P064

A Multivariate Analysis of the Phase 3 BRIGHTE Trial, Through Week 24, to Identify Predictors of Virologic Response to Fostemsavir in Heavily Treatment-Experienced People Living With HIV

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Key Takeaways

- **Fostemsavir (FTR) demonstrated efficacy and safety in heavily treatment-experienced (HTE) people with multidrug-resistant HIV-1 in the phase 3 BRIGHTE study; here, we evaluated parameters associated with virologic outcomes**
- **Virologic response to FTR functional monotherapy or treatment with FTR + optimized background therapy (OBT) in the Randomized Cohort (RC; participants with 1-2 fully active agents available) was significantly associated with well-established factors such as baseline CD4+ cell count, baseline log_{10} HIV-1 RNA, and temsavir (TMR) concentration**
- **Overall, baseline parameters associated with virologic response to FTR were not predictive of protocol-defined virologic failure (PDVF) with emergent changes through Week 24**

Introduction

- 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 because of resistance, intolerance, or safety concerns[1-3]
- In the ongoing phase 3 BRIGHTE study, FTR + OBT demonstrated durable virologic responses and clinically meaningful improvements in CD4+ T-cell count and CD4+/CD8+ ratio through 240 weeks in HTE adults with HIV-1[4-7]
- Understanding the predictors of virologic outcomes is important for prescribers when considering use of FTR

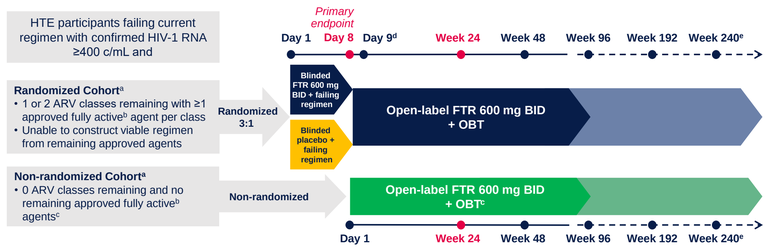
Objective

- To evaluate parameters associated with virologic outcomes through Week 24 in the phase 3 BRIGHTE study (post hoc analysis)

Methods

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

Figure 1. Study Design



[a]There were no screening TMR 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]Subsequent time points were measured from the start of open-label FTR 600 mg BID + OBT. [e]The study is expected to be conducted until participants can access FTR through other means (eg, marketing approval).

- Data from 272 RC and 99 NRC participants were evaluated in multivariate analyses to examine the influence of baseline viral and participant factors and drug concentration on change from baseline in log_{10} HIV-1 RNA at Day 8 for FTR-treated participants in the RC (n=203) and virologic outcome (HIV-1 RNA <40 c/mL by Snapshot) at Week 24 for the ITT-E population in both cohorts using multiple linear and logistic regression models, with stepwise selection (Table 1). A significance level of 0.15 was used for a variable to be accepted into the model and for a variable to remain in the model
  - A RC Day 8 stable viremia sub-population with lack of response to failing therapy was also evaluated (n=141), which excluded participants with evidence of residual activity of the failing regimen (defined as participants with baseline HIV-1 RNA <1000 c/mL or >0.3 log_{10} c/mL decline in HIV-1 RNA from screening to baseline)
- In a separate analysis, baseline parameters were further evaluated for association, alone or in combination, with the outcome of PDVF with treatment-emergent genotypic or phenotypic changes to FTR or agents in initial OBT

Table 1. Parameters Investigated in Multivariate Analyses

Parameter	Parameter type
Baseline CD4+ cell count	Continuous
Viral tropism	Categorical (CCR5, CXCR4, dual mixed, not reported)
Baseline HIV subtype	Binary (B vs non-B)
Baseline viral load	Continuous
Baseline gp120 substitutions at positions of interest	Categorical[a]
Baseline TMR IC_{50} fold change	Continuous
History of AIDS	Binary (yes vs no)
Number of prior ARV regimens	Categorical (2, 3, 4, ≥5)
Number of years on ART	Categorical (<10, 10-20, >20)
Use of DTG in initial OBT	Categorical (no DTG, DTG BID, DTG QD)
Use of DTG and DRV in initial OBT	Categorical (DTG− and DRV−, DTG+ and DRV+, DTG+ and DRV−, DTG− and DRV+)
Parameters specific to Day 8 analyses in the RC	
TMR C_{tau} at Day 8	Continuous
Inhibitory quotient[b]	Continuous
Parameters specific to Week 24 analyses in the RC and NRC	
Number of fully active and available ARVs in initial OBT	Categorical (0, 1, ≥2)
Observed TMR plasma concentration C_{tau} at Week 24	Continuous
Inhibitory quotient[c]	Continuous
OSS of initial OBT	Categorical (0, >0-1, >1-2, >2)

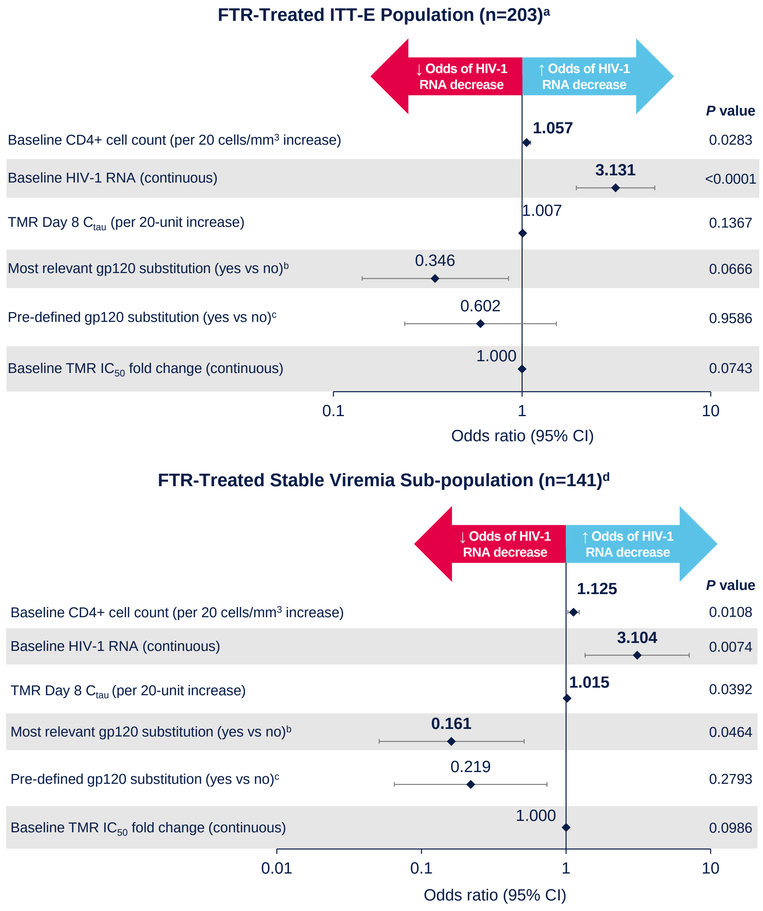
C_{tau}, trough concentration; CCR5, C-C chemokine receptor 5; CXCR4, C-X-C chemokine receptor 4; IC_{50}, half maximal inhibitory concentration; OSS, overall susceptibility score. [a]Amino acid substitutions in gp120 that were pre-defined for analysis in BRIGHTE (S375H/I/M/N/T, M426L/P, M434I/K, M475I) and most relevant substitutions (S375H/I/M/N/Y, M426L, M434K). Pre-defined substitutions included those that were shown as being important for determining TMR phenotypic susceptibility in prior studies. "Most relevant substitutions" included substitutions that were associated with a response of <0.5 log_{10} c/mL change in HIV-1 RNA from Day 1 to 8 during FTR functional monotherapy in the RC or that were previously shown to cause a substantial change (>3-fold) in TMR phenotypic susceptibility in vitro. [b]TMR Day 8 C_{tau}/EC_{50} adjusted for protein binding. [c]TMR Week 24 C_{tau}/EC_{50} adjusted for protein binding.

Results

Parameters Associated With Day 8 Virologic Outcomes in FTR-Treated Participants in the RC

- At Day 8, 65% (131/203) of participants in the RC receiving FTR functional monotherapy achieved a decrease of >0.5 log_{10} c/mL in HIV-1 RNA
- In the ITT-E population, parameters significantly associated with a decrease of >0.5 log_{10} c/mL in HIV-1 RNA at Day 8 included higher baseline CD4+ cell count and higher baseline HIV-1 RNA (Figure 2)
- In the stable viremia sub-population (participants with lack of response to their failing regimen), parameters significantly associated with a decrease of >0.5 log_{10} c/mL in HIV-1 RNA at Day 8 included higher baseline CD4+ cell count and HIV-1 RNA, and TMR Day 8 C_{tau}
- Presence of most relevant gp120 substitutions (S375H/I/M/N/Y, M426L, M434K) was significantly associated with lower odds of >0.5 log_{10} c/mL decrease in HIV-1 RNA in the stable viremia sub-population

Figure 2. Parameters Associated With Odds of >0.5 Log_{10} c/mL Decrease in HIV-1 RNA at Day 8: FTR-Treated RC Participants

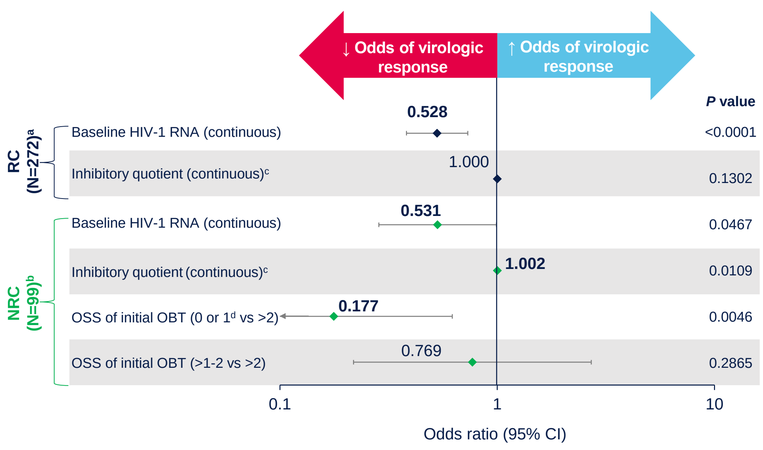


Bolded values indicate significance ($P<0.05$). C_{tau}, trough concentration; IC_{50}, half maximal inhibitory concentration. [a]Based on 180 observations. [b]S375H/I/M/N/Y, M426L, or M434K. [c]S375H/I/M/N/T, M426L/P, M434I/K, or M475I. [d]Excluding participants with baseline HIV-1 RNA <1000 c/mL or >0.3 log_{10} c/mL decline in HIV-1 RNA from screening to baseline; based on 124 observations.

Parameters Associated With Week 24 Virologic Outcomes in the RC and NRC

- At Week 24, 53% and 37% of participants in the RC and NRC, respectively, achieved virologic response (HIV-1 RNA <40 c/mL, Snapshot)
- In the RC and NRC, higher baseline viral load was significantly associated with lower odds of virologic response at Week 24 (Figure 3)
- In the NRC, higher TMR inhibitory quotient was significantly associated with higher odds of virologic response, and an overall susceptibility score of 0 or 1 vs >2 was associated with decreased odds of virologic response at Week 24

Figure 3. Parameters Associated With Odds of Virologic Response at Week 24: RC and NRC Participants

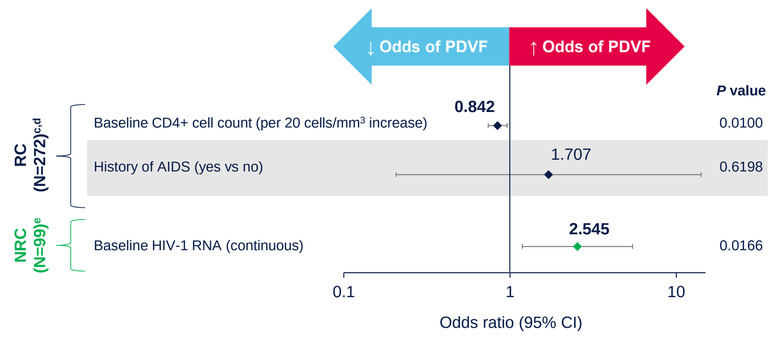


Bolded odds ratios indicate significance ($P<0.05$). OSS, overall susceptibility score. [a]215 observations used. [b]80 observations used. [c]TMR Week 24 C_{tau}/EC_{50} adjusted for protein binding. [d]In the NRC, the categories 0 and >0-1 were combined into a single category of 0 or 1.

Parameters Associated With PDVF With Emergent Changes

- Among evaluable participants at Week 24, 8% (22/263) and 25% (24/95) of participants in the RC and NRC, respectively, had PDVF with emergent genotypic or phenotypic changes to FTR or OBT
- In the RC, higher baseline CD4+ cell count was significantly associated with lower odds of PDVF with emergent changes at Week 24 (Figure 4)
- In the NRC, higher baseline viral load was significantly associated with increased odds of PDVF with emergent changes

Figure 4. Baseline Parameters Associated With Odds of PDVF[a] With Treatment-Emergent Genotypic or Phenotypic Changes[b]



[a]Before Week 24: confirmed, or last available before discontinuation, HIV-1 RNA ≥400 c/mL at any time after prior confirmed suppression to <400 c/mL OR confirmed, or last available before discontinuation, >1 log_{10} c/mL increase in HIV-1 RNA at any time above nadir level where nadir is ≥40 c/mL. At or after Week 24: confirmed, or last available before discontinuation, HIV-1 RNA ≥400 c/mL. [b]With emergent genotypic or phenotypic changes to FTR or OBT. [c]272 observations used. [d]Fixed independent variables used because no variables were selected through stepwise selection. [e]80 observations used.

Baseline Parameter Analysis

- In a separate analysis evaluating the impact of baseline CD4+ cell count <20 cells/mm^3, baseline HIV-1 RNA ≥100,000 c/mL, and presence of most relevant gp120 substitutions on incidence of PDVF with emergent changes, no significant differences were observed among participants with 0, 1, or ≥2 baseline parameters (Table 2)

Table 2. Association Between Identified Baseline Parameters[a] and PDVF With Treatment-Emergent Genotypic or Phenotypic Changes at Week 24

Baseline parameters	Association between baseline parameters and PDVF with emergent changes n/N (%)[b]							
	RC (N=272)				NRC (N=99)			
None	8/112 (7)				9/39 (23)			
1	7/94 (7)				11/36 (31)			
≥2	7/57 (12)				4/20 (20)			
Total	22/263 (8)				24/95 (25)			
Number missing	9				4			
Rate comparison	***P* value**				***P* value**			
1 vs none	>0.9999				0.6023			
≥2 vs none	0.2685				>0.9999			
≥2 vs 1	0.3889				0.5330			
Baseline parameters	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**
None	7.14	90.73	36.36	56.85	23.08	73.21	37.50	57.75
≥1	9.27	92.86	63.64	43.15	26.79	76.92	62.50	42.25
≥2	12.28	92.72	31.82	79.25	20.00	73.33	16.67	77.46

IC_{50}, half maximal inhibitory concentration; NPV, negative predictive value; OSS, overall susceptibility score; PPV, positive predictive value. [a]Identified parameters were baseline CD4+ cell count <20 cells/mm^3, baseline HIV-1 RNA ≥100,000 c/mL, and presence of most relevant gp120 substitutions (S375H/I/M/N/Y, M426L, M434K). [b]Defined as having emergent genotypic (gp120 substitutions) or phenotypic changes at PDVF (TMR IC_{50} fold change >3-fold increase) or reduced susceptibility (OSS or OSS-new) to any agents in initial OBT.

Limitations

- There are known challenges to optimal antiretroviral adherence among HTE individuals, and incomplete adherence to the treatment regimen may be contributing to the observed pattern of virologic responses
- Additional analyses are planned to explore the impact of individual gp120 substitutions on virologic response and evaluate factors impacting durability of response over longer time points

Conclusions

- Virologic response to FTR functional monotherapy or treatment with FTR + OBT in RC participants was significantly associated with well-established factors such as baseline CD4+ cell count, baseline log_{10} HIV-1 RNA, and TMR concentration
- Relevant baseline gp120 substitutions were significantly associated with reduced response to FTR functional monotherapy at Day 8 but not with virologic response to FTR + OBT at 24 weeks
- Overall, the presence of baseline parameters associated with virologic response to FTR was not predictive of PDVF with emergent changes in HTE people with multidrug-resistant HIV-1 in the RC or NRC of the BRIGHTE study

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