COMPARATIVE EFFICACY OF FOSTEMSAVIR VERSUS IBALIZUMAB IN HEAVILY TREATMENT-EXPERIENCED HIV PATIENTS

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Introduction

- Heavily treatment-experienced (HTE) people with HIV (PWH) have limited treatment options due to concerns with resistance, tolerability, and drug-drug interactions, resulting in significantly more clinical events and higher mortality rates compared with those initiating antiretroviral (ARV) therapy[1-3]
- 2 ARV agents have been approved specifically for use in the HTE population: fostemsavir, a prodrug of the first-in-class attachment inhibitor temsavir, and ibalizumab, a CD4-directed monoclonal antibody and viral-entry inhibitor[4,5]
- Both therapies were evaluated in phase 3 clinical trials, BRIGHTE (fostemsavir; NCT02362503) and TMB-301 (ibalizumab; NCT02475629), in HTE PWH in combination with optimized background therapy (OBT)[6,7]
- Head-to-head trial data are not available, but comparative evidence is typically required by healthcare payers for reimbursement assessments. Because of this, an indirect treatment comparison (matching-adjusted indirect comparison [MAIC]) was used to compare treatment outcomes between fostemsavir plus OBT and ibalizumab plus OBT

Methods

- Using the MAIC method,[8] individual participant data in the intervention trial (BRIGHTE) were re-weighted such that the weighted baseline characteristic summary statistics matched the summary statistics reported for the comparator cohort (TMB-301)
  - Participant-level outcomes were similarly weighted by these values to provide a measure of fostemsavir efficacy in the comparator cohort; outcomes were evaluated across balanced trial populations
- Clinical evidence for the efficacy of fostemsavir was obtained from the combined Randomized and Non-randomized Cohorts in the BRIGHTE study; published data from TMB-301 were used to inform the comparison with ibalizumab
  - Both the BRIGHTE and TMB-301 studies included adults aged ≥18 years[6,7]
    - TMB-301 required resistance to at least 1 drug in ≥3 ARV classes; BRIGHTE required exhaustion of treatment options in ≥4 classes
    - Compared with the TMB-301 study population, the pre-weighting (unadjusted) BRIGHTE population presented with a lower mean CD4+ T-cell count. TMB-301 included slightly older individuals, a lower proportion of participants with HIV-1 RNA >100,000 c/mL at baseline, and a higher proportion of male participants compared with BRIGHTE. Mean viral load was similar between studies
  - Adjustments were made to align inclusion criteria between trials; participants with HIV-1 RNA ≤1000 c/mL were removed from the BRIGHTE individual participant data to match baseline viral load specifications in TMB-301
  - The virologic suppression threshold of HIV-1 RNA <50 c/mL was used in line with reported results from TMB-301
- Variables considered for the purpose of matching included baseline viral load, CD4+ T-cell count, age, sex, and baseline overall susceptibility score (OSS; proportion with 0, 1, 2, and ≥3), reflecting factors prognostic of outcomes in HIV. OSS data at baseline were presented for TMB-301; OSS data for BRIGHTE reflect those for the initial OBT
- Outcomes included change from baseline in CD4+ T-cell count, rates of virologic suppression, and rates of treatment discontinuation
  - Secondary analyses compared the incidence of adverse events experienced by ≥5% of participants in either of the adjusted study populations

Results

- After re-weighting of BRIGHTE individual participant data (adjusted values), negligible differences were observed between the summary statistics of the TMB-301 study population and the BRIGHTE analysis population (Table 1)
- Characterization of the distribution of weights employed in the matching process demonstrated that weights were predominantly clustered around 1, indicating a reasonable degree of overlap between populations

Table 1. Baseline Characteristics of BRIGHTE Fostemsavir Study Versus TMB-301 Ibalizumab Study, Before and After Matching Adjustment at 24 Weeks

		BRIGHTE	
Covariate	TMB-301 (N=40)	Unadjusted (N=347)	Adjusted (N=236)
Log_{10} viral load, mean (SD)	4.5 (0.8)	4.5 (0.9)	4.5 (0.8)
CD4+ T-cell count, mean (SD)	150 (182)	126.6 (158.9)	150.0 (182.4)
Age, mean (SD)	50.5 (11.0)	45.5 (12.3)	51.0 (11.0)
Male, %	85.0%	77.8%	85.0%
OSS, %[a,b]	At baseline: 0 available: 13% 1 available: 30% 2 available: 44% ≥3 available: 13%	Initial OBT: 0 available: 9% 1 available: 27% 2 available: 45% ≥3 available: 20%	Adjusted: 0 available: 13% 1 available: 30% 2 available: 44% ≥3 available: 13%

OSS, overall susceptibility score. [a]TMB-301 scores normalized to sum to 100%. [b]BRIGHTE scores recalculated with partial scores (ie, score of 0.5) set to zero, to align with TMB-301 reporting.

- Adjusted estimates of mean change from baseline in CD4+ T-cell count at 24 weeks were marginally greater with fostemsavir plus OBT vs ibalizumab plus OBT (mean difference, 7.05 cells/mm^3); however, this was not statistically significant (*P*=0.834; Tables 2 and 3)
- A non-significant improvement in virologic suppression was observed with fostemsavir plus OBT vs ibalizumab plus OBT at 24 weeks (51.5% vs 43.0%; *P*=0.284)
- A non-significant reduction in discontinuations with fostemsavir plus OBT vs ibalizumab plus OBT at 24 weeks was also observed (5.1% vs 12.5%; *P*=0.073)

Table 2. MAIC Outcomes for Fostemsavir + OBT vs Ibalizumab + OBT

		BRIGHTE (24 weeks)	
Covariate	TMB-301 (24 weeks) (N=40)	Unadjusted (N=347)	Adjusted (N=236)
Change in CD4+ T-cell count from baseline, mean (95% CI)	62 (−4, 128)	81.17 (69.55, 92.78)	69.05 (52.31, 85.78)
Virologic suppression (<50 c/mL), % (95% CI)	43% (27%, 59%)	49.86% (44.47%, 55.24%)	51.53% (45.43%, 57.58%)
Discontinuation, % (95% CI)	12.5% (4%, 27%)	5.76% (3.56%, 8.76%)	5.10% (3.07%, 8.37%)

MAIC, matching-adjusted indirect comparison; OBT, optimized background therapy.

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Table 3. Tests of the Difference Between Outcomes for Fostemsavir + OBT vs Ibalizumab + OBT

	BRIGHTE 24 weeks unadjusted vs TMB-301		BRIGHTE 24 weeks adjusted vs TMB-301	
Covariate	Result	*P* value	Result	*P* value
Change in CD4+ T-cell count from baseline, mean difference (95% CI)	19.17 (−47.79, 86.13)	0.562	7.05 (−60.88, 74.98)	0.834
Virologic suppression, OR (95% CI)	1.35 (0.70, 2.64)	0.379	1.44 (0.74, 2.80)	0.284
Discontinuation, OR (95% CI)	0.43 (0.16, 1.35)	0.110	0.38 (0.13, 1.09)	0.073

OBT, optimized background therapy; OR, odds ratio.

- Rates of dizziness were lower with fostemsavir plus OBT compared with ibalizumab plus OBT (Table 4); however, the 95% CIs between treatments overlapped
- Rates of diarrhea and nausea were higher with fostemsavir plus OBT; however, the 95% CIs between treatments overlapped

Table 4. Adverse Events in BRIGHTE, Unadjusted and Adjusted, (Matched to TMB-301) at 24 Weeks

	TMB-301		BRIGHTE			
	Reported adverse event		Unadjusted		Adjusted	
Event	Proportion of participants affected (n; % [95% CI])	Events (n)	Proportion of participants affected (n; % [95% CI])[a]	Incidence (per 100 PY)	Proportion of participants affected (n; % [95% CI])[a]	Incidence (per 100 PY)
Diarrhea	3; 7.5% (1.6%, 20.4%)	9	14; 4.0% (2.2%, 6.7%)	11.8	9.7; 4.1% (2.1%, 7.7%)	12.5
Dizziness	3; 7.5% (1.6%, 20.4%)	4	4; 1.2% (0.3%, 2.9%)	2.6	2.0; 0.9% (0.1%, 3.0%)	1.9
Nausea	2; 5.0% (0.6%, 16.9%)	3	29; 8.4% (5.7%, 11.8%)	23.0	14.8; 6.3% (3.6%, 10.3%)	19.3

PY, patient-year. [a]To calculate the CIs, the effective number of participants (n) and the effective sample size were rounded to the nearest integer.

Conclusions

- While numerically larger improvements in efficacy were observed with fostemsavir plus OBT vs ibalizumab plus OBT, differences in this small data set over short-term follow-up did not reach statistical significance
- Inclusion of the Non-randomized Cohort from the BRIGHTE study is a potential confounding factor, as most participants had no approved fully active ARV agents in the initial OBT and would have been excluded from TMB-301, which required at least 1 fully active ARV agent in the OBT
- Additionally, OSS insufficiently accounts for archived resistance and therefore may not be a reliable predictor of treatment response in the HTE population.[9] Furthermore, available baseline OSS data for TMB-301 may be underestimating the activity of the OBT given the requirement to include at least 1 active agent in the OBT, yet 13% of patients had an OSS of 0
- Results may also be limited by the small trial size of TMB-301 (N=40). In BRIGHTE, ibalizumab was used in a subset of patients, and similarly, in TMB-301, fostemsavir was used. In TMB-301, to construct an OBT with at least 1 fully susceptible ARV agent, 17 patients (43%) required the addition of fostemsavir. It was not possible to exclude these patients from the analysis
- Data were only available through Week 24 for TMB-301, thus, a comparison of later endpoints was not possible. Notably, data from participants in BRIGHTE showed continued improvements in CD4+ T-cell count and virologic response at 96 weeks with fostemsavir plus OBT, which could not be captured in this analysis

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