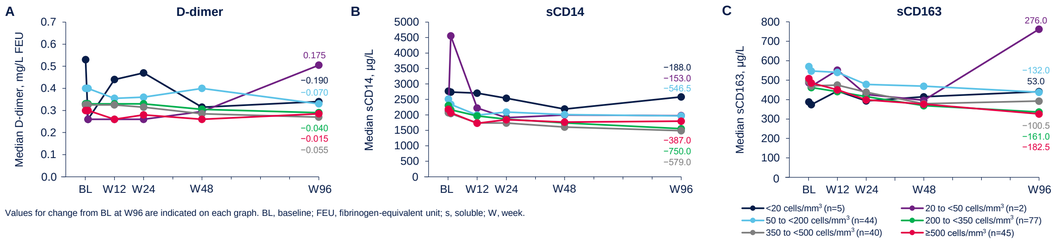
BL, baseline; FEU, fibrinogen-equivalent unit; s, soluble; W, week. [a]Reference range for D-dimer <0.500 mg/L FEU.

Figure 5. Inflammation Biomarkers by Viral Load at Week 96 (Randomized Cohort)



Values for change from BL at W96 are indicated on each graph. BL, baseline; FEU, fibrinogen-equivalent unit; s, soluble; W, week.

Figure 6. Inflammation Biomarkers by CD4+ T-cell Count at Week 96 (Randomized Cohort)



Values for change from BL at W96 are indicated on each graph. BL, baseline; FEU, fibrinogen-equivalent unit; s, soluble; W, week.

Conclusions

- Through 96 weeks of treatment with fostemsavir plus OBT in this HTE population, increases from baseline in CD4+ T-cell count and CD4+/CD8+ ratio and decreases in inflammation biomarkers were observed, even among participants who did not achieve virologic suppression
- Improvement in CD4+/CD8+ ratio through 96 weeks of fostemsavir treatment was associated with improved clinical outcomes in the Randomized Cohort[6]
- Elevated D-dimer, sCD14, and sCD163 levels have been correlated with HIV-1 disease progression, non-AIDS disease events, and risk of mortality in people living with HIV-1 in previous studies[5,8-11]
- These results suggest that the unique mechanism of action of temsavir, ie, targeting gp120, may favorably impact the persistent inflammatory milieu of HIV-1 infection

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