Baseline and Emergent Genotypic and Phenotypic Results in HIV-1-Infected, Heavily Treatment-Experienced (HTE) Participants Meeting Protocol-Defined Virologic Failure (PDVF) Criteria Through Week 96 in the Fostemsavir (FTR) Phase 3 BRIGHTE Study

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Introduction

- Fostemsavir (FTR) is a prodrug of temsavir (TMR), a first-in-class, investigational attachment inhibitor being developed for heavily treatment-experienced (HTE) adults living with multi-drug resistant (MDR) HIV-1 infection who are unable to form a viable combination ARV regimen out of remaining fully active agents.[1,2]
- TMR binds to HIV-1 gp120, preventing viral attachment to, and entry into, host CD4+ T cells and other immune cells (**Figure 1**).[1,2]
- BRIGHTE (NCT02362503) is an ongoing Phase 3 study investigating the efficacy and safety of FTR plus optimized background therapy (OBT) in HTE individuals who were failing their current regimen (confirmed HIV-1 RNA ≥400 c/mL).[1,2]
- As previously reported, for the Randomized Cohort (RC), through Week 96, FTR + OBT[1,2]:
  - 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/μL through Week 96).
  - Was well tolerated with no new safety signals and few adverse events leading to discontinuation.
- Previous studies have identified amino acid substitutions at 4 gp120 positions that may influence HIV-1 susceptibility to TMR: S375H/I/M/N/T, M426L/P, M434I/K, and M475I (**Figure 2**).[3-5]
- Here, we present Baseline and emergent virologic results among participants experiencing protocol-defined virologic failure (PDVF) through 96 weeks of FTR-based therapy in the BRIGHTE study (**Figure 3**).
- A clinical cut-off for FTR has not yet been determined.

Figure 1.
Mechanism of Action of TMR[1]

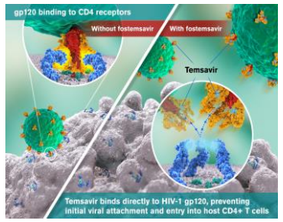
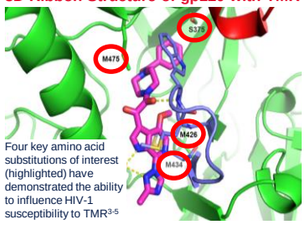
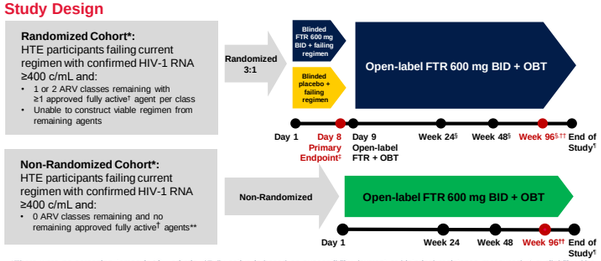


Figure 2.
3D Ribbon Structure of gp120 with TMR[6]



Four key amino acid substitutions of interest (highlighted) have demonstrated the ability to influence HIV-1 susceptibility to TMR[3-5]

Figure 3.
Study Design



*There were no screening temsavir IC_{50} 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

- Genotypic and phenotypic resistance testing was carried out by Monogram Biosciences for all participants at Screening, and at the time of virologic failure for participants meeting PDVF criteria.
  - **PDVF before Week 24:** confirmed or last available prior to discontinuation HIV-1 RNA ≥400 c/mL following confirmed suppression to <400 c/mL, or confirmed or last available prior to discontinuation >1 $\log_{10}$ c/mL increase in HIV-1 RNA above nadir where nadir is ≥40 c/mL; **PDVF on or after Week 24:** confirmed or last available prior to discontinuation HIV-1 RNA ≥400 c/mL.
  - In the investigational TMR phenotypic assay, a change in TMR IC_{50} fold-change (TMR IC_{50} FC) ≤3-fold is within the inherent variability of the assay.
  - Population sequencing of the entire gp160 envelope gene was carried out, and the presence of substitutions of interest (S375H/I/M/N/T, M426L/P, M434I/K, and M475I) was assessed.

Results

Baseline Genotype and Phenotype

- At Baseline, gp120 substitutions of interest were present in 46% of participants in the RC and 42% of participants in the Non-Randomized Cohort (NRC) (**Figure 4A**).
- TMR IC_{50} FC was ≤10-fold and ≤100-fold for 74% and 87% of the RC, respectively, and 78% and 88% of the NRC, respectively (**Figure 4B**).

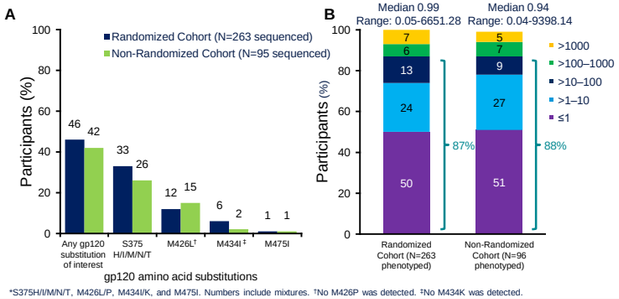
PDVF Over Time

- Through Weeks 24, 48 and 96, rates of PDVF were 11% (31/272), 18% (49/272) and 23% (63/272), respectively in the RC, and 28% (28/99), 46% (46/99) and 49% (49/99), respectively in the NRC.
  - Virologic suppression to <40 c/mL following PDVF through Week 96 was achieved in 27% (17/63) of RC participants and 10% (5/49) of NRC participants.

Incidence of PDVF by Baseline Factors

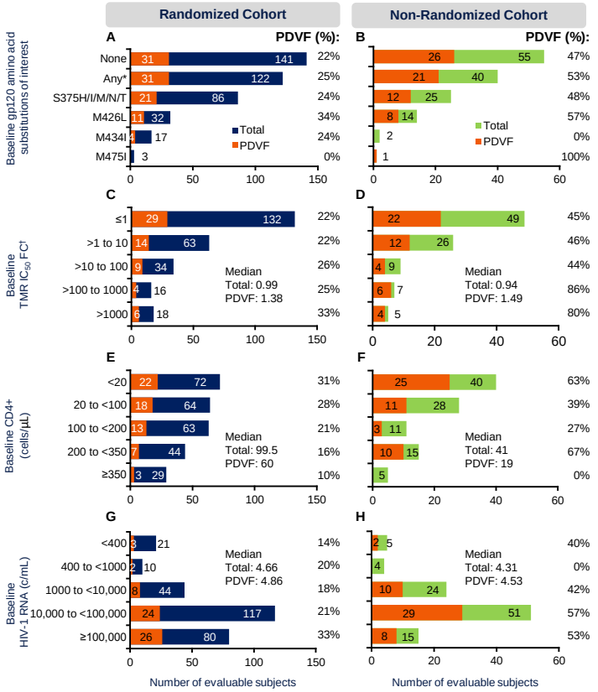
- Rates of PDVF among HTE participants were comparable regardless of gp120 substitutions of interest and TMR IC_{50} FC at Baseline (**Figure 5A**, **B**, **C**, and **D**).
  - There were higher rates of PDVF in NRC subjects with TMR IC50 FC >100-fold; however, the sample size was small.
- For each TMR IC_{50} FC category, higher rates of PDVF were observed among NRC vs RC participants (**Figure 5C** and **D**).
- Lower baseline CD4+ T-cell count (cells/μL), and higher baseline HIV-1 viral load (c/mL), correlated with higher rates of PDVF at Week 96 in both cohorts (**Figure 5E**, **F**, **G**, and **H**).

Figure 4.
(A) Baseline gp120 Substitutions of Interest* (B) Baseline TMR IC_{50} FC



*S375H/I/M/N/T, M426L/P, M434I/K, and M475I. Numbers include mixtures. †No M426P was detected. ‡No M434K was detected.

Figure 5. PDVF Through Week 96 for Randomized and Non-Randomized Cohorts by Baseline gp120 Substitutions of Interest (A and B), TMR IC_{50} FC (C and D), CD4+ T-Cell Count (E and F), HIV-1 Viral Load (G and H)



*Includes only gp120 substitutions of interest: S375T/H/I/M/N, M426L/P, M434I, and M475I. M426P and M434K were not present in this study population at baseline.
†IC_{50} FC is FC compared to a reference virus that has an IC_{50} of approximately 1nM in the Monogram PhenoSense Entry assay.

Treatment-Emergent Changes (Week 96 PDVF)

- Among participants with PDVF, 52% (26/50) in the RC and 25% (11/44) in the NRC had no treatment-emergent gp120 substitutions of interest (**Tables 1** and **2**).
  - In the RC participants, median change from Baseline in TMR IC_{50} FC for participants without treatment-emergent gp120 substitutions was 0.9-fold compared with 511-fold for participants with treatment-emergent gp120 substitutions.
  - In the NRC participants, median change from Baseline in TMR IC_{50} FC for participants without treatment-emergent gp120 substitutions was 0.7-fold compared with 2260-fold for participants with treatment-emergent gp120 substitutions.
- 55% and 29% of PDVF participants in the RC and NRC had a TMR IC_{50} FC ≤3-fold, respectively (**Table 2**).
- Treatment-emergent gp120 substitutions of interest correlated with higher median increase in TMR IC_{50} FC (**Table 2**).

Table 1. Treatment-Emergent Genotypic Changes Among Participants Meeting PDVF Criteria at Week 96

Number of Participants (%)	RC (N=272)	NRC (N=99)
Participants meeting PDVF	63 (23)	49 (49)
Sequenced, n	50	44
Treatment-emergent gp120* substitutions of interest		
None	26 (52)	11 (25)
Any	24 (48)	33 (75)
Specific substitutions		
S375H/I/M/N/T	15 (30)	22 (50)
M426L	16 (32)	21 (48)
M434I	5 (10)	4 (9)
M475I	6 (12)	5 (11)

*Includes only gp120 substitutions of interest: S375H/I/M/N/T, M426L, M434I, and M475I; M426P and M434K were not present in this study population at baseline.

Table 2. Treatment-Emergent Changes in TMR Susceptibility Among Participants Meeting PDVF Criteria at Week 96

	RC (N=272)		NRC (N=99)	
Participants meeting PDVF	63 (23)		49 (49)	
Median change from baseline in TMR IC_{50} FC*	1.7-fold (n=53)		470-fold (n=45)	
Change from baseline in TMR IC_{50} FC ≤3-fold, n (%)	55% (n=29)		29% (n=13)	
Participants with or without treatment-emergent gp120† substitutions of interest	WITH (n=24)	WITHOUT (n=26)	WITH (n=33‡)	WITHOUT (n=11)
Median change from baseline in TMR IC_{50} FC*	511-fold	0.9-fold	2260-fold	0.7-fold
Change in TMR IC_{50} FC from baseline to failure, n (%)				
≤3-fold	3 (13)	23 (88)	3 (9)	9 (82)
>3–10-fold	3 (13)	2 (8)	1 (3)	2 (18)
>10–100-fold	1 (4)	0	4 (13)	0
>100–3000-fold	9 (38)	1 (4)	12 (38)	0
>3000-fold	8 (33)	0	12 (38)	0
TMR IC_{50} FC at failure, n (%)				
≤1	2 (8)	12 (46)	1 (3)	1 (9)
>1–10	1 (4)	3 (12)	2 (6)	2 (18)
>10–100	2 (8)	4 (15)	2 (6)	1 (9)
>100–1000	5 (21)	4 (15)	5 (16)	2 (18)
>1000–5000	10 (42)	3 (12)	14 (44)	2 (18)
>5000	4 (17)	0	8 (25)	3 (27)

*On-treatment resistance testing data are shown at the time of confirmed VF where available, or the time of the suspected VF or a time point nearest, but subsequent, to the VF time point. †Includes only gp120 substitutions of interest: S375H/I/M/N/T, M426L, M434I, and M475I; M426P and M434K were not present in this study population at baseline. ‡Phenotypic data were not available for 1 participant. VF, virologic failure.

Conclusions

- Through Week 96 of the BRIGHTE Study, rates of PDVF in HTE participants in the RC were comparable to those observed in other ARV trials conducted in similar populations.[7,8]
- Baseline gp120 substitutions of interest and TMR IC_{50} FC were not reliably predictive of PDVF among HTE participants in BRIGHTE.
- Among participants with PDVF, emergent gp120 substitutions of interest correlated with greater median increase in TMR IC_{50} FC from baseline.
- Among participants with PDVF, 52% in the RC and 25% in the NRC had no emergent gp120 substitutions of interest, and 55% and 29% of RC and NRC participants, respectively, had a change in baseline TMR IC_{50} FC within the variability of the assay (≤3-fold).
- Among those meeting PDVF criteria, 27% of RC and 10% of NRC participants achieved virologic suppression post-PDVF through Week 96 data lock.
- A clinical cut-off for FTR has not yet been determined.

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