Original Research

Comparative Efficacy and Safety of Fostemsavir in Heavily Treatment-Experienced People With HIV-1

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ABSTRACT

Purpose: Heavily treatment-experienced (HTE) people with multidrug-resistant HIV-1 have limited treatment options. Treatment with the first-in-class attachment inhibitor fostemsavir in addition to optimized background therapy (OBT) resulted in sustained virologic and immunologic responses in HTE participants throughout 96 weeks in the BRIGHTE trial. In the absence of long-term direct comparative evidence between fostemsavir-based and other antiretroviral regimens, this analysis indirectly compares efficacy and safety across relevant available trials, adjusting for demographic and baseline characteristics.

Methods: A systematic literature review was conducted to identify trials with designs and populations comparable to BRIGHTE. Using matching-adjusted indirect comparison analyses, individual participant data from BRIGHTE were reweighted to create balanced populations across trials, and efficacy and safety outcomes were compared.

Findings: Three comparator trials were identified, 2 of which reflected an optimized therapy without fostemsavir (OBT alone): TMB-301 (ibalizumab and OBT), BENCHMRK-1/-2 (OBT alone), and VIKING-3 (OBT alone). Compared with ibalizumab and OBT (N = 40), fostemsavir and OBT (unadjusted, N = 347; adjusted, N = 236) were associated with numerically higher nonsignificant odds of virologic suppression (odds ratio [OR] = 1.44; 95% CI, 0.74–2.80; $P = 0.284$) and a similar increase in $CD4^+$ cell count of approximately 65 cells/mm^3 from baseline through week 24 (mean difference = 7.05 cells/mm^3; 95% CI, −60.88 to 74.98 cells/mm^3; $P = 0.834$). Compared with OBT from BENCHMRK-1/-2 (N = 237), fostemsavir and OBT (adjusted, N = 126) were associated with significantly higher odds of virologic suppression (OR = 3.26; 95% CI, 2.08–5.11; $P < 0.001$) and increased $CD4^+$ cell count (135.78 cells/mm^3; 95% CI, 91.93–179.63 cells/mm^3; $P < 0.001$) at week 96. Compared with OBT from VIKING-3 (N = 183), fostemsavir and OBT (adjusted, N = 78) were associated with numerically higher odds of virologic suppression (OR = 1.34; 95% CI, 0.78–2.30; $P = 0.297$) and a modest $CD4^+$ cell count increase (26.86 cells/mm^3; 95% CI, −10.79 to 64.52; $P = 0.162$) through week 48; however, differences were not significant. All-cause discontinuations and safety comparisons varied across studies.

Implications: Although matching-adjusted indirect comparison analyses have limitations, these results support the use of fostemsavir and OBT as an important treatment option in HTE people with multidrug-resistant HIV-1. (*Clin Ther.* 2022;44:886–900.)

Key words: attachment inhibitor, drug resistance, fostemsavir, heavily treatment-experienced, HIV, indirect comparison.

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INTRODUCTION

To evaluate the incremental benefits and limitations of introducing a new medicine, patient clinical outcomes with the new therapy must be compared with those of established therapies. Most randomized clinical trials include multiple treatment groups, allowing for direct comparison of long-term efficacy and tolerability between active comparators or placebo. However, in studies evaluating the use of a new drug to treat multidrug-resistant HIV-1 or for patients who have exhausted available treatment options, no other drugs exist for comparison; therefore, study designs have evolved to ethically evaluate these medicines using short-term (1–2 weeks) placebo-controlled trials.[1] An indirect treatment comparison can help inform decision making in the absence of head-to-head evidence.[2,3]

Fostemsavir is a first-in-class antiretroviral (ARV) with no cross-resistance to existing ARVs and provides a critical additional treatment option for people with multidrug-resistant HIV-1.[4] The efficacy and tolerability of fostemsavir in heavily treatment-experienced (HTE) individuals with multidrug-resistant HIV-1 were evaluated in the BRIGHTE study, a randomized, placebo-controlled, double-blind, Phase III clinical trial.[5] The BRIGHTE study compared outcomes in individuals receiving fostemsavir or placebo, combined with failing background regimen, for 8 days, after which all participants received open-label fostemsavir and optimized background therapy (OBT) for the remainder of the study. Although direct comparative data are not available for longer-term end points, it is necessary to explore the relative efficacy and tolerability of fostemsavir-based regimens compared with other regimens in HTE people with multidrug-resistant HIV-1 to support decision making beyond clinical practice (eg, for health technology assessment).

Population-adjusted indirect treatment comparison methods address situations in which head-to-head comparator data are not available from clinical trials and individual participant data (IPD) are not available for all studies of interest.[2,6] With the use of statistical techniques to adjust for differences in treatment effect–modifying variables, methods such as matching-adjusted indirect comparison (MAIC) analysis allow for comparison of treatments across balanced populations using data from different trials.[2,6] There is extensive literature on the use of such methods in a range of therapeutic areas.[7–9] However, application of these methods requires careful consideration of participant characteristics across trials of interest, prognostic or treatment effect–modifying variables, and appropriate comparator therapies.

Heavily treatment-experienced individuals with multidrug-resistant HIV have few viable treatment options available. There are 2 comparators of interest for the HTE population for whom fostemsavir is indicated: (1) a regimen of ibalizumab (administered intravenously every 14 days) and OBT and (2) an optimized regimen in the absence of ibalizumab, captured by OBT in the context of clinical trials in HTE participants. Optimized regimens are heterogeneous in the HTE population and are tailored to individual needs based on resistance profile, safety profile, tolerability, or drug-drug interactions. Ibalizumab is a CD4-directed postattachment inhibitor that was evaluated in the TMB-301 and rollover TMB-311 studies, contemporaneous with BRIGHTE and in a comparable patient population, although BRIGHTE included a cohort of participants with no fully active available ARVs who would not have met the inclusion criteria for TMB-301.[10] Ibalizumab is only reimbursed in a limited number of settings, and comparison with an optimized regimen reflective of the treatment options for settings in which ibalizumab is not available is also required. Identifying a representative optimized regimen comparator in these settings is complicated by the fact that optimized regimens in the HTE population are typically composed of combination ARV therapy tailored to a patient's specific needs, reflecting their resistance profile, tolerability considerations, and appropriateness for use given factors such as existing comorbidities.[11] Treatment guidelines specify principles of care, such as the inclusion of $\geq$1 ARV with a high barrier to resistance, a new mechanism of action, and no cross-resistance to other therapies.[12] Nonetheless, for the purposes of decision making beyond clinical practice (eg, health technology assessment and economic evaluation), it is important to evaluate comparator evidence in the absence of head-to-head trials. We conducted a systematic literature review to identify studies with designs and populations that were comparable to the BRIGHTE study and then used MAIC analyses to evaluate the relative efficacy and safety of fostemsavir and OBT in HTE individuals with multidrug-resistant HIV-1.

PARTICIPANTS AND METHODS

Systematic Literature Review and Feasibility Analysis

A systematic literature review was undertaken to identify clinical trials conducted in the HTE population published from January 1, 2003, to February 23, 2021. The literature search was informed by the inclusion criteria defining the HTE population for the BRIGHTE trial and is described fully in Supplemental Appendix Section 1.4. This study complied with all applicable laws regarding participant privacy. Analyses omitted participant identification, and no direct contact or collection of primary data from participants occurred. All trials included in the analysis obtained institutional review board or ethics committee approval before initiation. Because this study only used preexisting, deidentified participant data, institutional review board approval was not required.

Overall, 78 individual articles reporting 52 clinical trials met the inclusion criteria for the review. After excluding BRIGHTE, 51 trials underwent data extraction and were subsequently filtered based on suitability for informing the relevant comparator groups in the MAIC analyses. Factors considered when filtering studies for suitability included the following: (1) availability of key outcome data and alignment of study definitions; (2) expert clinical opinion on the comparability of trial populations with the HTE population recruited into BRIGHTE; (3) how well the ARV regimens in the comparator studies represented OBT comparable to that used in BRIGHTE; and (4) alignment of trial inclusion and exclusion criteria and reported drug resistance data (resistance to ≥3 ARV classes) or susceptibility data (genotypic susceptibility score [GSS], phenotypic susceptibility score [PSS], or overall susceptibility score [OSS]) with those of BRIGHTE. Susceptibility scores have been described in detail previously[13] and in Supplemental Appendix Section 1.5. Briefly, susceptibility scores are based on a participant's susceptibility ratings for each ARV. A score of 0 indicates resistance to an ARV, 0.5 indicates partial activity, and 1 indicates full activity. These resistance ratings are summed to provide insight into resistance for each participant. In the absence of a universal optimized regimen for comparison (ie, in this case optimized regimen reflects a heterogeneous group of regimens tailored to individual needs), multiple trials were considered for inclusion in the MAIC analyses, each with a unique set of limitations.

Three studies and respective comparators were identified for use in the MAIC analyses: TMB-301 (ibalizumab and OBT), BENCHMRK-1/-2 (OBT alone), and VIKING-3 (OBT alone).[10,14–17] In BRIGHTE, OBT primarily included dolutegravir, darunavir, and tenofovir disoproxil fumarate.[5] Complete information on OBT regimens is not available for all comparator studies. The OBT in TMB-301 was likely comparable to that used in BRIGHTE because it was conducted contemporaneously with BRIGHTE and TMB-301 had mostly similar recruitment criteria and participant characteristics.[10] In BENCHMRK, 58% of participants had ≥1 protease inhibitor in their antiretroviral therapy regimen, and dolutegravir was not yet available.[15] The OBT used for comparison with VIKING-3 was more similar to that in BRIGHTE and primarily included dolutegravir, darunavir, and tenofovir disoproxil fumarate/emtricitabine.[17] Notably, unlike typical indirect comparisons in which comparators are prespecified and evidence synthesis directed toward a specific treatment, in this study, the OBT-alone comparator, reflective of optimized regimens in the absence of ibalizumab, could refer to a wide range of treatment regimens. Furthermore, the diversity in the participants' resistance profiles added complexity to determining the expected activity of these regimens and matching based on these characteristics. Susceptibility scores (GSS, PSS, and OSS) were used as an indication of existing resistance, and consequently the expected activity of OBT and contribution to the overall efficacy of the regimen, but have limitations in terms of how predictive they are of outcomes.[18] Therefore, the systematic literature review focused on identifying treatments in patient populations comparable to BRIGHTE (eg, participants' treatment experience, resistance profile, and available remaining therapies). In the absence of a definitive comparator, 2 comparator trials were selected to inform the OBT-alone scenario (BENCHMRK-1/-2 and VIKING-3). Key study characteristics and inclusion criteria are presented in Table I.

MAIC Analysis

The BRIGHTE trial consisted of 2 cohorts, randomized and nonrandomized, reflecting underlying patient needs (the nonrandomized cohort had more extensive resistance and no fully active ARV options available).[5] To maximize sample size of the analysis population, the 2 cohorts (intention-to-treat–exposed [ITT-E]) were

Table I. Summary of key study characteristics and inclusion criteria.

Variable	BRIGHTE	TMB-301	BENCHMRK	VIKING-3
Key study characteristics				
Study design	Randomized Phase III study; randomized cohort had an 8-day, double-blind, randomized period (fostemsavir and failing regimen vs placebo and failing regimen) followed by open-label fostemsavir and OBT; nonrandomized cohort received open-label fostemsavir and OBT at study start	Single-group, open-label, Phase III study; participants received ibalizumab after a 7-day control period	Identical, randomized, double-blind, Phase III studies (raltegravir and OBT vs placebo and OBT); participants with virologic failure at or after week 16 could enter an open-label phase with raltegravir as part of a new regimen	Single-group, open-label, Phase III study; participants received twice-daily dolutegravir while continuing failing regimen without raltegravir or elvitegravir through day 7, after which dolutegravir treatment was continued and the regimen was optimized with ≥1 fully active ARV
Study drug	Fostemsavir	Ibalizumab	Raltegravir	Dolutegravir
Enrollment period	February 2015 to May 2016	July 2015 to October 2016	February 2006[a]	May 2011[a]
Virologic suppression, HIV-1 RNA	<40 copies/mL (FDA Snapshot)	<50 copies/mL (FDA Snapshot)	<50 copies/mL and treatment-related discontinuation considered failure; missing HIV-1 RNA was not counted as failure	<50 copies/mL (FDA Snapshot)
Key inclusion criteria				
Screening HIV-1 RNA	≥400 copies/mL	>1000 copies/mL	≥1000 copies/mL	≥500 copies/mL
Treatment history	ARV experienced with ≤2 classes and ≥1 but ≤2 fully active ARVs remaining	ARV experienced	ARV experienced	ARV and INSTI experienced and naive to dolutegravir
Virologic failure history	Failing on current regimen	Failing on current regimen	Failing current regimen	Current or prior failure on raltegravir or elvitegravir regimen

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Table I. (*continued*)

Variable	BRIGHTE	TMB-301	BENCHMRK	VIKING-3
Resistance status	Historical or baseline resistance, intolerability, and/or contraindications to ARVs in ≥3 classes	Genotypic or phenotypic resistance to ≥1 ARV in ≥3 classes	Documented phenotypic or genotypic resistance to ≥1 ARV in each of 3 classes[b]	Documented resistance to raltegravir and/or elvitegravir and to ≥2 other classes
Available treatment options	Randomized cohort: able to receive ≥1 fully active ARV as part of OBT; nonrandomized cohort: no fully active ARVs remaining	Full viral sensitivity or susceptibility to ≥1 ARV, other than ibalizumab, and willing or able to be treated with ≥1 ARV to which the participant was fully sensitive or susceptible according to screening resistance tests as part of OBT	Not reported	Able to receive ≥1 fully active ARV as part of OBT after day 8

ARV = antiretroviral; FDA, US Food and Drug Administration; INSTI = integrase strand transfer inhibitor; OBT = optimized background therapy.

[a] Study start date.

[b] Included oral nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors.

combined to represent the full BRIGHTE population eligible for fostemsavir. Notably, neither TMB-301 nor VIKING-3 included participants comparable to those in the nonrandomized cohort from BRIGHTE, but a similar group of participants was included in BENCHMRK.[10,15,17]

If key study definitions differed among trials (for inclusion criteria, matching variables, or outcomes), efforts were made to align these between the comparator trial and BRIGHTE, as described below and in detail in Supplemental Appendix Sections 2.2, 2.3, and 2.4. Differences in inclusion criteria, particularly those regarding viral load, were accounted for through exclusion of relevant BRIGHTE participants before the matching process.

The TMB-301 study was a single-group, open-label, Phase III clinical trial used to inform the ibalizumab and OBT comparator.[10] This trial enrolled participants contemporaneously with the BRIGHTE trial, and the recruitment criteria and participant characteristics were mostly similar; in the absence of published details of the OBT used in TMB-301, we assume that this was comparable to BRIGHTE. Notably, 17 of the 40 participants (43%) in the TMB-301 trial were receiving fostemsavir in their OBT, and 15 of 371 BRIGHTE participants (4%) were receiving ibalizumab in their OBT.

The BENCHMRK-1/-2 studies were selected as 1 of the OBT-alone comparator study candidates because the patient population was closely aligned with the BRIGHTE population. The GSS and PSS indicated that most participants had ≤2 ARV classes remaining and resistance to ≥3 ARV classes,[14–16] and BENCHMRK included an OBT-alone group in an HTE population. However, BENCHMRK, which evaluated raltegravir and OBT, began in 2006, and the ARVs used in the

OBT-alone group (eg, darunavir and tipranavir) do not reflect those used in BRIGHTE (notably, BENCHMRK lacked dolutegravir).

The VIKING-3 study was selected as the second OBT-alone comparator study. VIKING-3 was conducted in an HTE population comparable to that in BRIGHTE, and the therapies used were generally comparable to BRIGHTE.[17,19,20] Similar to the design of BRIGHTE, all participants received the investigational drug dolutegravir as functional monotherapy for a short period (7 days in VIKING-3) before receiving dolutegravir in combination with OBT.

Screening viral load inclusion criteria differed among the studies. Therefore, a screening HIV-1 RNA load >1000 copies/mL was selected for BRIGHTE participants (combined randomized and nonrandomized ITT-E study population, N = 371; 24 participants with screening HIV-1 RNA load ≤1000 copies/mL removed, N = 347) for comparison with TMB-301 and BENCHMRK. For comparison with VIKING-3, screening HIV-1 RNA load ≥500 copies/mL was selected for BRIGHTE participants (ITT-E study population, N = 371; 13 participants with screening HIV-1 RNA load <500 copies/mL removed, N = 358). Because the definition of virologic suppression differed among the studies, a threshold of HIV-1 RNA load <50 copies/mL was used.

Overall susceptibility rating scoring differed among the studies. Overall susceptibility ratings of 0.5 (partial susceptibility) from BRIGHTE were reassigned to 0 (no susceptibility) to match the TMB-301 scoring approach. To match resistance data between BRIGHTE and VIKING-3, reassignments were performed for OSS-new (susceptibility score for ARVs not previously used by the participant) reported for the OBT from the VIKING-3 trial to account for the activity of the investigational agent (dolutegravir) in addition to OBT. Dolutegravir was presumed to be fully active in VIKING-3 and assigned an overall susceptibility rating of 1 (full susceptibility) for all participants. Furthermore, partial overall susceptibility ratings from BRIGHTE were reassigned from 0.5 to 0 to match the VIKING-3 scoring approach. Further details of how susceptibility scores were harmonized between BRIGHTE and VIKING-3 are provided in Supplemental Appendix Section 2.4.2.

TMB-301 reported data through 24 weeks, and results were compared with 24-week data from BRIGHTE. In the comparison of BRIGHTE with BENCHMRK, end points were compared at week 96, the latest comparable time point for each study available at the time of this analysis. In VIKING-3, participants could withdraw once commercial dolutegravir was available after week 48, and these withdrawals were recorded as failures. Therefore, BRIGHTE was compared with VIKING-3 efficacy end points at week 48. Safety data available from VIKING-3 reported all events observed through the week 48 data cutoff (median [range] exposure, 507 [14–757] days). Thus, safety data were compared with the BRIGHTE week 48 data cutoff (median [range] exposure, 621 [1–1039] days).

We used MAIC analyses to reweight IPD from the BRIGHTE trial as the index cohort, such that the adjusted (weighted) baseline characteristic summary statistics matched the summary statistics reported for each comparator cohort, using previously described methods[2] and summarized below. Participant-level outcome data from the index trial were then weighted by these values, allowing for comparison of treatment outcomes across balanced populations.

For each MAIC analysis, a logistic propensity score model was fitted using the method of moments to derive weights for the index trial to balance the summary statistics of the baseline characteristics between BRIGHTE and the comparator cohort. Summary statistics and effective sample size were derived as described in Supplemental Appendix Section 2.1. Treatment effects were estimated using weighted regression with sandwich SEs. For all continuous outcome variables, mean differences between the index and comparator groups were estimated. For all binary outcome variables, odds ratios (ORs) were estimated to measure relative efficacy or tolerability, with a weighted logistic regression. Variables considered for the purpose of matching were determined using literature on factors prognostic of outcomes in HIV[21–23] and in consultation with clinical experts. Age, sex, number of years treated, disease duration, AIDS history, baseline viral load, baseline $CD4^+$ cell count, and number of active ARVs in initial OBT (based on susceptibility scores) were chosen. For each MAIC analysis, the final set of matching variables was determined by data availability, and conformation of the data with the statistical assumptions was required.

Where possible, analyses quantified efficacy in terms of differences in mean change from baseline

in CD4+ cell count and relative difference assessed by OR in proportions of participants with virologic suppression, protocol-defined virologic failure (PDVF), and treatment discontinuation. Secondary analyses assessed the safety profile of fostemsavir, considering proportions of participants with drug-related adverse events (AEs), serious AEs (SAEs), discontinuation because of AEs, and death, where appropriate.

RESULTS

Unadjusted and Adjusted Matching Variable Summary Statistics

Mean age in the unadjusted (preweighted) BRIGHTE analysis populations was 45.5 years, and 77.8% to 78.5% of participants were male (Table II). At baseline, mean viral load was 4.4 to 4.5 $\log_{10}$ copies/mL and mean CD4+ cell count was 126.6 to 131.5 cells/mm^3.

The TMB-301 study population had a similar mean baseline viral load and OSS distribution to the respective unadjusted BRIGHTE analysis population, although BRIGHTE participants had a lower mean baseline CD4+ cell count. In TMB-301, a higher proportion of participants were male, and mean age was slightly higher than in BRIGHTE.

The unadjusted BRIGHTE analysis population had similar mean baseline viral load and age compared with the BENCHMRK study population, but BRIGHTE participants had a lower mean baseline CD4+ cell count. BENCHMRK included a higher proportion of male participants than BRIGHTE. Higher proportions of BENCHMRK participants had a GSS and PSS of 0 or 1 compared with those in the BRIGHTE analysis population.

The proportion of male participants and mean baseline age were comparable between the unadjusted BRIGHTE analysis population and the VIKING-3 study population. The unadjusted BRIGHTE analysis population had more poorly controlled disease at baseline, with a higher mean viral load and a lower mean CD4+ cell count. The unadjusted BRIGHTE analysis population also presented with more advanced disease, indicated by higher proportions of participants with a history of AIDS and an OSS-new of 0.

After adjustment (weighting), all study populations had identical baseline age, proportion of male participants, viral load, CD4+ cell count, and ARV susceptibility scores (Table II). Furthermore, the effective sample sizes after adjustment were considered adequate for sufficiently robust comparisons for the TMB-301 (BRIGHTE unadjusted, N = 347; adjusted, N = 236; TMB-301, N = 40), BENCHMRK (BRIGHTE unadjusted, N = 347; adjusted, N = 126; BENCHMRK, N = 237), and VIKING-3 (BRIGHTE unadjusted, N = 358; adjusted, N = 78; VIKING-3, N = 183) MAIC analyses. Further information regarding weights used in the matching process is provided in Supplemental Appendix Sections 2.2.3, 2.3.3, and 2.4.3.

MAIC Analysis Efficacy and Safety Outcomes

Virologic Suppression

At week 24, fostemsavir and OBT were associated with nonsignificantly higher odds of virologic suppression (defined as HIV-1 RNA load <50 copies/mL) vs ibalizumab and OBT (OR = 1.44; 95% CI, 0.74–2.80; $P = 0.284$) (Figure 1). Compared with OBT informed by BENCHMRK, fostemsavir and OBT were associated with significantly higher odds of achieving virologic suppression at week 96 (OR = 3.26; 95% CI, 2.08–5.11; $P < 0.001$). Compared with OBT informed by VIKING-3, fostemsavir and OBT were associated with nonsignificantly higher odds of virologic suppression at week 48 (OR = 1.34; 95% CI, 0.78–2.30; $P = 0.297$).

Change From Baseline in CD4+ Cell Count

Fostemsavir and OBT as well as ibalizumab and OBT elicited similar increases in mean CD4+ cell counts of approximately 65 cells/mm^3 from baseline to week 24 (mean difference = 7.05 cells/mm^3; 95% CI, −60.88 to 74.98; $P = 0.834$) (Figure 2). Compared with OBT informed by BENCHMRK, fostemsavir and OBT were associated with a significant improvement in mean CD4+ cell count from baseline at week 96 (mean difference = 135.78 cells/mm^3; 95% CI, 91.93–179.63; $P < 0.001$). Fostemsavir and OBT were associated with a greater but nonsignificant mean CD4+ cell count increase from baseline compared with OBT informed by VIKING-3 at week 48 (mean difference = 26.86 cells/mm^3; 95% CI, −10.79 to 64.52; $P = 0.162$).

All-Cause Discontinuations

Compared with ibalizumab and OBT, fostemsavir and OBT were associated with nonsignificantly lower odds of experiencing all-cause discontinuation at week 24 (OR = 0.38; 95% CI, 0.13–1.09;

Table II. Unadjusted and adjusted matching variable summary statistics.

Parameter	Ibalizumab and OBT (TMB-301) (N = 40)	Fostemsavir and OBT (BRIGHTE)[a]	
		Unadjusted (N = 347)	Adjusted (N = 236)
TMB-301 and BRIGHTE			
Age at baseline, mean (SD), y	51.0 (11)	45.5 (12.3)	51.0 (11.0)
Male sex, %	85.0	77.8	85.0
Viral load at baseline, mean (SD), log_{10} copies/mL	4.5 (0.8)	4.5 (0.9)	4.5 (0.8)
$CD4^+$ cell count at baseline, mean (SD), cells/mm^3	150.0 (182)	126.6 (158.9)	150.0 (182.4)
OSS, %[b,c]			
0 available	13[d]	9	13
1 available	30	27	30
2 available	44	45	44
≥3 available	13	20	13
BENCHMRK and BRIGHTE			
		Fostemsavir and OBT (BRIGHTE)[a]	
	OBT (BENCHMRK) (N = 237)	Unadjusted (N = 347)	Adjusted (N = 126)
Age at baseline, mean (SD), y	45.1 (8.1)	45.5 (12.3)	45.1 (8.1)
Male sex, %	89.0	77.8	89.0
History of AIDS, %	90.0	87.0[e]	90.0[e]
Viral load at baseline, mean (SD), log_{10} copies/mL	4.6 (0.8)	4.5 (0.9)	4.6 (0.8)
$CD4^+$ cell count at baseline, mean (SD), cells/mm^3	158.0 (150.4)	126.6 (158.9)	158.0 (151.0)
GSS, %[b,c]			
0 available	28	11	28
1 available	41	33	41
2 available	21	41	21
≥3 available	10	15	10
PSS, %[b,c]			
0 available	19	8	19
1 available	31	24	31
2 available	29	44	29
≥3 available	21	24	21

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Table II. (*continued*)

	VIKING-3 and BRIGHTE		
		Fostemsavir and OBT (BRIGHTE)[f]	
	OBT (VIKING-3) (N = 183)	Unadjusted (N = 358)	Adjusted (N = 78)
Age at baseline, mean (SD), y	47.0 (9.3)	45.5 (12.3)	47.0 (9.3)
Male sex, %	77.1	78.5	77.1
History of AIDS, %	55.7[g]	86.9[e]	55.7[e]
Viral load at baseline, mean (SD), log_{10} copies/mL	4.3 (0.9)	4.4 (1.0)	4.3 (0.9)
$CD4^+$ cell count at baseline, mean (SD), cells/mm^3	199.9 (192.4)	131.5 (164.1)	199.9 (192.4)
OSS-new, %[h]			
0 available	0.00	31.50	0.00
1 available	37.16	35.26	37.16
2 available	42.62	31.21	42.62
>2 available	20.22	2.02	20.22

GSS = genotypic susceptibility score; OBT = optimized background therapy; OSS = overall susceptibility score; PSS = phenotypic susceptibility score.

[a] Restricted to participants with screening HIV-1 RNA load >1000 copies/mL.

[b] Scores normalized to sum to 100%.

[c] BRIGHTE scores recalculated with partial scores (ie, score of 0.5) set to 0 to align with comparator study reporting.

[d] Limited to fully active approved antiretrovirals at the time of the study; fostemsavir was not considered fully active.

[e] Defined as yes if participant had nadir $CD4^+$ cell count <200 cells/mm^3 or if response to the question, "Does participant have AIDS?" on disease history case report form was yes.

[f] Restricted to participants with screening HIV-1 RNA load ≥500 copies/mL.

[g] Defined as US Centers for Disease Control and Prevention classification C at baseline.

[h] OSS-new is the OSS for new antiretroviral agents in the initial OBT. If an antiretroviral agent was taken as part of a prior regimen, then the susceptibility rating for that component is assumed to be 0 (resistant).

$P = 0.073$) (Figure 3). Compared with OBT informed by BENCHMRK, the odds of experiencing all-cause discontinuation at 96 weeks were nonsignificantly higher with fostemsavir and OBT (OR = 1.14; 95% CI, 0.66–1.99; $P = 0.634$). At week 48, fostemsavir and OBT were associated with statistically significantly lower odds of experiencing all-cause discontinuation vs OBT informed by VIKING-3 (OR = 0.23; 95% CI, 0.11–0.47; $P < 0.001$) and discontinuation because of PDVF (OR = 0.27; 95% CI, 0.15–0.48; $P < 0.001$), broadly defined as an HIV-1 RNA load ≥400 copies/mL (Supplemental Appendix Section 2.4.1). Additional data on discontinuations in BRIGHTE are provided in Supplemental Appendix Section 3.1.

Safety Outcomes

At week 24, odds of discontinuing use of the study drug because of AEs were lower in the BRIGHTE adjusted population vs TMB-301 (OR = 0.26; 95% CI, 0.08–0.89) (Table III). Lower odds of mortality were also observed in both the BRIGHTE adjusted (OR = 0.11; 95% CI, 0.02–0.54) and unadjusted (OR = 0.19; 95% CI, 0.05–0.74) populations vs TMB-301. Compared with OBT informed by BENCHMRK, in the unadjusted BRIGHTE population, the odds of mortality (OR = 2.33; 95% CI, 1.03–5.96) and experiencing any SAE (OR = 1.79; 95% CI, 1.23–2.62) were significantly higher at week 96; however, neither of these results remained statistically significant in the

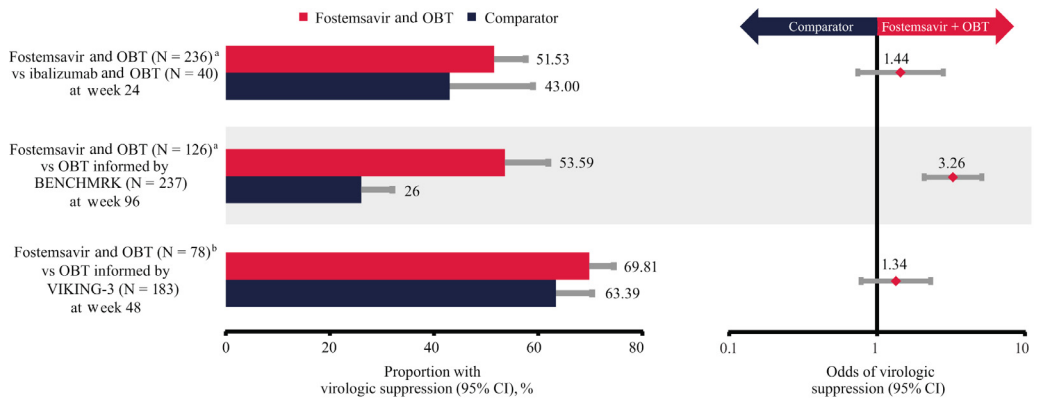

Figure 1. Proportion of participants with virologic suppression defined as HIV-1 RNA load <50 copies/mL in BRIGHTE vs comparator studies. OBT = optimized background therapy. [a]Restricted to participants with screening HIV-1 RNA load >1000 copies/mL. [b]Restricted to participants with screening HIV-1 RNA load ≥500 copies/mL.

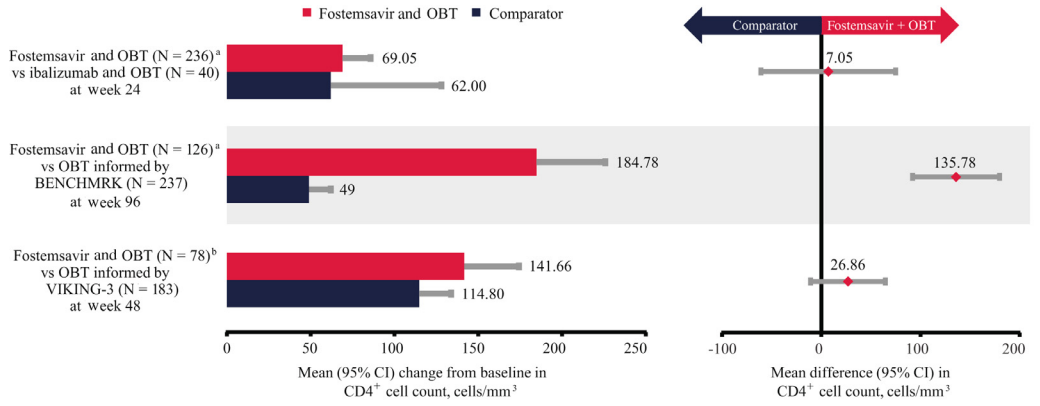

Figure 2. Mean change from baseline in $CD4^+$ cell count in BRIGHTE vs comparator studies. OBT = optimized background therapy. [a]Restricted to participants with screening HIV-1 RNA load >1000 copies/mL. [b]Restricted to participants with screening HIV-1 RNA load ≥500 copies/mL.

adjusted BRIGHTE population (OR = 0.92; 95% CI, 0.21–3.23 and OR = 1.41; 95% CI, 0.86–2.30, respectively). Compared with OBT from VIKING-3, the odds of experiencing any SAE were higher with fostemsavir and OBT than with OBT alone at the week 48 data cutoff (OR = 1.50; 95% CI, 0.83–2.70; $P = 0.177$). In addition, fostemsavir and OBT were associated with nonsignificantly lower odds of experiencing discontinuation because of AEs (OR = 0.93; 95% CI, 0.31–2.77; $P = 0.896$) and nonsignificantly higher odds of death (OR = 1.72; 95% CI, 0.35–8.39; $P = 0.502$).

DISCUSSION

Fostemsavir offers an important treatment option for HTE individuals who have multidrug resistance and limited available ARV options.[4,5] The MAIC analyses are useful because of the absence of a long-term OBT-alone control group in the BRIGHTE trial and the need to compare outcomes with ibalizumab,[10] another ARV indicated for the HTE population.

The comparison of fostemsavir and OBT with ibalizumab and OBT using the BRIGHTE and TMB-301 studies is strengthened by the generally comparable participant demographic characteristics

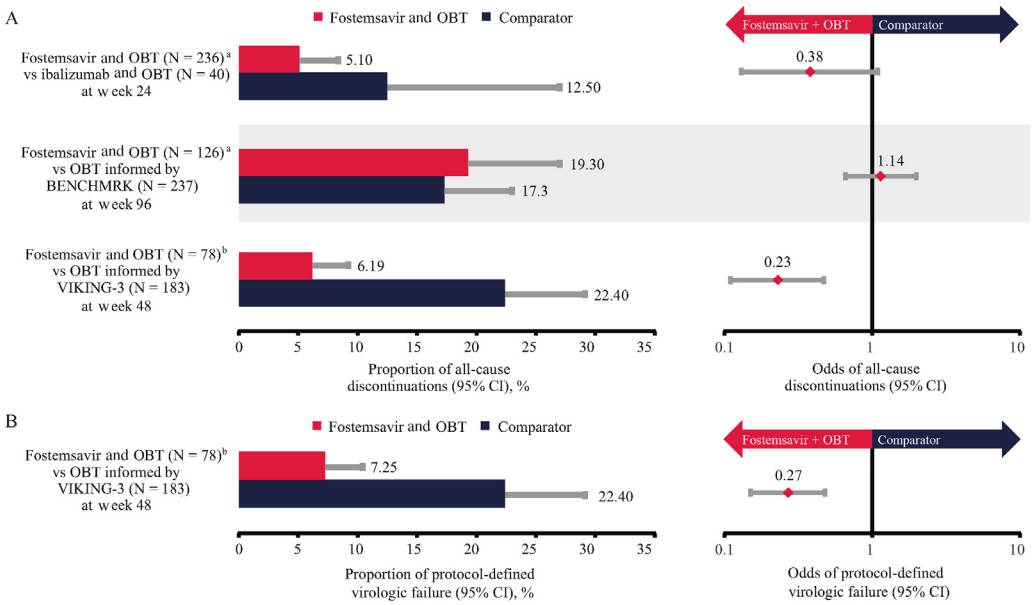

Figure 3. Proportion of participants with (A) all-cause discontinuations in BRIGHTE vs comparator studies and (B) with protocol-defined virologic failure (broadly defined as HIV-1 RNA load ≥400 copies/mL) in BRIGHTE vs VIKING-3 (see Supplemental Appendix Section 2.4.1 for more details). OBT = optimized background therapy. [a]Restricted to participants with screening HIV-1 RNA load >1000 copies/mL. [b]Restricted to participants with screening HIV-1 RNA load ≥500 copies/mL.

and concurrent study periods. However, TMB-301 did not include participants who were comparable to the nonrandomized cohort in BRIGHTE who had no fully active ARVs available (the TMB-301 OSS did not count fostemsavir as a fully active ARV). There were higher odds of virologic suppression and lower odds of discontinuing treatment for fostemsavir and OBT vs ibalizumab and OBT, although differences in this small data set during 24-week follow-up were not statistically significant. There were lower odds of discontinuing use of fostemsavir and OBT and mortality compared with TMB-301. Both studies had similar increases in $CD4^+$ cell counts at 24 weeks. Through 96 weeks, results from the BRIGHTE trial showed sustained improvement in $CD4^+$ cell count (mean [SD] increase = 205 [191] cells/mm^3 in the randomized cohort and 119 [202] cells/mm^3 in the nonrandomized cohort) and virologic response (proportion with HIV-1 RNA load <40 copies/mL: 60% in the randomized cohort and 37% in the nonrandomized cohort) with fostemsavir and OBT, which is the first time this has been observed in the HTE population[5]; however, longer-term treatment comparisons using data for this time point cannot be undertaken because of the lack of corresponding data from TMB-301. Inclusion of the nonrandomized cohort from BRIGHTE in this analysis is a potential confounding factor because the participants in this cohort would have been excluded from TMB-301, which required ≥1 fully active ARV in the OBT. Matching based on OSS may insufficiently account for minority HIV-1 species or variants archived in the lymphoid system and therefore may not be a reliable predictor of treatment response in the HTE population.[18,24] Importantly, a considerable proportion of participants in the TMB-301 trial were receiving fostemsavir as part of their OBT (43%), and likewise a small proportion of BRIGHTE participants were receiving ibalizumab in their OBT (4%); however, these participants could not be removed or adjusted for in the analysis because these data from TMB-301 were not published, obscuring results of comparison between fostemsavir and OBT vs ibalizumab and OBT in this analysis.

Comparison with existing optimized regimens used in the HTE population is necessary for settings in which ibalizumab is not available. Use of data from other

Table III. Matching-adjusted indirect comparison analyses safety outcomes.

Variable	Drug-related AEs	SAEs	Discontinuation for AEs	Deaths
TMB-301 vs BRIGHTE at week 24[a]				
BRIGHTE unadjusted vs TMB-301, OR (95% CI)	2.13 (0.97–5.38)	0.68 (0.33–1.58)	0.34 (0.12–1.08)	0.19 (0.05–0.74)
BRIGHTE adjusted vs TMB-301, OR (95% CI)	2.02 (0.90–5.17)	0.65 (0.30–1.56)	0.26 (0.08–0.89)	0.11 (0.02–0.54)
BENCHMRK vs BRIGHTE at week 96[a]				
BRIGHTE unadjusted vs BENCHMRK, OR (95% CI)	0.40 (0.28–0.56)	1.79 (1.23–2.62)	1.46 (0.73–3.06)	2.33 (1.03–5.96)
BRIGHTE adjusted vs BENCHMRK, OR (95% CI)	0.35 (0.22–0.54)	1.41 (0.86–2.30)	0.66 (0.19–1.91)	0.92 (0.21–3.23)
VIKING-3 vs BRIGHTE at week 48 data cutoff				
OBT VIKING-3 (N = 183), proportion (95% CI)		0.21 (0.16–0.28)	0.04 (0.02–0.08)	0.01 (0.00–0.04)
Fostemsavir and OBT BRIGHTE (N = 78), proportion (95% CI)[b]		0.29 (0.24–0.34)	0.04 (0.02–0.07)	0.02 (0.01–0.04)
OR (95% CI)		1.50 (0.83–2.70)	0.93 (0.31–2.77)	1.72 (0.35–8.39)
P value		0.177	0.896	0.502

AE = adverse event; OBT = optimized background therapy; OR = odds ratio; SAE = serious adverse event.
[a] Restricted to participants with HIV-1 RNA load >1000 copies/mL.
[b] Restricted to participants with HIV-1 RNA load ≥500 copies/mL.

trials to inform optimized regimens (OBT alone) in the HTE population presents a considerable challenge in interpreting the results. In this study, OBT consists of a wide range of ARV regimens, and determining the expected activity of these regimens is difficult because of participants' extensive treatment histories and varied resistance profiles. Multiple trials were considered for inclusion in the MAIC analyses, and 2 trials, BENCHMRK and VIKING-3, were selected to inform OBT comparators, each with its own unique set of limitations that require careful interpretation from methodologic and clinical perspectives. Of note, details on OBT were not available for all studies, adding complexity to the comparison with BRIGHTE. In addition, participants in BRIGHTE may have previously been enrolled in these earlier trials and, as a result, would have comparatively greater treatment experience by the start of the BRIGHTE trial.

The BENCHMRK comparison found greater relative benefits with fostemsavir and OBT vs OBT alone compared with the VIKING-3 comparison, including statistically significant improvements in odds of virologic suppression and mean $CD4^+$ cell count increase; however, BENCHMRK started 9 years earlier than BRIGHTE, OBT regimens used at that time may not reflect the more contemporary regimens used in BRIGHTE (eg, dolutegravir was not available during BENCHMRK), and differences could exist in resistance measurement over time. Therefore, the efficacy of OBT in BENCHMRK may have been underestimated in the present analysis despite participants having comparable susceptibility scores to OBT. Smaller, nonsignificant improvements in mean $CD4^+$ cell count and numerically higher odds of virologic suppression were observed in the VIKING-3 comparison with fostemsavir and OBT

vs OBT alone (twice-daily dolutegravir in VIKING-3). Management with fostemsavir plus OBT was associated with notably lower rates of all-cause discontinuation and PDVF, which may in part be driven by different discontinuation criteria in VIKING-3. In VIKING-3, discontinuation was required for confirmed PDVF unless there was an agreed-on rationale for the participant to be maintained in the study. Criteria for BRIGHTE were not as explicit; efficacy and level of viremia were noted more generally in the BRIGHTE criteria, with the latter for consideration in the context of limited available future treatment options and the risks of clinical deterioration. Given the limited number of treatment options and high unmet need in the HTE population, an approach similar to that adopted in the BRIGHTE trial can be expected in clinical practice, and discontinuation rates can thus be considered representative. Furthermore, the odds of experiencing any SAE were higher in BRIGHTE, but this may be partially attributable to differences in inclusion criteria because BRIGHTE enrolled participants with no fully active ARVs (ie, the nonrandomized cohort), whereas VIKING-3 required participants to have ≥1 fully active ARV in their OBT.[5,17] Because 303 of 371 BRIGHTE participants (82%) received dolutegravir as part of their OBT,[4] the VIKING-3 comparison more closely matches the ARVs included in OBT in BRIGHTE. However, the adjusted population primarily represented participants in BRIGHTE with more treatment options remaining (BRIGHTE vs VIKING-3 adjusted OSSs) (Table II) and was not representative of the full population eligible for fostemsavir, specifically those with highly resistant disease in greatest need of new treatment options.

The construction of OBT regimens is dependent on multiple factors, including ARVs available at the time and in the setting of interest. Fostemsavir is indicated for HTE individuals with multidrug-resistant HIV-1 who are failing their current ARV regimen. For this reason, it could be argued that there is no suitable comparator for this patient group and that by definition a comparator regimen is not available. These analyses should be considered in the context of real-world treatment options available to people with multidrug-resistant HIV-1 who may have already exhausted all therapies. As a result, the comparisons presented here are not appropriate comparators for such a patient group, and instead viral load and $CD4^+$ cell count trajectory in the absence of fostemsavir would reflect that of a failing regimen and should be compared with the efficacy of fostemsavir observed in BRIGHTE in the subset of participants with a similar resistance profile. Indeed, outcomes from BRIGHTE indicate that even in participants with an OSS-new of 0 (ie, no new agents available for the OBT without resistance), 31% achieved virologic suppression at week 96, demonstrating the direct benefits of fostemsavir.[13]

Because IPD were not available for all of the comparator studies, the MAIC approach was used because it is suitable for situations in which IPD are only available for 1 study and allows for a consistent method across all comparisons presented.[2,3,6] Although other methods are also possible, they typically require IPD from both the index and comparator trials.[2,3,25] Furthermore, exclusively IPD-based approaches were not expected to provide results that differed in conclusion from aggregate-based approaches. Accurate representation of prognostic variables and treatment-effect modifiers are required for MAIC analyses.[2,6] In this study, we used literature and clinical opinion to inform the matching variables; however, other variables not included may have affected the outcome of the study. Where possible, definitions for variables used in the analyses were homogenized among studies. Matching was performed on as many relevant covariates and effect modifiers as possible, including key clinical variables, such as baseline $CD4^+$ cell count and viral load. However, there remains the risk of systematic differences among the populations in each study that affect health status and response to treatment, which were not measured or adjusted for.

Susceptibility scores (GSS, PSS, and OSS) were used to provide an indication of existing resistance and, consequently, the expected activity of OBT and its contribution to the overall efficacy of the regimen. Most of the selected trials (TMB-301, VIKING-3, and BRIGHTE) did not have a comparator group receiving control treatment for >8 days. This lack of a comparator group affected how susceptibility score data were matched with the BRIGHTE trial because scores are typically reported for OBT, but single-group trials assessed the activity of the investigational agent in combination with OBT.

CONCLUSIONS

These analyses support the use of fostemsavir and OBT as a key treatment option in HTE people with multidrug-resistant HIV-1 and highlight the challenges of conducting indirect treatment comparisons in the context of highly heterogeneous existing optimized regimens and patient populations. The suitability of comparator data was further complicated by the changing availability of therapies over time and data limitations attributable to trial design (no long-term comparator data because of the medical needs of this patient population). Interpretation of these results and application to health technology assessment and economic evaluation require careful consideration of the therapies likely to be available to HTE people with multidrug-resistant HIV-1 and their resistance profiles to understand what the true comparator would be if fostemsavir were not available.

DECLARATION OF INTEREST

S.-J. Anderson is an employee of and owns stock in GlaxoSmithKline. A. van Doornewaard, M. Turner, and I. Jacob were employees of HEOR Ltd at the time of this analysis; HEOR Ltd received fees in relation to the reported analyses. I. Jacob, A. Clark, D. Browning, and M. Schroeder are employees of ViiV Healthcare and own stock in GlaxoSmithKline.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.04.007.

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