Impact of Susceptibility Scoring on Virologic Response in Heavily Treatment-Experienced Participants with HIV-1 Receiving a Fostemsavir-Based Antiretroviral Regimen: Week 96 Results from the Randomized Cohort of the Phase 3 BRIGHTE Study

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Introduction

- Fostemsavir (FTR) is a prodrug metabolized to temsavir (TMR), a first-in-class attachment inhibitor that binds to the HIV-1 envelope gp120, preventing attachment to CD4+ cell-surface receptors thereby preventing viral entry into, and infection of, host T cells and other immune cells (**Figure 1**).[1-6]
- FTR is being developed for heavily treatment-experienced (HTE) adults living with multi-drug resistant (MDR) HIV-1 who are unable form a viable cART regimen out of remaining fully active agents.
- BRIGHTE is an ongoing Phase 3 study evaluating FTR plus optimized background therapy (OBT) in HTE participants (**Figure 2**).[7-9]
- In the Randomized Cohort (RC), through Week 96, FTR + OBT:
  - Resulted in increased rates of virologic response (HIV-1 RNA <40 c/mL by Snapshot analysis) between Week 24 (53%; 144/272) and Week 96 (60%; 163/272), and continued, clinically significant increase in CD4+ T-cell count (mean: +205 cells/uL through Week 96).
  - Was well tolerated with no new safety signals and few adverse events leading to discontinuation.
- To better understand possible predictors of virologic response to FTR-based cART in HTE participants, we analyzed virologic efficacy outcomes in RC participants by different methods of susceptibility scoring applied to the initial OBT.

Figure 1. Mechanism of Action of Temsavir

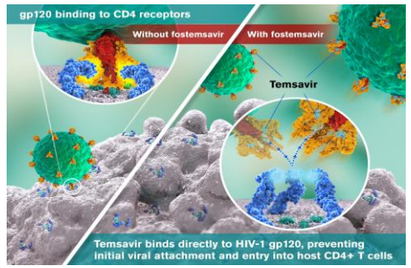
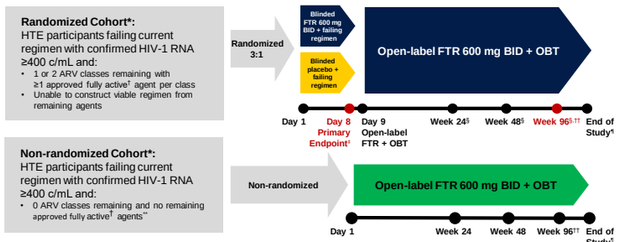


Figure 2. Study Design

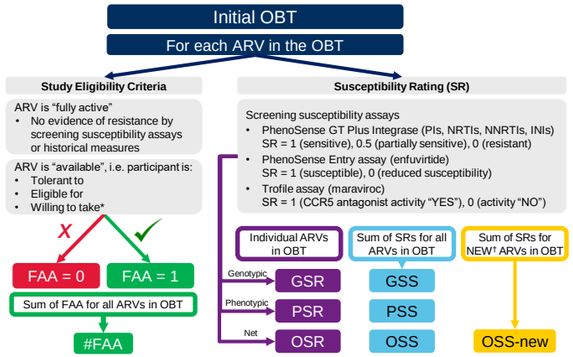


*There were no screening TMR IC50 criteria. †Fully active is based on susceptibility (current or historical resistance measures) & availability (the participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide] the ARV). ‡FTR demonstrated superior efficacy compared with placebo after 8 days of functional monotherapy. §Measured from the start of open-label FTR 600 mg BID + OBT. The last participant initiated OBT in August 2016. ¶The study is expected to be conducted until an additional option, rollover study, or marketing approval is in place. **Use of investigational agents as part of OBT was permitted. ††Week 96 database lock August 14, 2018. BID, twice daily. ClinicalTrials.gov Identifier: NCT02362503; EudraCT Number: 2014-002111-41

Methods

- Virologic response (HIV-1 RNA <40 c/mL, by Snapshot analysis) through Week 96 in the RC was analyzed by the initial OBT genotypic, phenotypic, and overall susceptibility scores (GSS, PSS, OSS, OSS-new) and by number of fully active and available ARVs (#FAA) (Figure 3).

Figure 3. Susceptibility Ratings and Scores



*For enfuvirtide only (twice-daily injectable). †New ARVs are those which have *never* been previously taken by the participant. FAA, fully active and available; G, genotypic; O, overall; P, phenotypic; SR, susceptibility rating; SS, susceptibility score.

Results

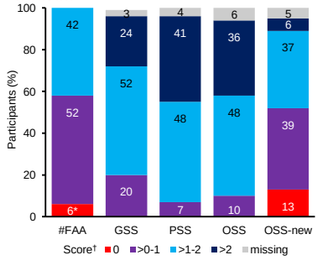
- The RC included 272 participants (**Table 1**), most of whom included 1 or 2 FAA ARVs in their initial OBT (**Figure 4**)
- Dolutegravir was the most common ARV included in the initial OBT (**Figure 5**)

Table 1: Baseline Characteristics

Parameter	Randomized Cohort (N=272)
Age, years, median (range)	48 (18–73)
≥50 years, n (%)	110 (40)
Gender, n (%)	
Female	72 (26)
Race, n (%)	
White	185 (68)
Black/African American	60 (22)
HIV-1 RNA $\log_{10}$ c/mL, median (IQR)	4.7 (3.9–5.1)
≥100,000 c/mL, n (%)	80 (29)
CD4+ T cells/µL, median (IQR)	99 (15–207)
<50 cells/µL, n (%)	97 (36)
AIDS history,* n (%)	231 (85)

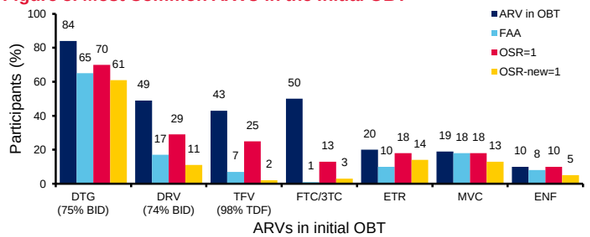
*AIDS history recorded if a participant has nadir CD4+ count <200 cells/µL, or prior history of AIDS-defining illness.

Figure 4. Initial OBT Susceptibility Scores



*Included participants who: i) discontinued from the study during the double-blind period and never initiated OBT; ii) had no active ARV available at screening and were incorrectly assigned to the Randomized Cohort; or iii) had one or more active ARVs available at screening but did not use these as part of the initial OBT. †Scores for #FAA are whole numbers only (0, 1, or 2); GSS, PSS, OSS and OSS-new can include ARVs with partial activity (contributing a score of 0.5 to the sum).

Figure 5. Most Common ARVs in the Initial OBT



3TC, lamivudine; BID, twice daily; DRV, darunavir; DTG, dolutegravir; ENF, enfuvirtide; ETR, etravirine; FTC, emtricitabine; MVC, maraviroc; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

- The strongest correlation for increased rates of virologic response was with increasing baseline OSS-new (**Figures 6** and **7**).
- This trend was less pronounced for OSS and inconsistent for PSS, GSS, and #FAAs.

Figure 6. Virologic Response Through Week 96 by Initial OBT Susceptibility Scores (HIV-1 RNA <40 c/mL, Snapshot Analysis)

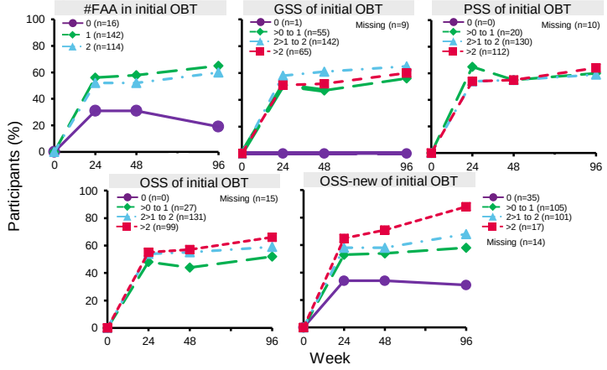
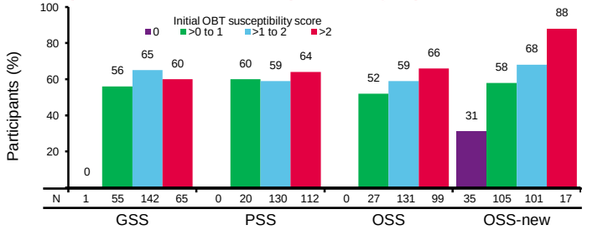


Figure 7. Virologic Response at Week 96 by Initial OBT Susceptibility Scores (HIV-1 RNA <40 c/mL, Snapshot Analysis)



- **Table 2** shows virologic response at Week 96 by whether the initial OBT included (or did not include) a common ARV that was fully active by OSR or OSR-new score

Table 2: HIV-1 RNA <40 c/mL at Week 96 by Most Common ARVs in Initial OBT (Snapshot Analysis, ITT-E, N=272)

ARV	OSR n/N (%)		OSR-new n/N (%)	
	Yes *	No n/N (%)†	Yes n/N (%)*	No n/N (%)†
Dolutegravir	127/190 (67)	36/82 (44)	118/167 (71)	45/105 (43)
FTC/3TC	22/36 (61)	141/236 (60)	8/9 (89)	155/263 (59)
Tenofovir‡	39/68 (57)	124/204 (61)	4/6 (67)	159/266 (60)
Darunavir	50/79 (63)	113/193 (59)	25/31 (81)	138/241 (57)
Etravirine	34/48 (71)	129/224 (58)	29/39 (74)	134/233 (58)
Maraviroc	24/49 (49)	139/223 (62)	19/36 (53)	144/236 (61)
Enfuvirtide	13/26 (50)	150/246 (61)	6/13 (46)	157/259 (61)

*Denominator: number of participants who included the ARV in their initial OBT and for whom the ARV has an OSR or OSR-new of 1. †Denominator: number of participants who either (1) included the ARV in their initial OBT, but for whom the ARV is has an OSR or OSR-new score of 0 or 0.5 or a missing OSR or OSR-new score; or (2) did not include the ARV in their initial OBT. ‡Tenofovir disoproxil fumarate or tenofovir alafenamide.

Conclusions

- Long-term virologic responses in an HTE population receiving FTR-based cART may be better predicted by considering a combination of available resistance results plus prior ARV exposure (OSS-new) rather than resistance measures alone (GSS, PSS, or OSS).
- Among the most common ARVs in the initial OBT, inclusion (vs non-inclusion) of dolutegravir with an OSR or OSR-new of 1 yielded the greatest difference in virologic response.
- The correlation between OSS-new and virologic outcomes in individuals with MDR HIV-1 is consistent with that seen in studies conducted in similar populations.[10]

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