Rapid Improvement by Day 8 in CD4/CD8 Ratio With Fostemsavir Treatment in Individuals With Multidrug-Resistant HIV-1

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Key Takeaways

- **FTR added to a failing regimen improved immunologic parameters from baseline by Day 8, with significantly greater increases in CD4+ T-cell percentage and CD4+/CD8+ ratio compared with placebo plus a failing regimen**
- **These findings suggest an early immunologic response with FTR, with improvements in key immune biomarkers evident by Day 8**

Plain Language Summary

- BRIGHTE is a study in people with HIV who have limited treatment options. Here, we measured the immune response 8 days after fostemsavir or placebo
- After 8 days, several measures of immune health improved in people receiving fostemsavir. Two important measures, CD4+ T-cell percentage and the CD4+/CD8+ ratio, improved more with fostemsavir than with placebo
- These results suggest that improvements in immune health may begin soon after starting fostemsavir, with significant changes in key measures seen within the first 8 days

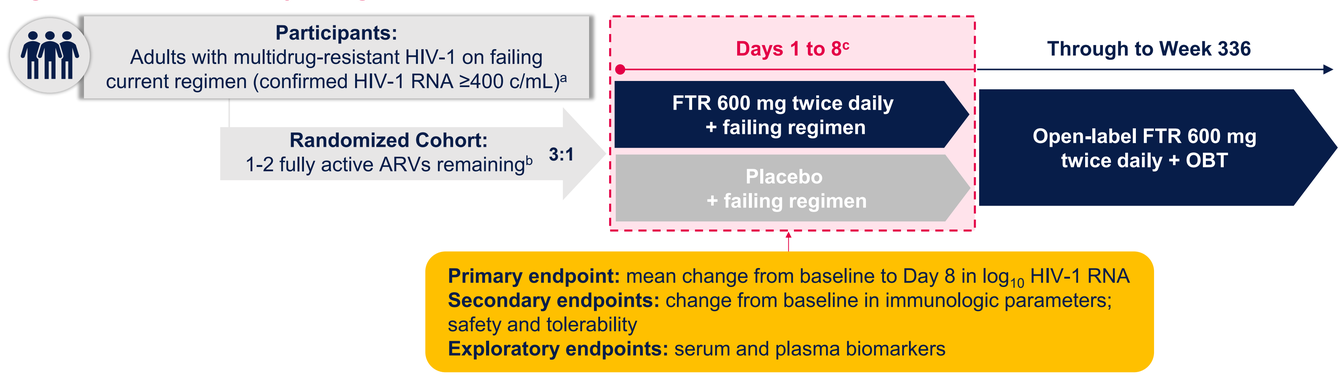
Introduction

- Viral suppression remains essential to HIV management; restoration and preservation of immune function are also important to treatment success, with early immune recovery potentially helping to restore immune competence and support better long-term clinical outcomes[1]
- Fostemsavir (FTR), the prodrug of temsavir, is a first-in-class attachment inhibitor that prevents gp120-mediated binding of HIV-1 to CD4+ T cells with durable improvements in immune recovery with FTR observed through Week 336 (~7 years), with no new safety signals emerging over this extended follow-up period[2-5]
- Rapid viral suppression controls HIV; rapid CD4+ T-cell recovery may be key to restoring immune competence and reducing the period of clinical vulnerability
- Here, we evaluated the early immune response to FTR compared with placebo, focusing on changes during the first 8 days of treatment in BRIGHTE

Methods

- BRIGHTE (NCT02362503) is an ongoing, multinational, phase 3 study in adults with multidrug-resistant HIV-1
- In the Randomized Cohort (RC; n=272), participants with 1 or 2 fully active antiretroviral (ARV) agents received FTR 600 mg twice daily (n=203) or placebo (n=69) added to a failing regimen for 8 days, followed by open-label FTR with optimized background therapy (OBT) (Figure 1)
- In the RC, changes from baseline to Day 8 in immunologic parameters (T-cell subsets) and inflammatory biomarkers were assessed as secondary and exploratory endpoints, respectively
- Within-treatment mean change from baseline for immunologic parameters was assessed using a 1-sample *t* test, and the difference in change from baseline between FTR and placebo was evaluated using a 2-sample *t* test

Figure 1. BRIGHTE Study Design



[a]A Non-randomized Cohort of participants with no fully active ARVs remaining was enrolled alongside the RC and received open-label FTR 600 mg twice daily with OBT starting at Day 1.
[b]Fully active based on susceptibility (current or historical resistance) and availability (participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the ARV).
[c]Participants in the RC were randomly assigned 3:1 to receive FTR 600 mg twice daily or placebo + current failing regimen for 8 days, after which all participants received open-label FTR.

Results

Baseline Demographics and Characteristics

- Baseline demographics and characteristics were generally comparable between groups (Table 1)

Table 1. Demographics and Clinical Characteristics Among Participants Receiving FTR or Placebo in the RC of BRIGHTE[a]

Characteristic	FTR + failing regimen (n=203)	Placebo + failing regimen (n=69)
Age,[b] n (%), y		
<35	45 (22)	16 (23)
35-49	70 (34)	30 (43)
≥50	88 (43)	23 (33)
Assigned female sex at birth, n (%)	59 (29)	12 (17)
Race, n (%)		
Black or African American	42 (21)	18 (26)
White	137 (67)	48 (70)
Other races[c]	24 (12)	3 (4)
Baseline HIV-1 RNA, n (%), c/mL		
<400	14 (7)	7 (10)
400-<1000	7 (3)	3 (4)
≥1000	182 (90)	59 (86)
Baseline CD4+ T-cell count, n (%), cells/mm³		
<20	55 (27)	17 (25)
20-<200	95 (47)	32 (46)
200-<350	32 (16)	12 (17)
350-<500	10 (5)	4 (6)
≥500	11 (5)	4 (6)
Number of fully active ARVs in initial OBT, n (%)		
0[d]	14 (7)	1 (1)
1	109 (54)	33 (48)
2	80 (39)	35 (51)

[a]All participants who received ≥1 dose of study treatment. [b]Age was imputed when full date of birth not provided. [c]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, individuals of multiple races, and individuals of other races. [d]Includes participants who discontinued the study during the blinded period and never started OBT, were not treated with a fully active ARV in initial OBT despite having a fully active ARV available at screening, and were inadvertently assigned to the RC despite having no fully active ARV available at screening.

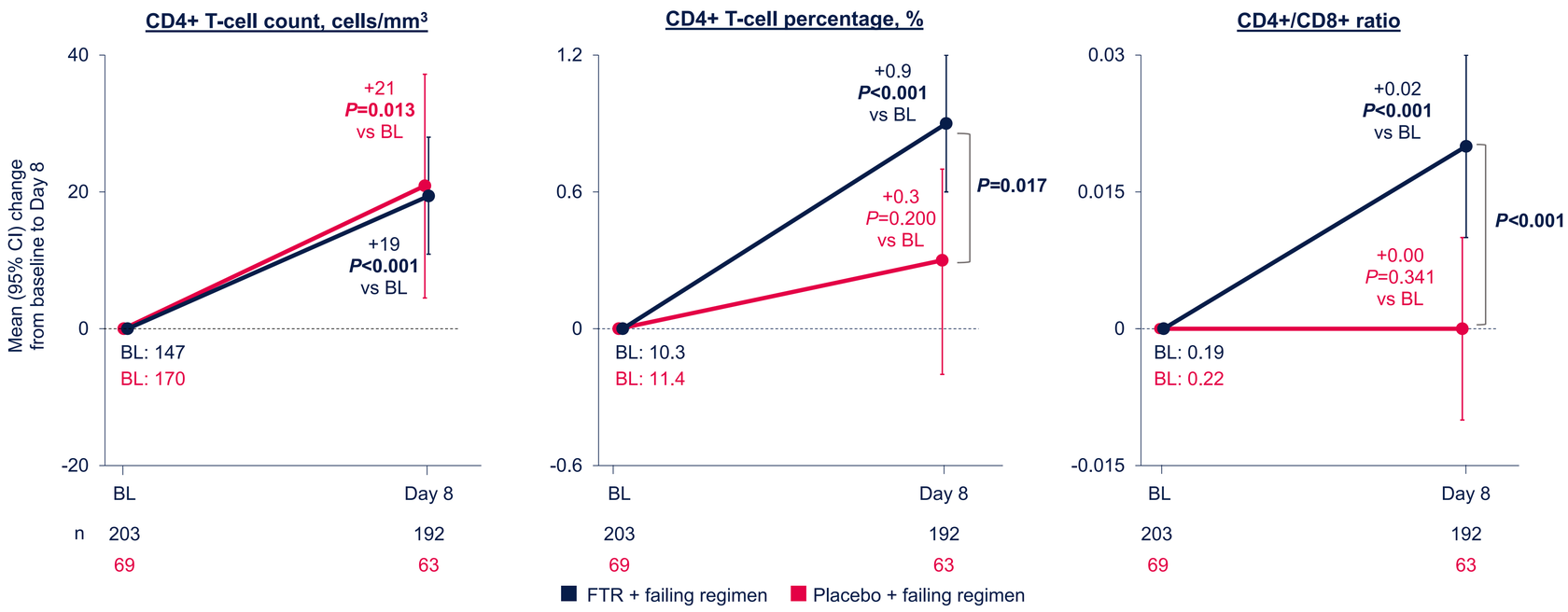
Change From Baseline in Viral Load

- Mean viral load decreased by 0.82 log_{10} c/mL at Day 8 in the FTR group, compared with 0.17 log_{10} c/mL in the placebo group, consistent with prior FTR monotherapy studies[6,7] and as previously reported[2]

Immunologic Parameters

- The FTR group showed statistically significant improvements in mean CD4+ T-cell percentage (*P*=0.017) and CD4+/CD8+ ratio (*P*<0.001) from baseline to Day 8 compared with placebo (Figure 2)
- All immunologic parameters at Day 8 demonstrated a statistically significant improvement from baseline with FTR (Figure 2)
  - In contrast, CD4+ T-cell count was the only immunologic parameter to demonstrate a statistically significant improvement from baseline to Day 8 in the placebo group (*P*=0.013)

Figure 2. Change in Immunologic Parameters From Baseline to Day 8



BL, baseline. Bolded *P* values indicate statistical significance (*P*<0.05). Within-treatment differences (baseline vs Day 8) were assessed using a 1-sample *t* test. Between-treatment differences (FTR vs placebo) were evaluated using a 2-sample *t* test and statistically significant differences are indicated by brackets.

Inflammatory Biomarkers

- A statistically significant reduction in soluble CD163 levels (*P*=0.002) was observed from baseline to Day 8 for the FTR group but not the placebo group (Table 2)
- No significant changes in soluble CD14 or D-dimer levels were observed from baseline to Day 8 in either group
- Changes in inflammatory biomarkers from baseline to Day 8 did not differ significantly between the FTR and placebo groups

Table 2. Change in Inflammatory Biomarkers From Baseline to Day 8[a]

Inflammatory biomarker	Treatment	Baseline n	Baseline Mean (SD)	Change from baseline (Day 8) n	Change from baseline (Day 8) Mean (SD)	95% CI	Within-treatment difference *P* value[b]	FTR vs placebo *P* value[c]
sCD14, µg/L	FTR + failing regimen	192	2542.2 (1045.6)	185	-60.7 (1013.7)	-207.7, 86.3	0.417	0.766
	Placebo + failing regimen	66	2387.0 (1000.6)	62	-98.8 (816.8)	-306.3, 108.6	0.344	
sCD163, µg/L	FTR + failing regimen	190	537.7 (205.4)	184	-23.8 (104.0)	-38.9, -8.7	**0.002**	0.368
	Placebo + failing regimen	66	566.8 (232.1)	63	-11.1 (94.0)	-34.8, 12.5	0.351	
D-dimer, mg/L FEU	FTR + failing regimen	194	0.495 (0.384)	188	0.020 (0.530)	-0.056, 0.096	0.609	0.889
	Placebo + failing regimen	65	0.467 (0.368)	61	0.029 (0.399)	-0.074, 0.131	0.577	

FEU, fibrinogen equivalent units; s, soluble. [a]Bold indicates significant *P* value. [b]*P* value from 1-sample *t* test for within-treatment mean change from baseline to Day 8. [c]*P* value from 2-sample *t* test for the difference in mean change from baseline to Day 8 between FTR vs placebo.

Conclusions

- BRIGHTE provided insight into early immunologic effects that are not typically assessed in HIV clinical trials, demonstrating significant improvements in CD4+ T-cell percentage and CD4+/CD8+ ratio with FTR versus placebo by Day 8
- Systemic inflammatory biomarkers were generally stable from baseline to Day 8, with a significant reduction from baseline in sCD163 with FTR, a marker independently associated with morbidity and mortality in people with HIV-1[8]
- These findings indicate that favorable changes in key immune and inflammatory biomarkers may be observed as early as Day 8 following FTR initiation

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