Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study

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Summary

Background Fostemsavir, a prodrug of the first-in-class attachment inhibitor, temsavir, is indicated for heavily treatment-experienced individuals with multidrug-resistant HIV-1. We previously reported superior efficacy of fostemsavir versus placebo in the randomised cohort of the BRIGHTE study after 8-day functional monotherapy (primary endpoint); here we report planned interim analyses through week 96.

Methods BRIGHTE (NCT02362503) is an ongoing multicentre, two-cohort, phase 3 trial, done at 108 centres in 22 countries. We enrolled heavily treatment-experienced adults (≥18 years) failing antiretroviral therapy (HIV-1 RNA ≥400 copies per mL) into two cohorts: the randomised cohort, in which patients with one or two fully active antiretrovirals remaining received oral fostemsavir (600 mg twice a day) or placebo in combination with their failing regimen for 8 days, followed by fostemsavir plus optimised background therapy; or the non-randomised cohort, in which patients with no remaining antiretroviral options received oral fostemsavir (600 mg twice a day) plus optimised background therapy from day 1. Endpoints for the week 96 interim analyses included the proportions of participants with plasma HIV-1 RNA of less than 40 copies per mL, changes from baseline in CD4 cell counts, and the frequency of adverse events, adverse events leading to discontinuation, and deaths. The intention-to-treat exposed population and the safety population both included all participants who received at least one dose of study treatment. The response rates (proportion of participants with HIV-1 RNA <40 copies per mL) in the intention-to-treat exposed population were calculated via snapshot analysis at weeks 24, 48, and 96.

Findings Between Feb 23, 2015, and Aug 11, 2016, 371 participants were enrolled and treated, of which 272 participants were in the randomised cohort and 99 in the non-randomised cohort. 320 (86%) of 371 reported a history of AIDS. In the randomised cohort, rates of virological suppression (HIV-1 RNA <40 copies per mL) increased from 53% (144 of 272) at week 24 to 60% (163 of 272) at week 96. Response rates in the non-randomised cohort were 37% (37 of 99) at week 24 and week 96. Mean increases in CD4 counts from baseline at week 96 were 205 cells per µL (SD 191) in the randomised cohort and 119 cells per µL (202) in the non-randomised cohort. Mean CD4/CD8 ratio increased from 0·20 at baseline to 0·44 at week 96 in the randomised cohort. Few adverse events led to discontinuation (26 [7%] of 371). 12 (4%) of 272 people in the randomised cohort and 17 (17%) of 99 in the non-randomised cohort died; the median baseline CD4 count for participants who died was 11 cells per µL.

Interpretation In heavily treatment-experienced individuals with advanced HIV-1 disease and limited treatment options, fostemsavir-based antiretroviral regimens were generally well tolerated and showed a distinctive trend of increasing virological and immunological response rates through 96 weeks; these findings support fostemsavir as a treatment option for this vulnerable population.

Funding ViiV Healthcare.

Introduction

Combination antiretroviral therapy (ART) has transformed HIV-1 infection into a manageable chronic condition for many people living with HIV.[1] However, effective ART is not always possible. For some individuals, a viable regimen no longer exists because of multidrug resistance, contraindications, previous intolerance, or other safety concerns with current antiretrovirals.[1] The health-related quality of life (HRQoL) for these heavily treatment-experienced individuals is often low because of a combination of poor clinical status as a consequence of viral replication leading to advanced immunosuppression, and accumulating side-effects from multiple antiretrovirals and concomitant medications.[2] For this population, there is a continued need for the development of new classes of antiretrovirals with novel mechanisms of action that are well tolerated and do not have cross-resistance to available therapies.

Research in context

Evidence before this study

On Sept 20, 2019, we searched PubMed for clinical trials in people living with HIV-1 using the search terms "BMS-663068", "fostemsavir", and "entry inhibitors", "treatment-experienced", and "multidrug resistance," and reviewed HIV conference abstracts to identify prospective trials done in heavily treatment-experienced adults from 2008 onwards (after the approval of raltegravir [the first integrase inhibitor] and maraviroc [CCR5 antagonist] as treatment options). Our search yielded reports on two clinical trials of fostemsavir, including the phase 2b study and earlier reports of the week 48 results from BRIGHTE. The primary analysis of BRIGHTE showed superior reduction in HIV-1 RNA over 8 days of fostemsavir treatment compared with placebo, both added to a failing antiretroviral regimen. We also identified nine phase 3 trials done in participants living with multidrug-resistant HIV-1, investigating the safety and efficacy of the anti-CD4 antibody ibalizumab, the CCR5 antagonist maraviroc (MOTIVATE 1 and 2), the integrase inhibitors raltegravir (BENCHMARK I and II) and dolutegravir (VIKING 3 and 4), and the non-nucleoside reverse transcriptase inhibitor etravirine (DUET 1 and 2) all in combination with optimised background therapy. These studies included participants with documented resistance to at least one agent in three or more antiretroviral classes. Results through 96 weeks were available for pooled maraviroc studies, pooled raltegravir studies, and pooled etravirine studies. Rates of suppression to HIV-1 RNA of less than 50 copies per mL at week 96 ranged from 41% to 57% and in all cases had decreased between weeks 48 and 96.

Added value of this study

This report provides long-term data (through 96 weeks) on the safety and efficacy of fostemsavir, a first-in-class attachment inhibitor, in heavily treatment-experienced individuals with advanced HIV disease who were unable to construct a viable antiretroviral regimen because of limited remaining treatment options. One could make a case that BRIGHTE has recruited the most heavily treatment-experienced population of people living with multidrug-resistant HIV given the level of resistance to antiretroviral agents seen in this trial and the strict entry criteria. Furthermore, results from this long-term follow-up are expanding essential knowledge of how to care for people living with multidrug-resistant HIV for both participants and health-care providers, along with the overall field, as well as how the immune system and the virus respond to a new mechanism of action such as fostemsavir, even in participants with long-term exposure to the virus and antiretroviral agents. A remarkable and unique finding of BRIGHTE was the increasing response rates between week 24 and week 96 in the randomised cohort, despite the expected continued attrition over time. This finding has not been seen with other multidrug-resistant trials with 96 weeks of data. Possible reasons for this increase, which could be related to the unique mode of action of fostemsavir, are the subject of ongoing research. CD4 cell counts and CD4/CD8 ratios also continuously increased up to week 96, even in participants with very low baseline CD4 cell counts, suggesting improvement of immune function, which was consistent with an observed decline in AIDS-defining events. A novel aspect of BRIGHTE was the inclusion of the non-randomised cohort, allowing assessment of responses in individuals with no approved fully active antiretrovirals remaining at study entry. Although reduced compared with the randomised cohort, observed virological and immunological responses in this cohort increased steadily over time. Fostemsavir-based regimens were generally well tolerated with few adverse events leading to discontinuation. Fostemsavir-based regimens in the BRIGHTE study were life-changing for participants living with multidrug-resistant HIV-1, most of whom had AIDS.

Implications of all the available evidence

There is continued need for antiretroviral agents with new mechanisms of action to address the needs of heavily treatment-experienced individuals with HIV. Temsavir, the active metabolite of fostemsavir, has a unique mechanism of action, binding to gp120 and preventing attachment to CD4, the first step in the HIV-1 entry process. Data from the BRIGHTE study, showing long-term efficacy in heavily treatment-experienced individuals with multidrug-resistant HIV-1, are consistent with in-vitro evidence showing no cross-resistance between temsavir and currently available antiretroviral classes. Added to the favourable safety and drug-drug interaction profiles reported for fostemsavir, these data support its use as a therapeutic option for this vulnerable population. On the basis of results from BRIGHTE, fostemsavir was approved by the US Food and Drug Administration on July 2, 2020, in combination with other antiretrovirals for heavily treatment-experienced adults with multidrug-resistant HIV-1 infection. The compassionate use programme has been reopened, and is accepting requests for fostemsavir globally.

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Fostemsavir, a prodrug of the first-in-class attachment inhibitor temsavir, which was approved by the US Food and Drug Administration on July 2, 2020, is indicated for the treatment of heavily treatment-experienced people with multidrug-resistant HIV-1.[3,4] Temsavir has a unique mechanism of action, binding directly to the viral envelope gp120, close to the CD4 binding site, locking gp120 into a closed state that prohibits the conformational change necessary for initial interaction between the virus and CD4 cell-surface receptors, thereby preventing attachment and subsequent entry into host T cells and other immune cells (appendix p 3).[4–7] Fostemsavir has no in-vitro cross-resistance with other antiretroviral classes, and is active against CCR5-tropic, CXCR4-tropic, and dual-tropic strains of HIV-1.[4–7] The in-vitro temsavir 50% inhibitory concentration (IC_{50}) varies widely (10 pM to >10 μM),

See Online for appendix

which might be linked to heterogeneity in HIV-1 gp120; however, for most laboratory and clinical isolates of temsavir-naive HIV-1, the IC_{50} is less than 10 nM.[6,7]

In the ongoing BRIGHTE study, we are evaluating fostemsavir in heavily treatment-experienced individuals who have limited remaining approved fully active antiretrovirals available as treatment options to form a viable ART regimen (one or two fully active antiretrovirals in the randomised cohort and zero fully active antiretrovirals in the non-randomised cohort).[3] Over an initial 8 days of functional monotherapy in the randomised cohort, fostemsavir added to the failing antiretroviral regimen showed superior antiviral efficacy compared with placebo added to failing antiretroviral regimen (primary study endpoint: mean HIV-1 RNA decrease from baseline 0·8 log_{10} copies per mL *vs* 0·2 log_{10} copies per mL; p<0·0001).[3] Subsequent open-label treatment with fostemsavir in combination with optimised background therapy resulted in a virological response (HIV-1 RNA <40 copies per mL) at week 24 in 53% of participants in the randomised cohort and 37% in the non-randomised cohort, and at week 48 in 54% of participants in the randomised cohort and 38% in the non-randomised cohort, with mean increases in CD4 count from baseline to week 48 of 139 cells per µL in the randomised cohort and 63 cells per µL in the non-randomised cohort.[3] We also saw improvements in patient-reported HRQoL measures (EQ visual analogue scale and the Functional Assessment of HIV Infection [FAHI]), with greater improvements in those with lower CD4 cell counts and higher viral loads at baseline.[8] Here we present cumulative safety and efficacy results through week 96 of the BRIGHTE study.

Methods

Study design and participants

BRIGHTE (NCT02362503) is a multicentre, two-cohort, phase 3 clinical trial; we enrolled participants at 108 international investigational sites across Africa, Asia-Pacific, Europe, North America, and South America between Feb 23, 2015, and May 27, 2016.[3] The study design has been previously described and full details are provided in the study protocol. We included adults (≥18 years) who had confirmed HIV-1 RNA of 400 copies per mL or more on ART at screening and had no more than two approved antiretroviral options remaining that were fully active. Full activity was based on susceptibility (according to screening or historical resistance testing, or both) and availability (tolerance, eligibility, and, in the case of enfuvirtide only, willingness to receive a twice-daily injectable). We assigned participants with one or two approved fully active antiretroviral options to the randomised cohort and assigned those with zero approved fully active antiretrovirals remaining to the non-randomised cohort (appendix p 4). In the randomised cohort, we followed an 8-day double-blind period by open-label treatment with oral fostemsavir (600 mg twice a day) plus optimised background therapy. In the non-randomised cohort, we started open-label oral fostemsavir (600 mg twice a day) plus optimised background therapy from day 1, and could include other investigational antiretrovirals in the optimised background therapy (including ibalizumab, which was investigational at the time the study was initiated).

For the **study protocol** see https://www.viiv-studyregister.com/en/study/?id=205888

We did the study in accordance with international laws and guidelines consistent with the Declaration of Helsinki principles, with oversight from national, regional, or institutional review boards or ethics committees. All study participants provided written informed consent. We expect BRIGHTE to continue until participants can access fostemsavir through other means.

Procedures

We did HIV-1 RNA measurements (RealTime HIV-1 Viral Load assay; Abbott Laboratories, Abbott Park, IL, USA) and other serologies at central laboratory facilities. Monogram Biosciences (South San Francisco, CA, USA) did genotypic and phenotypic antiretroviral susceptibility testing for all screening samples and for samples from participants identified as meeting the criteria for protocol-defined virological failure. We have expressed phenotypic temsavir susceptibility as the fold-change in IC_{50} for the test sample relative to a laboratory control of HIV-1. On-treatment changes in temsavir IC_{50} fold-change of more than three-fold relative to baseline are outside the three-fold variability of the assay and are considered meaningful.

At baseline, and after every 12 weeks, we asked the participants to complete patient-reported outcome assessments using the EuroQoL 5-dimension 3-level instrument (EQ-5D-3L; a generic health status measure including descriptive metrics and a visual analogue scale),[9] and the FAHI (an HRQoL questionnaire specific to patients living with HIV).[10,11]

Outcomes

Endpoints for the week 96 analysis were proportions of participants with plasma HIV-1 RNA of less than 40 copies per mL; changes from baseline in CD4 cell counts and percentages; emergence of genotypic changes of interest in HIV-1 gp120 in participants with protocol-defined virological failure; emergence of phenotypic changes in in-vitro HIV-1 susceptibility to temsavir in participants with protocol-defined virological failure; the frequency of adverse events, serious adverse events, adverse events leading to discontinuation, and grades 3–4 laboratory abnormalities; and the occurrence of new AIDS-defining events (US Centers for Disease Control and Prevention [CDC] class C events) or death. We determined protocol-defined virological failure as follows: before week 24, a confirmed, or last available measurement before discontinuation, HIV-1 RNA of 400 copies per mL or more at any time following previous confirmed suppression to less than 400 copies per mL, or a confirmed or last available measurement before discontinuation of more than 1 log_{10} increase in HIV-1 RNA above nadir at

any time, where nadir is 40 copies per mL or more; or on or after week 24, a confirmed, or last available measurement before discontinuation, HIV-1 RNA of 400 copies per mL or more. We collected confirmatory samples within 4 weeks of the original sample. For those with protocol-defined virological failure, we did susceptibility testing on the confirmatory sample. Exploratory outcomes included analyses of safety and efficacy in the non-randomised cohort and changes from baseline in patient-reported HRQoL measures.

Statistical analysis

The intention-to-treat exposed population and the safety population both included all participants who received at least one dose of study treatment. We determined response rates (proportion of participants with HIV-1 RNA <40 copies per mL) in the intention-to-treat exposed population using the snapshot algorithm[12] at weeks 24, 48, and 96, with missing HIV-1 RNA or change of antiretrovirals in the optimised background therapy for lack of efficacy classified as treatment failure. We did the planned subgroup analyses, including subgroups based on day 1 HIV-1 RNA and CD4 cell counts, HIV subtype, age, gender, geographic region, and number of fully active antiretrovirals in the initial optimised background therapy. We summarised safety data by cohort and for the total population. We used the software SAS (version 9.4) for all analyses.

Role of the funding source

The study was initially funded by Bristol-Myers Squibb, who participated in the study design and initial data collection. In February, 2016, funding of the study and all aspects of study management transitioned to GlaxoSmithKline/ViiV Healthcare, who participated in data collection, data analysis, and data interpretation. All authors had full access to the data and vouch for the completeness and accuracy of the data analyses presented, and the fidelity of the study to the protocol. The first draft of the manuscript was prepared by a professional medical writer (paid for by the funder), under the guidance of the corresponding author, and was edited and revised by all authors. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Feb 23, 2015, and Aug 11, 2016, 731 individuals were screened, of whom 371 were enrolled and treated with 272 in the randomised cohort and 99 in the non-randomised cohort.[3] The last participant's last visit for the week 96 analysis was June 22, 2018, and the data cutoff was Aug 14, 2018. At week 48, 57 (21%) of 272 participants from the randomised cohort and 32 (32%) of 99 from the non-randomised cohort discontinued.[3] Through the week 96 data cutoff, two additional participants in the randomised cohort (death [n=1] and lost to follow-up [n=1]) and six additional participants in the non-randomised cohort (non-adherence [n=1], met stopping criteria [n=2], and death [n=3]) discontinued, resulting in a total of 59 (22%) of 272 discontinuations from the randomised cohort and 38 (38%) of 99 from the non-randomised cohort (appendix p 4). Overall, 82 (22%) of 371 participants were women, 83 (22%) were Black or African American, and 107 (29%) were of Hispanic or Latinx ethnicity. Pre-existing comorbidities were reported in 361 (97%) of 371 participants, and 320 (86%) reported a history of AIDS (appendix p 6). In the randomised cohort, median baseline CD4 counts were 100 cells per µL (IQR 15–207), and 72 (26%) of 272 participants had fewer than 20 cells per µL. In the non-randomised cohort, median baseline CD4 counts were 41 cells per µL (IQR 6–161), and 40 (40%) of 99 had fewer than 20 cells per µL (appendix p 6).

	Randomised cohort (n=272)	Non-randomised cohort (n=99)
Previous exposure to antiretroviral classes		
NRTI	270 (99%)	97 (98%)
NNRTI	248 (91%)	93 (94%)
PI	257 (94%)	97 (98%)
INSTI	204 (75%)	94 (95%)
CCR5 antagonist	72 (26%)	40 (40%)
Fusion inhibitor	107 (39%)	67 (68%)
Antiretroviral classes with no fully active and approved* agents at baseline†		
NRTI	239 (88%)	99 (100%)
NNRTI	221 (81%)	98 (99%)
PI	202 (74%)	99 (100%)
INSTI	79 (29%)	98 (99%)
CCR5 antagonist	212 (78%)	99 (100%)
Fusion inhibitor	232 (85%)	97 (98%)
Fully active antiretrovirals‡ in initial OBT		
0 agents	16 (6%)§	80 (81%)
1 agent	142 (52%)	19 (19%)¶
2 agents	114 (42%)	0
>2 agents	0	0

Data are n (%).INSTI=integrase strand-transfer inhibitor. NRTI=nucleoside reverse-transcriptase inhibitor. NNRTI=non-nucleoside reverse-transcriptase inhibitor. PI=protease inhibitor. OBT=optimised background therapy. *Ibalizumab was not approved when this study was initiated. †Proportions of participants for whom there were no remaining fully active and approved antiretroviral agents within the indicated class based on the screening criteria of activity (per screening and historical resistance measures) and availability (tolerability, contraindications, and, in the case of enfuvirtide only, willingness to receive an injectable). ‡Including investigational antiretrovirals. §These included participants who discontinued from the study during the double-blind period and never initiated OBT, had no active antiretroviral available at screening and were incorrectly assigned to the randomised cohort, or had one or more active antiretrovirals available at screening but did not use these as part of the initial OBT. ¶15 of these 19 participants received the investigational antiretroviral ibalizumab and four received an approved antiretroviral (n=2 enfuvirtide, n=1 etravirine, and n=1 dolutegravir) and were classified as protocol deviations.

Table 1: **Summary of previous antiretroviral experience and optimised background regimen**

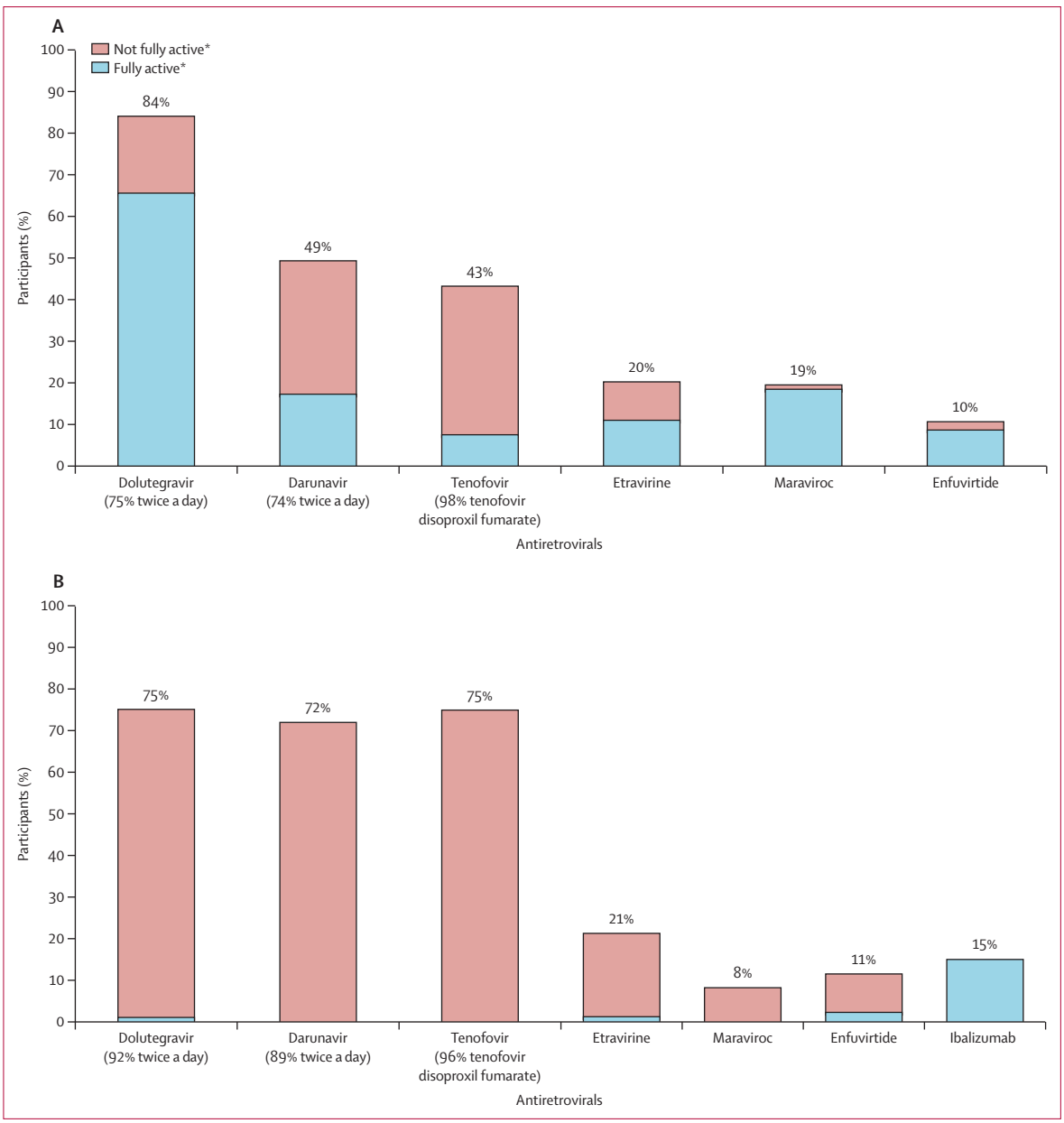

Figure 1: **Most common antiretroviral agents in the initial optimised background therapy for randomised and non-randomised cohorts**
Antiretrovirals included those that were in the initial optimised background therapy for at least 10% of study participants in either cohort. (A) The randomised cohort had 272 participants. (B) The non-randomised cohort had 99 participants. *Based on the screening criteria of activity (per screening and historical resistance measures) and availability (tolerability, contraindications, and, in the case of enfuvirtide only, willingness to receive an injectable).

Both cohorts had high rates of previous exposure across available antiretroviral classes (table 1). In the randomised cohort, the initial optimised background therapy included one fully active antiretroviral by screening criteria for 52% and two fully active antiretrovirals for 42% of participants (table 1). The most common component of the initial optimised background therapy for participants in the randomised cohort was dolutegravir (mostly twice a day), taken by 229 (84%), among whom it was classified as fully active at screening in 178 (78%; figure 1A). Darunavir (134 [49%] of 272) and tenofovir (116 [43%]) were included in the optimised background therapy, but were classified as fully active at screening for fewer than half of participants (figure 1A). In the non-randomised cohort, the initial optimised background therapy included zero approved fully active antiretrovirals for 81% of participants (table 1). Dolutegravir, darunavir, and tenofovir were the most commonly used antiretrovirals in the initial optimised background therapy for the non-randomised cohort; however, in almost all cases (99–100%) they were

not classified as fully active at screening (figure 1B). Four participants had one fully active antiretroviral and were recorded as protocol deviations: enfuvirtide (n=2), dolutegravir (n=1), and etravirine (n=1). 15 participants received investigational ibalizumab as permitted per protocol (figure 1B).

In the randomised cohort, the proportion of participants with a virological response (ie, HIV-1 RNA <40 copies per mL) by snapshot analysis increased over time from 53% (144 of 272) at week 24 to 60% (163 of 272) at week 96 (figure 2A; appendix p 7). By observed analysis (including only participants with observed HIV-1 RNA measures for each visit), the proportions of participants with a virological response increased from 57% (141 of 246) at week 24 to 79% (170 of 214) at week 96 (figure 2B). Rates of virological response by snapshot analysis at week 96 were similar across most baseline subgroups, including between participants with one or two fully active antiretrovirals in their initial optimised background therapy (table 2). The lowest virological response rates were seen among participants with baseline viral loads of 100 000 copies per mL or more or those with baseline CD4 cell counts of less than 20 cells per µL, whereas the highest virological response rates were among those with baseline viral loads of less than 1000 copies per mL or baseline CD4 cell counts of 200 cells per µL or more. Nevertheless, response rates by snapshot analysis in participants with high viral load (from 35% at week 24 to 49% at week 96) or low CD4 cell count (32% at week 24 to 46% at week 96) did increase over time.

CD4 counts also increased steadily through week 96 in the randomised cohort (figure 3A): at week 96, the mean increase from baseline was 205 (SD 191) cells per µL and the median increase was 175 (IQR 89–288) cells per µL. Increases in CD4 counts were generally consistent across subgroups, including for participants with fewer than 20 cells per µL at baseline who had a mean increase from baseline of 240 cells per µL (median 212 cells per µL; table 2). Most participants either maintained or improved their CD4 count category from baseline to week 96 (appendix p 8): 56% (40 of 71) shifted from fewer than 50 cells per µL to 200 cells per µL or more, and 57% (31 of 54) from fewer than 20 cells per µL to 200 cells per µL or more. CD4/CD8 ratios also increased over time (figure 3B).

In the non-randomised cohort, 37% (37 of 99) at week 24 and week 96 achieved virological response by snapshot analysis (figure 2A). Among the 15 participants who received ibalizumab in their initial optimised background therapy, response rate at week 24 was 53% (eight of 15) compared with 35% (29 of 84) for those who did not receive ibalizumab, and at week 96 was 33% (five of 15) compared with 38% (32 of 84) for those who did not receive ibalizumab. Three individuals receiving ibalizumab who were classified as virological failure at week 96 after previous virological response had died in the interim period (data not shown). The mean increase in CD4 count at week 96 in the non-randomised cohort was 119 cells per µL (SD 202); the median increase

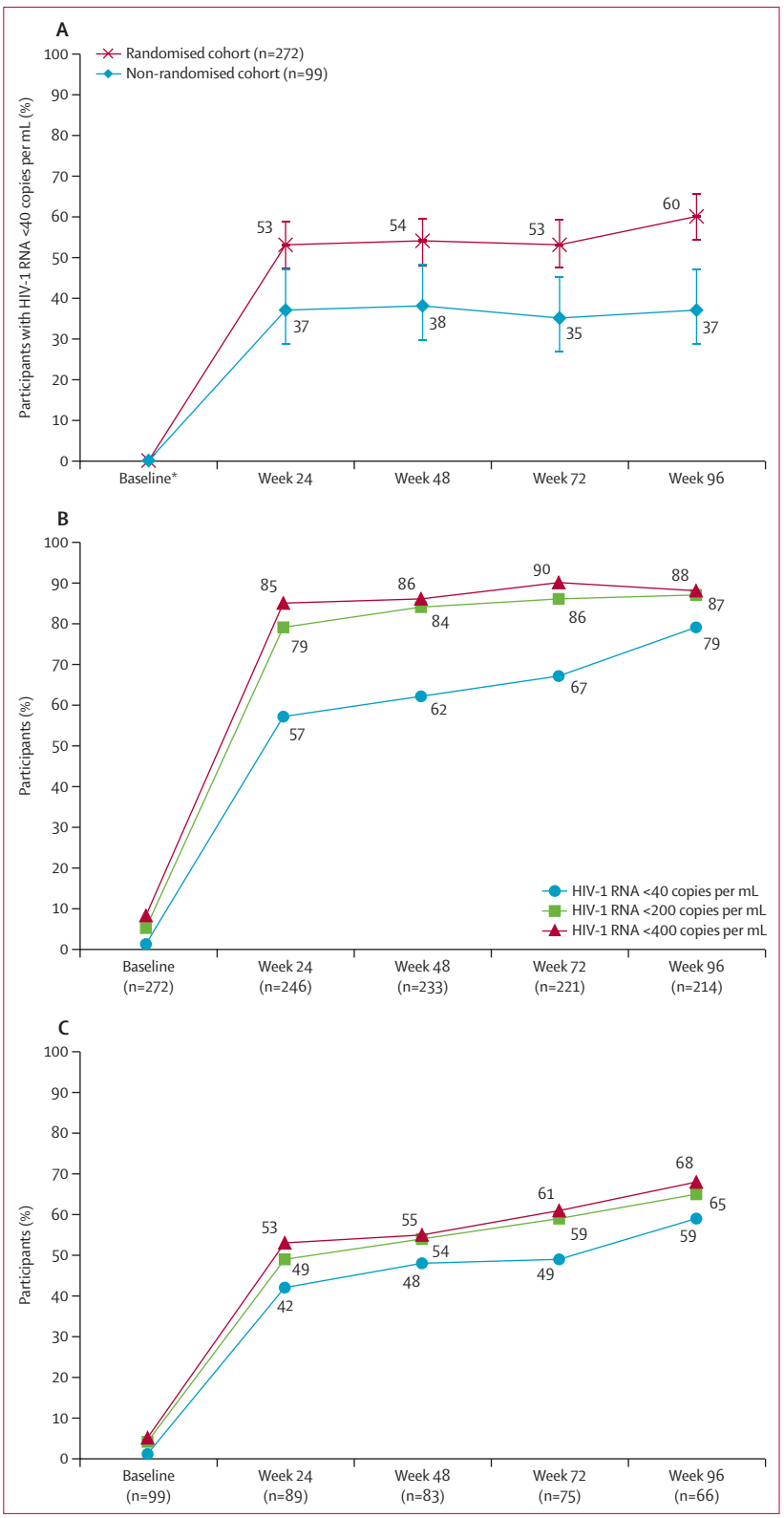

Figure 2: **Virological responses through week 96 by snapshot analysis for the intention-to-treat exposed populations (A) and by observed analysis for the randomised cohort (B) and non-randomised cohort (C)**
Error bars are 95% CIs. *Snapshot analysis did not include baseline. One participant in each cohort had HIV-1 RNA of less than 40 copies per mL at baseline.

	HIV-1 RNA <40 copies per mL		Change from baseline in CD4 T-cell count (cells per µL)		
	N	n (%)	n	Mean (SD)	Median (IQR)
Total randomised cohort	272	163 (60%)	213	205 (191)	175 (89–288)
Age (years)					
<35	61	35 (57%)	48	292 (231)	270 (139–374)
35 to <50	101	61 (60%)	81	166 (149)	126 (68–249)
≥50	110	67 (61%)	84	193 (190)	165 (119–263)
Sex					
Male	200	118 (59%)	157	187 (166)	165 (79–264)
Female	72	45 (63%)	56	255 (244)	222 (126–373)
Race					
White	185	103 (56%)	137	210 (199)	176 (109–286)
Black, African American	60	41 (68%)	51	204 (179)	169 (84–311)
Geographic region					
North America	108	61 (56%)	82	147 (160)	141 (65–217)
South America	105	67 (64%)	89	211 (170)	175 (102–309)
Europe	51	28 (55%)	37	306 (260)	267 (144–452)
Rest of world	8	7 (88%)	8	289 (81)	262 (231–300)
Baseline viral load (copies per mL)					
<1000	31	23 (74%)	25	137 (202)	101 (53–268)
1000 to <10 000	44	32 (73%)	38	147 (190)	133 (81–200)
10 000 to <100 000	117	69 (59%)	91	218 (181)	184 (94–288)
≥100 000	80	39 (49%)	59	250 (190)	222 (124–342)
Baseline CD4 count (cells per µL)					
<20	72	33 (46%)	54	240 (196)	212 (105–306)
20 to <50	25	14 (56%)	17	201 (77)	181 (138–222)
50 to <100	39	21 (54%)	26	199 (124)	171 (125–262)
100 to <200	63	41 (65%)	52	172 (140)	145 (77–236)
≥200	73	54 (74%)	64	205 (255)	150 (40–331)
Fully active antiretrovirals in initial optimised background therapy					
0	16	3 (19%)	6	322 (305)	222 (141–313)
1	142	92 (65%)	120	206 (178)	167 (88–294)
2	114	68 (60%)	87	195 (200)	181 (84–264)

Table 2: **Week 96 virological response rate (ie, HIV-1 RNA <40 copies per mL; Snapshot analysis) and CD4 cell count change from baseline (observed analysis) at week 96 by subgroups in the randomised cohort**

was 75 cells per µL (IQR –1 to 162; figure 3A). The mean increase in CD4/CD8 ratio was 0·08 (SD 0·13); the median increase was 0·10 (IQR 0·00–0·20). The 15 participants with ibalizumab in their initial optimised background therapy had mean baseline CD4 count of 114 cells per µL (SD 121) and median baseline count of 73 cells per µL (IQR 7–230). The mean CD4 count increase for this subgroup at week 96 (n=9) was 18 cells per µL (SD 95) compared with 135 cells per µL (210) for participants without ibalizumab in their initial optimised background therapy, and the median increase was 32 cells per µL (IQR –67 to 88) compared with 90 cells per µL (1 to 183) for those without ibalizumab in their initial optimised background therapy.

Up to week 96, 63 (23%) of 272 participants in the randomised cohort and 49 (49%) of 99 in the non-randomised cohort met the criteria for protocol-defined virological failure. On-treatment gp120 sequencing data were obtained for 50 (79%) of 63 participants in the randomised cohort and 44 (90%) of 49 in the non-randomised cohort, and phenotypic temsavir susceptibility data were obtained for 53 (84%) of 63 participants in the randomised cohort and 45 (92%) of 49 in the non-randomised cohort. In the randomised cohort, the incidence of protocol-defined virological failure at week 96 was similar regardless of the presence of gp120 substitutions of interest or elevated temsavir IC_{50} fold-change at baseline: 31 (22%) of 141 participants without gp120 substitutions at baseline, compared with 31 (25%) of 122 participants with relevant gp120 substitutions, had protocol-defined virological failure; and 29 (22%) of 132 participants with temsavir IC_{50} fold-change of one or less, compared with ten (29%) of 34 with IC_{50} fold-change of more than 100, had protocol-defined virological failure. In the protocol-defined virological failure population through week 96, treatment-emergent gp120 substitutions at one or more of the four amino acid positions previously associated with reduced phenotypic susceptibility to temsavir[7,13,14] (most frequently Ser375Asn and Met426Leu) were found in 48% of participants in the randomised cohort and 75% in the non-randomised cohort (table 3). In the randomised cohort, the median increase in temsavir IC_{50} fold-change from baseline to protocol-defined virological failure in participants with emergent gp120 substitutions of interest (n=24) was 511-fold. In participants with no emergent gp120 substitutions of interest (n=26), the median increase in temsavir IC_{50} fold-change from baseline to protocol-defined virological failure was 0·9-fold, and 23 (88%) had a change in temsavir IC_{50} fold-change from baseline to protocol-defined virological failure of three-fold or less. In the non-randomised cohort, the median increase in temsavir IC_{50} fold-change from baseline to protocol-defined virological failure in participants with emergent gp120 substitutions of interest (n=32) was 2260-fold. In participants with no emergent gp120 substitutions of interest (n=11), the median change in temsavir IC_{50} fold-change from baseline to protocol-defined virological failure was 0·7-fold, and 82% (n=9) had a change in temsavir IC_{50} fold-change from baseline to protocol-defined virological failure of three-fold or less.

Analysis of nadir HIV-1 RNA values after protocol-defined virological failure showed that through the week 96 data cutoff date, virological suppression to less than 40 HIV-1 RNA copies per mL after protocol-defined virological failure was achieved for 17 (27%) of 63 participants in the randomised cohort and five (10%) of 49 in the non-randomised cohort.

94% of participants reported at least one adverse event (table 4). Consistent with findings through week 48,[3] the most commonly reported adverse events were diarrhoea, nausea, and headache. These adverse events were generally low grade in intensity, were self-limited, and resolved

without interruption of the study drug. Greater proportions of participants in the non-randomised cohort reported grade 3 or 4 adverse events, serious adverse events, fatalities, and adverse events leading to discontinuation compared with those in the randomised cohort. The only grade 3 or 4 adverse events to be reported in at least 2% of all participants were pneumonia (n=10 [3%]) and diarrhoea (n=7 [2%]). Few drug-related serious adverse events (12 [3%] of 371) and adverse events leading to discontinuation (26 [7%]) were reported (table 4). Most events resulting in discontinuation were related to infections (n=10 [3%]). CDC class C AIDS-defining events were reported in 23 (8%; 34 events) participants in the randomised cohort and 15 (15%; 28 events) in the non-randomised cohort, most commonly oesophageal candidiasis and *Pneumocystis jirovecii* pneumonia. For participants in the randomised cohort, a steady decline over time through week 96 was observed in the occurrence of AIDS-defining events (22 events through week 24, nine additional events through week 48, and three additional events through week 96). No significant safety signals related to emergent electrocardiogram abnormalities were observed, including no confirmed changes of more than 60 ms from baseline QTcF interval over time. There were 29 deaths reported at the time of the week 96 data cutoff: 12 (4%) of 272 in the randomised cohort and 17 (17%) of 99 in the non-randomised cohort (appendix p 9). Seven (24%) of the 29 deaths were AIDS related, 11 (38%) were acute infections, six (21%) were non-AIDS-related malignancies, and the remaining five (17%) resulted from other conditions. The median baseline CD4 count for all participants who died was 11 cells per µL (mean 49 cells per µL).

The mean total FAHI score at baseline was higher for the randomised cohort than for the non-randomised cohort (123 [SD 29] *vs* 114 [34]), with higher scores across all the subscales. The median total FAHI score at baseline was 128 (range 50–176) for the randomised cohort compared with 121 (36–172) in the non-randomised cohort. There was a positive change from baseline to week 96 in the randomised cohort in mean total score (5·3 [95% CI 2·0–8·5]; median 3·9 [range −69 to 81]) and in physical wellbeing (2·1 [95% CI 1·1–3·2]; median 1·0 [range −26 to 32]) and emotional wellbeing subscales (3·0 [95% CI 1·9–4·1]; median 3·0 [range −22 to 27]). In the non-randomised cohort, the mean total score was 4·9 (95% CI −1·8 to 11·5; median 2·0 [range −57 to 118]), physical wellbeing was 1·7 (95% CI −0·2 to 3·6; median 0·0 [range −17 to 32]), and emotional wellbeing was 1·6 (95% CI −0·6 to 3·8; median 1·0 [range −19 to 39]). In both cohorts there was little (or small negative) change in the function or global wellbeing, social wellbeing, and cognitive function subscale scores. For the EQ-5D-3L analyses, baseline mean single index utility scores and visual analogue scores were nominally higher in the randomised cohort than in the non-randomised cohort. Through 96 weeks, a small positive trend of improvement was seen in the randomised cohort, but this trend was inconsistent in the non-randomised cohort.

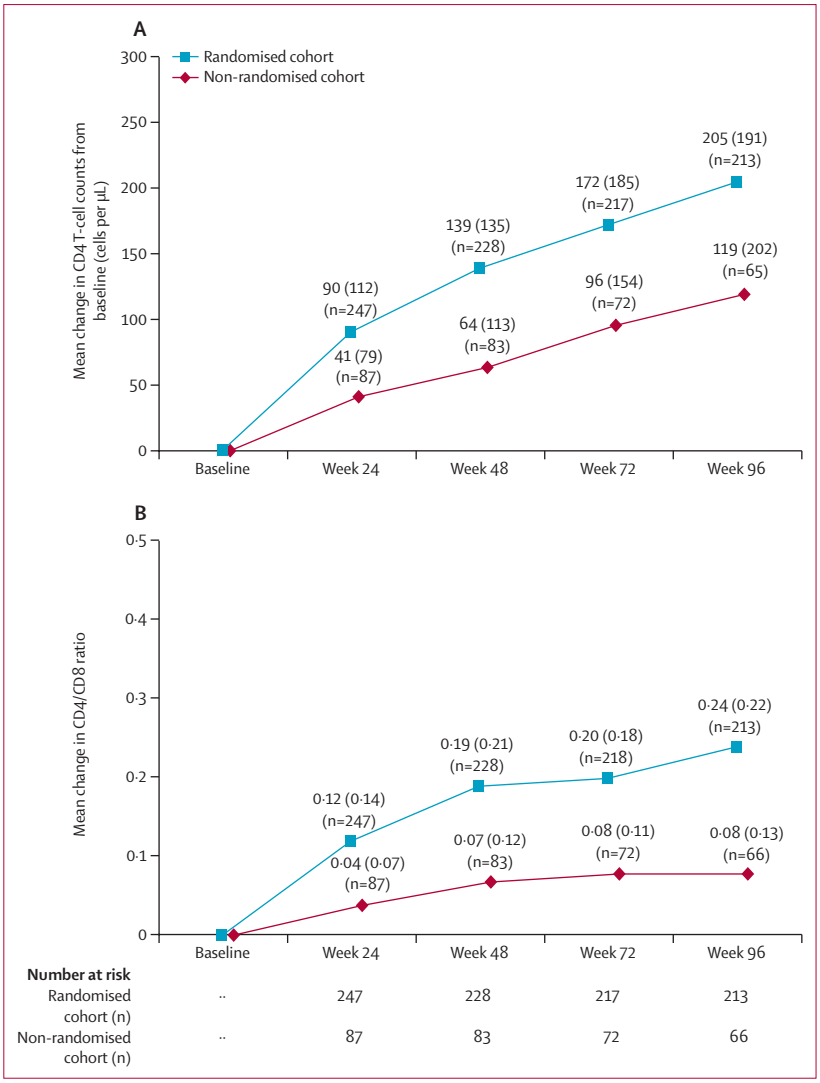

Figure 3: **Mean change in CD4 cell counts (A) and CD4/CD8 ratio (B) from baseline through week 96 (observed analysis)**
Data are mean (SD), unless otherwise specified.

Discussion

The week 96 results of the international phase 3 BRIGHTE study showed a sustained improvement in virological response (HIV-1 RNA <40 copies per mL) and immunological response (increase in CD4 cell count) to treatment with fostemsavir in a population of heavily treatment-experienced individuals with multidrug-resistant HIV-1, advanced HIV disease, including severe immune suppression, complex comorbidities, and limited remaining treatment options.

Despite restrictive inclusion criteria, rates of virological response by snapshot analysis through week 96 among the participants in the randomised cohort of the BRIGHTE

	Randomised cohort (n=63)	Non-randomised cohort (n=49)	Total (n=112)
Sequenced*	50 (79%)	44 (90%)	94 (84%)
Substitutions of interest in gp120†	24 (48%)	33 (75%)	57 (61%)
Ser375	15 (30%)	22 (50%)	37 (39%)
Ser375His	0	1 (2%)	1 (1%)
Ser375His/Asn	1 (2%)	1 (2%)	2 (2%)
Ser375Met	0	3 (7%)	3 (3%)
Ser375Asn	7 (14%)	8 (18%)	15 (16%)
Ser375Asn/Thr	1 (2%)	2 (5%)	3 (3%)
Ser375Ser/Ile	0	1 (2%)	1 (1%)
Ser375Ser/Met/Thr	1 (2%)	0	1 (1%)
Ser375Ser/Asn	4 (8%)	6 (14%)	10 (11%)
Ser375Ser/Thr	1 (2%)	0	1 (1%)
Met426	16 (32%)	21 (48%)	37 (39%)
Met426Leu	10 (20%)	13 (30%)	23 (24%)
Met426Met/Leu	7 (14%)	8 (18%)	15 (16%)
Met434	5 (10%)	4 (9%)	9 (10%)
Met434Ile	1 (2%)	1 (2%)	2 (2%)
Met434Met/Ile	4 (8%)	3 (7%)	7 (7%)
Met434Met/Ile/Thr	1 (2%)	0	1 (1%)
Met475	6 (12%)	5 (11%)	11 (12%)
Met475Ile	4 (8%)	1 (2%)	5 (5%)
Met475Met/Ile	2 (4%)	4 (9%)	6 (6%)

Data are n (%). Sequencing results at additional on-treatment timepoints around the time of virological failure are included where available (not limited to only the protocol-defined virological failure timepoint). Up to week 96, 63 (23%) of 272 participants in the randomised cohort and 49 (49%) of 99 in the non-randomised cohort had protocol-defined virological failure. *Sequenced percentages are based on the population with protocol-defined virological failure. Other percentages are based on participants with sequencing results. †Amino-acid substitutions at positions within the gp120 domain that have previously been associated with reduced susceptibility of virus to temsavir (Ser375His/Ile/Met/Asn/Thr, Met426Leu/Pro, Met434Ile/Lys, and Met475Ile).

Table 3: **Summary of emergent viral genotypic substitutions of interest in gp120 (protocol-defined virological failure population at week 96)**

study are similar to or better than those reported in previous antiretroviral trials done in participants living with multidrug-resistant HIV-1 (eg, BENCHMRK 1–2 and DUET 1–2).[15–20] This finding is notable because inclusion criteria in our study required exhaustion of treatment options in at least four of six antiretroviral classes whereas previous multidrug-resistant trials have required resistance to just one agent in three or more antiretroviral classes.[16,18–22] In BRIGHTE, participants with only one fully active antiretroviral agent as part of their initial optimised background therapy did as well in terms of virological response through week 96 as participants with two fully active agents. This finding might seem counterintuitive, but it has previously been reported in clinical trials done in participants with multidrug-resistant HIV-1.[19] One possible explanation for this finding might be the antiviral activity of the single fully active antiretroviral, and the contribution of partially active agents in the overall regimen. In the randomised cohort, participants with fully active dolutegravir had higher rates of virological response through week 96 than those who did not have fully active dolutegravir as part of their initial optimised background therapy (118 [71%] of 167 *vs* 45 [43%] of 105). The effect of background therapy and other factors on treatment response to fostemsavir-based therapy is being further explored.

A unique finding from BRIGHTE is the increase in virological response rates between week 24 and week 96, despite the continued attrition over time. Although direct comparisons cannot be made between studies with different designs and populations, it is notable that in previous clinical trials done in participants with multidrug-resistant HIV-1, rates of virological suppression by snapshot analysis generally declined over time. For example, the percentage of participants with virological response decreased from 62% at week 24 to 57% at week 96 in the BENCHMRK trials.[17,19] In the randomised cohort, the absolute number of participants classified as virological responders by snapshot analysis (HIV-1 RNA <40 copies per mL) went up by 19 from week 24 (n=144) to week 96 (n=163). These virological responses were not attributable to changes in the optimised background therapy because such changes were counted as treatment failures in the snapshot analysis. Although the mechanism behind this increase in efficacy by snapshot analysis over time is not completely understood, many individuals must have first achieved a virological response after week 24, otherwise response rates would have declined as a result of discontinuations or withdrawals. Several factors could hypothetically contribute to this late response. For example, since clearance of HIV-1 infection requires some contribution from the immune system, including CD4 cells,[23] the low baseline CD4 cell counts in individuals with advanced disease might have hindered initial reduction in HIV-1 RNA, while subsequent CD4 cell recovery contributed to the later reduction in HIV-1 RNA. Furthermore, the advanced disease state of study participants also implies high baseline levels of viral transactivation and possibly inflammation;[24] therefore, the initial and gradual decrease in viraemia might have enabled a better response to treatment of some infections and a decrease in inflammation leading to a cumulative virological response. Additionally, a slow but persistent reduction in HIV-1 RNA could result from partial activity of the initial optimised background therapy against a highly mutated and fitness-impaired viral population. Persistent detectable HIV-1 RNA in the earlier stages of treatment could also result from the unique mechanism of action of temsavir, blocking viral entry and trapping virus particles in the extracellular space. Lastly, temsavir binding to gp120 might also promote host immune recognition (via neutralising antibodies) and, over time, enhance clearance of the virus (possibly via antibody-dependent cellular cytotoxicity).[25–27] Further research is being done to evaluate these hypotheses.

Continuous increases were observed from baseline over time in CD4 cell count. Although participants in our study had low baseline CD4 cell counts, the mean increase through 96 weeks among fostemsavir-treated individuals in the randomised cohort (increase of 205 cells per µL) was numerically better than that seen in other multidrug-resistant studies with 96 weeks of data.[16,19,20] Perhaps the most important and clinically impactful finding for the heavily treatment-experienced population is that participants in the randomised cohort, who were the most profoundly immunosuppressed at baseline with CD4 counts less than 20 cells per µL, achieved a life-changing mean increase of 240 cells per µL at week 96. Among participants in the randomised cohort who started the study with CD4 counts of less than 50 cells per µL, 56% had counts of 200 cells per µL or more at week 96, an increase that represents a reduction in the risk of opportunistic infection and a transition to no requirement for opportunistic infection prophylaxis,[1] a meaningful and important milestone for many HIV-infected patients and their providers. CD4/CD8 ratio has been identified as a marker of risk for both AIDS-related and non-AIDS-related morbidity and mortality, independent of CD4 cell count. A ratio of more than 0·45 has been associated with a two-fold decrease in risk of progression to severe non-AIDS-defining event or death compared with a ratio less than 0·30.[28] Among the participants in the randomised cohort treated in our study, the mean CD4/CD8 ratio increased from 0·20 at baseline to 0·44 by observed analysis through week 96, suggesting improvement of immune function and overall health status and consistent with the observed decline in AIDS-defining events.

BRIGHTE incorporated a non-randomised compassionate use cohort for participants with no fully active and approved antiretrovirals remaining. Although reduced compared with the randomised cohort, the virological response rate by snapshot analysis in this cohort remained stable from week 24 to week 96 (37%). At week 96, by observed analysis, the mean CD4 count increase from baseline was 119 cells per µL, and 39 (59%) of 66 participants achieved HIV-1 RNA of less than 40 copies per mL. Individuals in the non-randomised cohort could simultaneously enrol into clinical trials of other investigational agents, and 15 participants included the CD4-directed post-attachment HIV-1 inhibitor ibalizumab in their optimised background therapy. The virological response rate by snapshot analysis in these 15 individuals was similar to the randomised cohort through week 48 (53% *vs* 54%) but by week 96 was lower than the randomised cohort (33% *vs* 60%). This finding could be explained by the small sample size, lack of active antiretrovirals in the optimised background therapy, and the impact of extensive comorbidities. Ibalizumab (post-attachment HIV-1 inhibitor) and temsavir (pre-attachment HIV-1 inhibitor) have non-overlapping mechanisms of action and show no evidence of cross-resistance.[5]

	Randomised cohort (n=272)*	Non-randomised cohort (n=99)	Total treated participants (n=371)
Any adverse event†	249 (92%)	98 (99%)	347 (94%)
Drug-related grade 2–4 adverse events	57 (21%)	22 (22%)	79 (21%)
Adverse events leading to discontinuation	14 (5%)	12 (12%)	26 (7%)
Drug related	7 (3%)	3 (3%)	10 (3%)
Serious adverse events‡	92 (34%)	48 (48%)	140 (38%)
Drug related§	9 (3%)	3 (3%)	12 (3%)
Fatal serious adverse events¶	12 (4%)	17 (17%)	29 (8%)
CDC class C AIDS-defining events	23 (8%)	15 (15%)	38 (10%)
Drug-related adverse events (grade 2–4) occurring in ≥2% of participants in either cohort			
Nausea	9 (3%)	5 (5%)	14 (4%)
Diarrhoea	6 (2%)	3 (3%)	9 (2%)
Headache	6 (2%)	1 (1%)	7 (2%)
Immune reconstitution inflammatory syndrome	6 (2%)	0	6 (2%)
Vomiting	4 (1%)	2 (2%)	6 (2%)
Fatigue	3 (1%)	2 (2%)	5 (1%)
Asthenia	2 (<1%)	2 (2%)	4 (1%)
Adverse events leading to discontinuation in ≥2 participants‖			
Abdominal pain	2 (<1%)	0	2 (<1%)
Electrocardiogram QT prolonged	2 (<1%)	1 (1%)	3 (<1%)
Non-cardiac chest pain	1 (<1%)	1 (1%)	2 (<1%)
Hepatic failure	0	2 (2%)	2 (<1%)
CDC class C AIDS-defining events occurring in ≥2% of participants in either cohort			
Candidiasis oesophageal (definitive diagnosis)	4 (1%)	2 (2%)	6 (2%)
Candidiasis oesophageal (presumptive diagnosis)	3 (1%)	3 (3%)	6 (2%)
Pneumocystis jirovecii pneumonia clinically diagnosed	3 (1%)	2 (2%)	5 (1%)
Cytomegalovirus retinitis	0	3 (3%)	3 (<1%)
HIV wasting syndrome	0	3 (3%)	3 (<1%)
Pneumocystis jirovecii pneumonia histologically proven	1 (<1%)	2 (2%)	3 (<1%)
Immunoblastic sarcoma	0	2 (2%)	2 (<1%)

Data are n (%). CDC=Centers for Disease Control and Prevention. All safety data reflect cumulative results collected through the week 96 interim data cutoff date. *Includes participants randomised to the placebo group who received fostemsavir (600 mg twice a day) during the open-label phase; only data from initiation of open-label fostemsavir dosing are presented. †Adverse events were coded according to MedDRA (version 19.1); severity (Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; version 2.0) and relationship to study drug was determined by the treating investigator. ‡Serious adverse events occurring in ≥2% of participants were pneumonia (n=15 [4%]), cellulitis (n=8 [2%]), and acute kidney injury (n=6 [2%]). §Drug-related serious adverse events included nephrolithiasis (n=2), immune reconstitution inflammatory syndrome (n=3), acute kidney injury (n=1), renal impairment (n=1), hyperglycaemia (n=1), hyperkalaemia (n=1), loss of consciousness (n=1), myocarditis (n=1), hepatocellular injury (n=1), rhabdomyolysis (n=1), foetal growth restriction (n=1), disorientation (n=1), and rash (n=1). ¶Five deaths occurred after the participants discontinued from the study; 18 (62%) of 29 deaths resulted from AIDS-related events or acute infections (one case was considered treatment related: immune reconstitution inflammatory syndrome, related to recurrent atypical mycobacterial infection). ‖Including five (56%) of nine adverse events that were considered drug related (abdominal pain [n=1], non-cardiac chest pain [n=2], and QTc prolongation [n=2]).

Table 4: **Week 96 safety summary**

The rate of protocol-defined virological failure through week 96 (23% in the randomised cohort) was not unexpected for this heavily treatment-experienced population and was consistent with rates seen in other studies in individuals with multidrug-resistant HIV-1.[16,22,29] As would be anticipated, in the non-randomised cohort, where

most participants had zero fully active antiretrovirals, rates of protocol-defined virological failure and emergent gp120 substitutions of interest were higher, and median increase from baseline in temsavir IC_{50} fold-change was greater, compared with the randomised cohort. Overall, emergent gp120 substitutions of interest correlated with higher median increases from baseline in temsavir IC_{50} fold-change; however, virological failure was not consistently associated with the emergence of known genotypic substitutions of interest or phenotypic changes in temsavir susceptibility. In the randomised cohort, 52% of participants with protocol-defined virological failure did not have any emergent gp120 substitutions of interest. Other factors, such as treatment non-adherence, emergence of genotypic changes yet to be understood, or new resistance to components of the background regimen might be contributing to virological failure. To date, no clinical cutoff or genotypic algorithm has been established that can reliably predict clinical efficacy outcomes to fostemsavir-based therapy. Further analyses are being done to better understand the effect of HIV-1 gp120 substitutions and changes in temsavir IC_{50}, along with other baseline or emergent factors, on virological response to fostemsavir.

Consistent with the advanced disease status of the study population, both cohorts had low baseline scores for measures of HRQoL with a meaningful difference[11] in mean total FAHI score indicating a better HRQoL in the randomised cohort than in the non-randomised cohort. Although the open-label nature of BRIGHTE limits the interpretability of patient-reported outcomes, changes in FAHI suggested an improvement in HRQoL from baseline to week 96 in the randomised cohort, with smaller and more variable changes for the non-randomised cohort.

The safety assessment in BRIGHTE was complicated by a study population with advanced HIV disease at baseline often compounded by the presence of multiple comorbidities with complex concomitant medication profiles. Nevertheless, fostemsavir-based regimens were generally well tolerated with a low rate of discontinuation for adverse events, particularly in the randomised cohort. The most commonly reported adverse events were diarrhoea, nausea, and headache, consistent with those observed in the phase 2b study.[30] These events were mostly low grade in intensity and were self-limited. Infections and the progression of HIV disease accounted for the majority of the clinically significant safety events (ie, grade 3 or 4 adverse events, serious adverse events, and deaths) through week 96, reflecting the immune compromised state of the study population. Pneumonias were the most common serious adverse events and most of the 29 deaths reported were AIDS-related events, events related to immune reconstitution inflammatory syndrome, or acute infections. Severe safety events occurred more often in the non-randomised cohort and those who were most immune suppressed at baseline.

Limitations of BRIGHTE include the inability to include a comparator group beyond the primary endpoint analysis and the confounder of highly individualised background therapies required by this population. These limitations are unavoidable and inherent to the treatment needs of these heavily treatment-experienced individuals. Overall, the compelling results from the study support the use of fostemsavir in heavily treatment-experienced people living with multidrug-resistant HIV-1. Fostemsavir in combination with an optimised background therapy was well tolerated with no new safety signals, and resulted in continued improvements in both virological and immunological responses from baseline through week 96.

Contributors

JPL, MK, JAA, GP, PC, MT, J-MM, SM, BG, RSD, AC, PNK, GHL, and EDJ enrolled participants. ML, MK, SC, PA, and CL were involved in the design of the study. MW, SC and MG did the data analyses, which were reviewed and interpreted by ML, MG, AP, PA, and CL. Preparation of the first draft by a professional medical writer was overseen by ML, MG, AP, PA, and CL. All authors reviewed and interpreted analyses of data, contributed edits of the final report, and approved the draft manuscript for submission. ML submitted the manuscript for publication.

Declaration of interests

MK served as the Principal Investigator for clinical trials and laboratory research at Yale University that received grant funding from ViiV Healthcare and Gilead Sciences. JAA reports grants from Bristol-Myers Squibb and ViiV Healthcare to their institution for multicentre clinical trial support relating to this study; grants and personal fees from Gilead Sciences and ViiV Healthcare to their institution for multicentre clinical trial support and advisory board participation; personal fees from Merck and Janssen for advisory board participation; and grants from Frontier Technology and Shionogi to their institution for multicentre clinical trial support. GP reports personal fees from ViiV Healthcare for advisory board participation relating to this study; grants and personal fees from Gilead Sciences and Bristol-Myers Squibb for advisory board participation; and personal fees from Boehringer Ingelheim, Merck Sharp & Dohme, AbbVie, and Nephrotek for advisory board participation. PC reports grants and personal fees from ViiV Healthcare for advisory board participation relating to this study; grants and personal fees from Merck for advisory board participation; and personal fees from Gilead Sciences for speaker work. MT reports a research contract with the AIDS Research Consortium of Atlanta to conduct this clinical trial; and research contracts for clinical trials from Bristol-Myers Squibb, Cepheid, Cytodyn, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, and Frontier Biotechnologies. J-MM reports personal fees from Gilead Sciences, Merck, and ViiV Healthcare for advisory board participation. SM reports grants, personal fees, and non-financial support from ViiV Healthcare and Gilead Sciences; personal fees from Merck Sharp & Dohme; and grants and personal fees from Janssen. PNK reports grants and personal fees relating to this study from GlaxoSmithKline for advisory board participation, and also holds stock in GlaxoSmithKline; holds stock in Pfizer and Johnson & Johnson; reports grants and personal fees from Merck for advisory board participation, and also holds stock in Merck; reports grants from Gilead Sciences, and holds stock in Gilead Sciences; and reports grants and personal fees from Theratechnologies for advisory board participation. EDJ reports personal fees from Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, Janssen Pharmaceuticals, and Theratechnologies for advisory board and speaker bureau participation. MW is an employee of and holds stock interest in GlaxoSmithKline. ML, SC, MG, AP, PA and CL are employees of ViiV Healthcare and hold stock interests in GlaxoSmithKline. JPL, BG, RSD, AC, and GHL declare no competing interests.

Data sharing

Anonymised individual participant data and study documents can be requested for further research at the end of the study.

To request **participant data and study documents** see https://clinicalstudydatarequest.com/

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