Durable Efficacy and Robust CD4+ T-cell Count Improvement Observed Across Age, Race, Sex, and Geographic Subgroups of Heavily Treatment-Experienced People With Multidrug-Resistant HIV-1 After 240 Weeks of Fostemsavir Treatment

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Key Takeaways

- **The BRIGHTE study evaluated the efficacy and safety of fostemsavir (FTR) + optimized background therapy (OBT) in heavily treatment-experienced (HTE) adults with multidrug-resistant HIV-1 through Week 240**
- **For all subgroups in the Randomized Cohort, virologic response rates were generally consistent with the overall response rate, and mean change from baseline in CD4+ T-cell count exceeded 200 cells/mm^3**
- **Results further demonstrate FTR to be a key treatment option for HTE individuals with multidrug-resistant HIV-1, regardless of demographics or baseline disease characteristics**

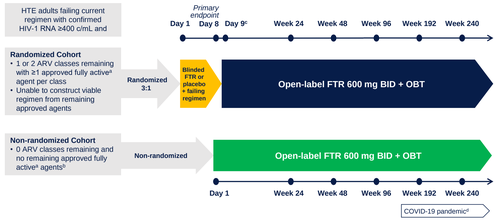
Introduction

- FTR, the prodrug of temsavir (TMR), 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]
- TMR binds directly to HIV-1 gp120 and locks it in a closed conformation, allosterically interfering with the ability of gp120 to attach to CD4 on target cells[4]
- In the phase 3 BRIGHTE study, which evaluated the efficacy and safety of FTR + OBT in HTE adults with multidrug-resistant HIV-1, overall virologic response rate (HIV-1 RNA <40 c/mL, Snapshot) after 240 weeks was 45% (120/267) in the Randomized Cohort and 22% (20/92) in the Non-Randomized Cohort[5]
  - In the observed analysis at Week 240, HIV-1 RNA was <40 c/mL in 82% (135/164) of the Randomized Cohort and 66% (23/35) of the Non-randomized Cohort and <400 c/mL in 95% (155/164) of the Randomized Cohort and 80% (28/35) of the Non-randomized Cohort
- Here, we present long-term virologic and immunologic efficacy of FTR + OBT among subgroups of BRIGHTE participants based on demographics and baseline disease characteristics

Methods

- Participants with 1 or 2 ARVs remaining were assigned to the Randomized Cohort and received open-label FTR (600 mg twice daily) + OBT after an 8-day blinded placebo-controlled period; those with 0 ARVs remaining were assigned to the Non-randomized Cohort and received open-label FTR + OBT from Day 1 (Figure 1)

Figure 1. Study Design



[a]Fully active was based on susceptibility (current or historical resistance measures) and availability (participant was tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the ARV). [b]Use of investigational agents as part of OBT was permitted in the Non-randomized Cohort only. [c]Subsequent time points were measured from the start of open-label FTR 600 mg twice daily + OBT. [d]The COVID-19 pandemic impacted study participation during Weeks 192 through 240. Participants who were on study but unable to attend visits due to the pandemic were treated as missing data in efficacy analyses.

- Virologic response (HIV-1 RNA <40 c/mL by Snapshot) and immunologic response (mean change from baseline in CD4+ T-cell count) were examined among subgroups of participants based on age, sex, race, geographic region, baseline viral load, baseline CD4+ T-cell count, and number of fully active ARVs in initial OBT

Results

Study Population and Baseline Characteristics

- At the Week 240 data cutoff, 133/272 (49%) participants in the Randomized Cohort and 23/99 (23%) in the Non-randomized Cohort were ongoing in the study (Table 1)
  - 80 participants (Randomized Cohort, n=55; Non-randomized Cohort, n=25) had completed the study and transitioned to commercially available FTR, 12 of whom did so before their Week 240 site visit

Table 1. Demographics and Baseline Disease Characteristics: ITT-E Population

Characteristic, n (%)	Randomized Cohort (N=272)[a]	Non-randomized Cohort (N=99)[a]	Total (N=371)
Age, y			
<35	61 (22)	14 (14)	75 (20)
35 to <50	100 (37)	30 (30)	130 (35)
≥50	111 (41)	55 (56)	166 (45)
Sex			
Male	201 (74)	89 (90)	290 (78)
Female	71 (26)	10 (10)	81 (22)
Race			
White	185 (68)	74 (75)	259 (70)
Black or African American	60 (22)	23 (23)	83 (22)
Other races[b]	27 (10)	2 (2)	29 (8)
Geographic region[c]			
North America	108 (40)	56 (57)	164 (44)
South America	105 (39)	14 (14)	119 (32)
Europe	51 (19)	27 (27)	78 (21)
Baseline HIV-1 RNA, c/mL			
<1000	31 (11)	9 (9)	40 (11)
1000 to <10,000	44 (16)	24 (24)	68 (18)
10,000 to <100,000	117 (43)	51 (52)	168 (45)
≥100,000	80 (29)	15 (15)	95 (26)
Baseline CD4+ T-cell count, cells/mm^3			
<20	72 (26)	40 (40)	112 (30)
20 to <50	25 (9)	14 (14)	39 (11)
50 to <100	39 (14)	14 (14)	53 (14)
100 to <200	63 (23)	11 (11)	74 (20)
≥200	73 (27)	20 (20)	93 (25)
No. of fully active ARVs in initial OBT			
0	15 (6)[d]	79 (80)	94 (25)
1	142 (52)	20 (20)[e]	162 (44)
2	115 (42)	—	115 (31)

[a]N=267 and N=92 at Week 240 after 12 participants completed the study. [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. [e]4 participants had 1 fully active ARV available at screening, and 16 received ibalizumab, which was investigational at study start.

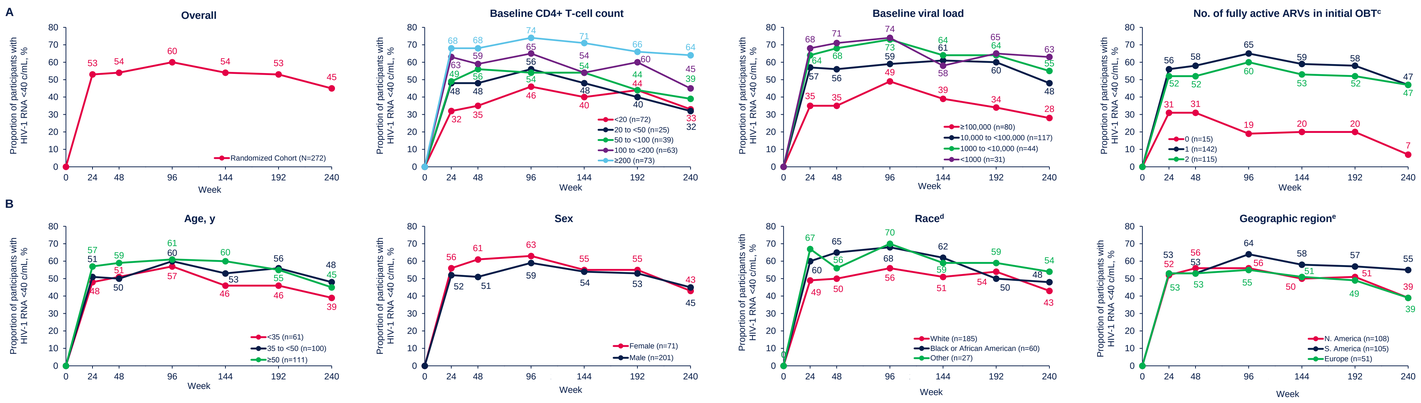
Virologic Response in the Randomized Cohort by Subgroup

- Similar efficacy was observed in participants with 1 or 2 fully active ARVs in their OBT; participants with high baseline viral loads or low baseline CD4+ T-cell counts had lower response rates (Figure 2A)
- Virologic response rates were generally comparable among demographic subgroups and consistent with the overall response rate (Figure 2B)

Immunologic Response in the Randomized Cohort by Subgroup

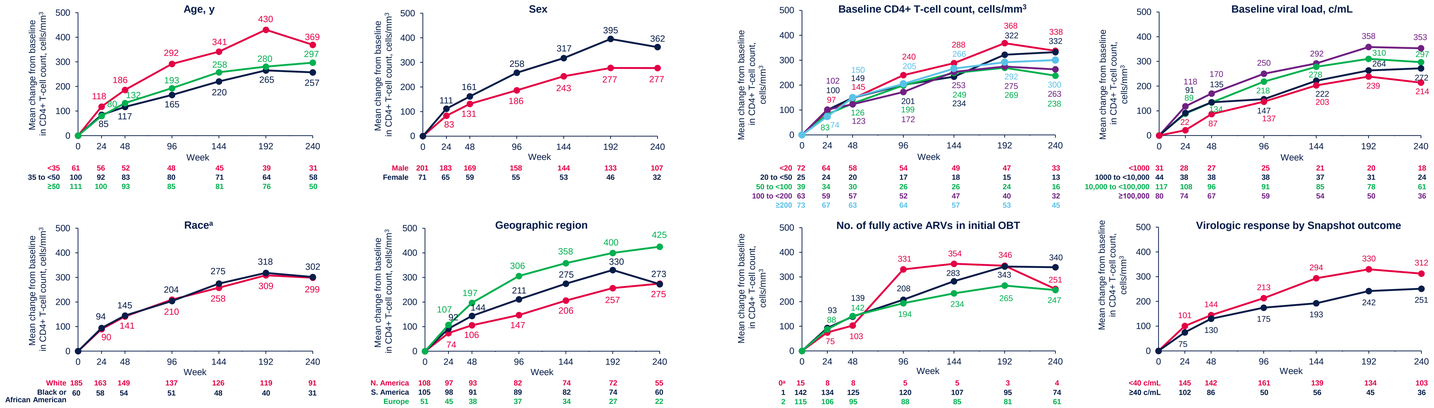
- All demographic subgroups demonstrated robust and continuous increases in CD4+ T-cell count through Week 240, with mean change from baseline exceeding 250 cells/mm^3 at Week 240 (Figure 3)
- Robust and durable improvements in CD4+ T-cell count were observed in all baseline disease characteristics subgroups, including those with baseline viral loads ≥100,000 c/mL or CD4+ T-cell counts <20 cells/mm^3 (Figure 4A-C)
- Substantial mean increases in CD4+ T-cell count were also observed among participants with Week 240 Snapshot HIV-1 RNA <40 c/mL (312 cells/mm^3) and ≥40 c/mL (251 cells/mm^3), reflecting immunologic improvement regardless of virologic response (Figure 4D)

Figure 2. Snapshot Analysis of Virologic Response at Weeks 96 and 240[a,b] by (A) Baseline Disease Characteristics and (B) Demographic Subgroups (Randomized Cohort, ITT-E Population)



[a]19 participants were on study but had no virologic data at Week 240 due to COVID-19 pandemic–related disruptions to site access. [b]5 participants completed the study before Week 240 and were not included in the Week 240 analysis. [c]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. [d]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, individuals of multiple races, and individuals of other races. [e]Subgroup categories with few participants not shown.

Figure 3. Mean Change From Baseline in CD4+ T-cell Count Over Time by Demographic Subgroups (Randomized Cohort, Observed Analysis)



Number of participants in the observed population for each subgroup shown below each plot. [a]Data for subgroups other than White and Black or African American not available.

Virologic and Immunologic Response in the Non-randomized Cohort by Subgroup

- Virologic response rates were generally similar among subgroups, although participants with worse baseline disease status had lower response rates; however, interpretation was limited by low participant numbers
- Median (range) change from baseline in CD4+ T-cell count was robust at Week 240 for most subgroups, including among participants with baseline viral loads ≥100,000 c/mL (176 [20, 383] cells/mm^3) or baseline CD4+ T-cell counts <20 cells/mm^3 (216 [16, 1191] cells/mm^3)

Figure 4. Mean Change From Baseline in CD4+ T-cell Count Over Time by Baseline Disease Characteristics Subgroups and Virologic Response by Snapshot Analysis (Randomized Cohort, Observed Analysis)

Number of participants in the observed population for each subgroup shown below each plot. [a]Includes participants who discontinued the study during the blinded period and never started OBT, not treated with a fully active ARV in their 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.

Conclusions

- Virologic response with FTR + OBT in HTE adults with advanced HIV-1 and limited treatment options was durable over ~5 years, with no major differences among subgroups based on age, sex, race, or geographic region
- Robust and continuous CD4+ T-cell count increases were also observed, with numerically greater improvements in subgroups with the highest baseline viral loads or lowest baseline CD4+ T-cell counts
- These data highlight the role of FTR as a treatment option for HTE people with multidrug-resistant HIV-1 regardless of demographic or disease characteristics

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