Long-term Safety and Impact of Immune Recovery in Heavily Treatment-Experienced Adults Receiving Fostemsavir for up to 5 Years in the BRIGHTE Study

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Key Takeaways

- **In the phase 3 BRIGHTE study, heavily treatment-experienced (HTE) adults treated with fostemsavir (FTR) + optimized background therapy (OBT) experienced durable virologic responses and clinically meaningful improvements in CD4+ T-cell count and CD4+/CD8+ ratio through Week 240**
- **Infections and HIV-1 disease progression accounted for the majority of grade 3/4 adverse events (AEs), serious AEs (SAEs), and deaths, likely reflecting the severity of immune compromise in the study population**
- **After Week 48, there were no new AIDS-defining events reported among HTE adults with any on-treatment CD4+ T-cell count ≥200 cells/mm³ at least once during the analysis period**
- **These findings highlight the importance of initiating salvage regimens before the development of advanced disease, whenever possible**

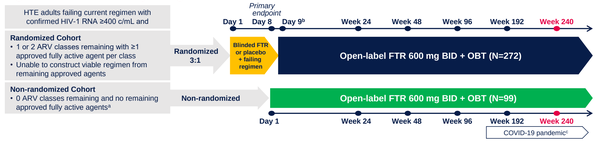
Introduction

- Advanced infection with multidrug-resistant HIV-1 and low CD4+ T-cell count is associated with significant morbidity and mortality, where both viral control and CD4+ T-cell recovery are important for improved outcomes
- FTR, a prodrug of the first-in-class gp120-directed attachment inhibitor temsavir, is approved for the treatment of multidrug-resistant HIV-1 in HTE adults who are otherwise unable to form a suppressive antiretroviral (ARV) regimen due to resistance, prior intolerance, or other safety concerns[1-4]
- In the previously published Week 96 interim analysis of the phase 3 BRIGHTE study, FTR + OBT was generally well tolerated with low rates of discontinuations due to AEs, and the majority of clinically significant severe safety events were attributed to infections and progression of HIV[4]
- Through Week 240, HTE adults treated with FTR + OBT experienced durable virologic responses and clinically meaningful improvements in CD4+ T-cell count and CD4+/CD8+ ratio[5]
- Here we report the long-term safety, including impact of immune recovery, of FTR + OBT in HTE adults with multidrug-resistant HIV-1 in the BRIGHTE study through Week 240

Methods

- BRIGHTE included HTE adults (aged ≥18 years) with HIV-1 who were failing their current ARV regimen (confirmed HIV-1 RNA ≥400 c/mL) and had ≤2 fully active and available ARV classes remaining
  - Fully active was based on susceptibility (current or historical resistance measures) and availability (the participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the ARV)
- Participants with 1 to 2 fully active ARVs remaining were randomly assigned (3:1) to receive FTR 600 mg twice daily or placebo + current failing regimen (Randomized Cohort) for 8 days followed by open-label FTR + OBT for all participants
- Participants with no fully active and available ARVs remaining received open-label FTR + OBT starting on Day 1 (Non-randomized Cohort; Figure 1)

Figure 1. BRIGHTE Study Design



[a]Use of investigational agents as part of OBT was permitted in the Non-randomized Cohort only. [b]Subsequent time points were measured from the start of open-label FTR 600 mg twice daily + OBT. [c]The COVID-19 pandemic impacted study participation during Weeks 192 and 240. Participants who were on study but unable to attend visits due to the pandemic were treated as missing data in efficacy analyses.

- Cumulative safety data through Week 240 were assessed; safety assessments included monitoring of AEs, clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations
- In participants with baseline CD4+ T-cell count <200 cells/mm³, exposure-adjusted AE rates were assessed among subgroups with or without CD4+ T-cell count ≥200 cells/mm³ at any time during 48-week analysis periods through Week 192
  - Week 192 was used as the data cutoff for these analyses because subsequent results were impacted by study completion and the COVID-19 pandemic

Results

Study Population

- Of the 371 BRIGHTE participants (Randomized Cohort, n=272; Non-randomized Cohort, n=99), 290 (78%) were male, 259 (70%) identified as White, and 166 (45%) were aged ≥50 years
- Baseline characteristics were consistent with advanced HIV-1 disease: 278/371 (75%) had CD4+ T-cell count <200 cells/mm³ (112/371 [30%] had CD4+ T-cell count <20 cells/mm³)[5]

Safety Overview

- Median duration of exposure to FTR for the total population was 258 weeks (range, 1 day to 319 weeks)
- Across both cohorts at Week 240, 357/371 (96%) participants reported at least 1 AE and 30/371 (8%) discontinued due to AEs (Table 1)
- SAEs occurred more frequently in the Non-randomized Cohort vs the Randomized Cohort
  - 16 drug-related SAEs were reported in 13 participants (Randomized Cohort, n=10; Non-randomized Cohort, n=3; only 1 occurred after Week 96)
- COVID-19–related events occurred in 25 (7%) participants; 18 events were confirmed with a positive PCR test and 7 were reported as an SAE; all resolved without sequelae, and no COVID-19–related deaths occurred

Table 1. Cumulative Summary of Safety: Week 240

Parameter, n (%)	Randomized Cohort (N=272)	Non-randomized Cohort (N=99)	Total (N=371)
Any AE	259 (95)	98 (99)	357 (96)
Any grade 2-4 AE	242 (89)	94 (95)	336 (91)
Drug-related grade 2-4 AEs	65 (24)	23 (23)	88 (24)
Any grade 3-4 AE	110 (40)	60 (61)	170 (46)
Any SAE	122 (45)	55 (56)	177 (48)
SAEs occurring in ≥2% of the total population			
Pneumonia	21 (8)	4 (4)	25 (7)
Cellulitis	7 (3)	3 (3)	10 (3)
Acute myocardial infarction	5 (2)	3 (3)	8 (2)
Acute kidney injury[a]	3 (1)	5 (5)	8 (2)
Drug-related SAEs[b]	10 (4)	3 (3)	13 (4)
AEs leading to discontinuation[c]	17 (6)	13 (13)	30 (8)
CDC class C events	25 (9)	19 (19)	44 (12)
Deaths[d]	15 (6)	20 (20)	35 (9)
Reported cause of death, n (% of deaths)			
AIDS-related	4 (27)	8 (40)	12 (34)
Acute infections	8 (53)	4 (20)	12 (34)
Non-AIDS malignancies	3 (20)	3 (15)	6 (17)
Other causes	0	5 (25)	5 (14)
COVID-19 diagnoses[e]	19 (7)	6 (6)	25 (7)
Confirmed with positive PCR test	15 (6)	3 (3)	18 (5)
COVID-19 reported as an SAE	7 (3)	0	7 (2)
Any ventricular tachyarrhythmia-related AEs of special interest[f]	13 (5)	1 (1)	14 (4)

[a]The 8 participants with acute kidney injury had identified and reversible causes of kidney injury not related to study drug, including comorbid conditions, infections, and concomitant medication. Most cases did not necessitate discontinuation of study treatment, and creatinine levels resolved to baseline after the acute event. [b]Drug-related SAEs (16 events in 13 participants) included immune reconstitution inflammatory syndrome (n=3); nephrolithiasis (n=2); and 1 each of acute kidney injury, hyperglycemia, hyperkalemia, loss of consciousness, myocarditis, hepatocellular cytolysis, rhabdomyolysis, fetal growth restriction, disorientation, and rash through the Week 96 data cutoff and supraventricular tachycardia (n=1) after the Week 96 data cutoff. [c]The most common AEs leading to discontinuation were related to infections (n=12); 4 participants discontinued because of an AE after the Week 96 cutoff (1 each for pneumonia, cytomegaloviral pneumonia, polyneuropathy, and rash). [d]By the Week 48 data cutoff, 25 participants had died: 11 (4%) in the Randomized Cohort and 14 (14%) in the Non-randomized Cohort. [e]Diagnosis based on World Health Organization definition. [f]AEs identified under the standardized MedDRA query Torsades de Pointes/QT prolongation (broad), which includes all preferred terms in ICH E14 except seizure.

- Among participants with baseline CD4+ T-cell count <200 cells/mm³, 122/162 (75%) achieved CD4+ T-cell count ≥200 cells/mm³ at Week 192
- SAEs and AIDS-defining events were less frequent in participants with vs without CD4+ T-cell count ≥200 cells/mm³ at Week 192 (56/122 [46%] vs 26/40 [65%] and 7/122 [6%] vs 6/40 [15%], respectively; Table 2)
- Deaths were also less frequent in participants with vs without CD4+ T-cell count ≥200 cells/mm³ at Week 192 (1/122 [<1%] vs 2/40 [5%])

Table 2. Summary of AEs Through Week 192 by CD4+ T-cell Count at Week 192 for Participants With Baseline CD4+ T-cell Count <200 Cells/mm³[a]

	CD4+ T-cell count <200 cells/mm³ at Week 192[b]			CD4+ T-cell count ≥200 cells/mm³ at Week 192[b]		
Participants, n (%)	Randomized Cohort (N=21)	Non-randomized Cohort (N=19)	Total (N=40)	Randomized Cohort (N=105)	Non-randomized Cohort (N=17)	Total (N=122)
Any AE	21 (100)	19 (100)	40 (100)	103 (98)	17 (100)	120 (98)
Drug-related AEs	8 (38)	6 (32)	14 (35)	45 (43)	10 (59)	55 (45)
Any grade 3-4 AE	14 (67)	10 (53)	24 (60)	39 (37)	10 (59)	49 (40)
Any SAE	16 (76)	10 (53)	26 (65)	45 (43)	11 (65)	56 (46)
Drug-related SAEs	0	1 (5)	1 (3)	0	1 (6)	1 (<1)
All discontinuations	2 (10)	3 (16)	5 (13)	6 (6)	0	6 (5)
AEs leading to discontinuation	0	0	0	2 (2)	0	2 (2)
AEs in infections and infestations SOC	19 (90)	18 (95)	37 (93)	89 (85)	17 (100)	106 (87)
AIDS-defining events (CDC class C events)	3 (14)	3 (16)	6 (15)	6 (6)	1 (6)	7 (6)
Deaths	1 (5)	1 (5)	2 (5)	1 (<1)	0	1 (<1)

CDC, Centers for Disease Control and Prevention; SOC, system organ class. [a]Table only includes participants who had a Week 192 CD4+ T-cell count as well as a baseline CD4+ T-cell count <200 cells/mm³; for this reason, numbers are low in most groups due to discontinuation. [b]Week 192 was used as the data cutoff for these analyses because subsequent results were impacted by study completion and the COVID-19 pandemic.

Deaths

- 35 deaths occurred (9%; Randomized Cohort, 15/272 [6%]; Non-randomized Cohort, 20/99 [20%]) and were primarily related to AIDS (n=12) or acute infections (n=12; Table 3); 6 deaths (3 per cohort) occurred after Week 96
- Most deaths (32/35 [91%]) occurred in participants with a last recorded CD4+ T-cell count <200 cells/mm³, and only 2 participants who died had a baseline CD4+ T-cell count >200 cells/mm³

Exposure-Adjusted AE Assessment by CD4+ T-cell Count During the Analysis Period

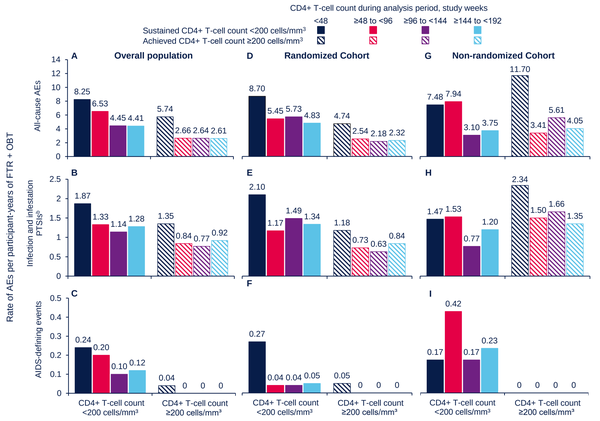
- Exposure-adjusted rates of all-cause AEs, infection and infestation preferred terms of special interest (PTSIs), and AIDS-defining events were lower among participants achieving CD4+ T-cell count ≥200 cells/mm³ at any time vs those sustaining <200 cells/mm³ during the same analysis period (Figure 2)
- For all types of AEs, the highest exposure-adjusted rates occurred in the first 48 weeks
- No new AIDS-defining events were reported after Week 48 in participants with CD4+ T-cell count ≥200 cells/mm³ achieved at least once within each 48-week analysis period

Table 3. All Deaths Through Week 240

Cause of death			CD4+ T-cell count (cells/mm³)	
Category	Primary cause	Study day of death	Baseline	Last before death
Randomized Cohort (n=15)				
AIDS-related (4/15 [27%])	Pneumonia	1821	92	171
	Pneumonia	199	1	1
	Anal squamous cell carcinoma[a]	765	249	257
	Progressive multifocal leukoencephalopathy	287	55	55
Acute infections (8/15 [53%])	Pulmonary septic shock	1266	5	0
	Meningoencephalitis viral	101	11	8
	Septic shock[b]	334	12	37
	Acute respiratory failure (community-acquired pneumonia)[b]	11	14	14
	IRIS[c]	32	1	5
	Pseudomonal sepsis	603	160	172
	Staphylococcal sepsis	466	166	176
	Pneumonia[a]	228	1	1
Non-AIDS malignancies (3/15 [20%])	Rectal cancer[d]	NR	98	160
	Squamous cell carcinoma[a]	535	27	30
	Cholangiocarcinoma	875	349	494
Non-randomized Cohort (n=20)				
AIDS-related (8/20 [40%])	HIV wasting syndrome	1112	1	4
	Progression of AIDS disease	1772	80	2
	Acute kidney injury (advanced AIDS)	350	1	4
	Disseminated cytomegaloviral infection	661	1	3
	Cytomegalovirus colitis[a]	354	3	1
	Kaposi's sarcoma	160	2	10
	Encephalitis cytomegalovirus	158	4	6
	Lymphoma	33	42	24
Acute infections (4/20 [20%])	Clostridium difficile colitis	511	1	3
	Sepsis	504	7	37
	Sepsis	580	35	18
	Septic rash (pulmonary/cutaneous sepsis)	392	42	234
Non-AIDS malignancies (3/20 [15%])	Hodgkin's disease	660	0	5
	Hodgkin's disease	1094	28	148
	Tonsil cancer[a]	515	173	7
Other causes (5/20 [25%])	Dyspnea	1089	4	1
	Hepatic failure (due to hepatitis B)	537	1	2
	Hepatic failure	142	1	2
	Cardiovascular disorder	530	6	34
	Cerebrovascular accident (left middle cerebral artery stroke)	879	22	189

[a]5 deaths occurred after the participant discontinued from the study. [b]Participants randomly assigned to placebo during the double-blind period. [c]Death was considered treatment related (recurrent atypical mycobacterial infection due to immune reconstitution inflammatory syndrome). [d]Date of death was unknown; last CD4+ T-cell count was measured on Study Day 1387.

Figure 2. Exposure-Adjusted Rates of (A, D, G) All-Cause AEs, (B, E, H) Infection and Infestation PTSIs, and (C, F, I) AIDS-Defining Events Through Week 192[a] by CD4+ T-cell Count During the Analysis Period for Participants With Baseline CD4+ T-cell Count <200 Cells/mm³



In participants randomized to placebo, only data from start of open-label FTR are included. For each panel, AE rates are based on the number of reported AEs for the specified category (y-axis) with a start date within the specified analysis period (legend). [a]Week 192 was used as the data cutoff for these analyses because subsequent results were impacted by study completion and the COVID-19 pandemic. [b]Infectious disorders and ectoparasitic infestations. Infections and infestations included PTSIs from the MedDRA infections and infestations system organ class, which were selected to exclude terms associated with non-specific infections and infections that were non-serious and/or typically not related to immunosuppression. [c]Number of participants who received FTR, had ≥1 CD4+ T-cell count during the specified analysis period, and had CD4+ T-cell count <200 cells/mm³ for all measures throughout the specified analysis period (<200 subgroup) or had at least 1 measure of ≥200 cells/mm³ at any time during the specified analysis period (≥200 subgroup). [d]Total number of participant-years of treatment with FTR for subgroup participants over the specified analysis period.

Laboratory Parameters

- No new trends in clinical chemistry parameters were identified from Weeks 96 to 240; the most common post-baseline grade 3 or 4 laboratory abnormalities were increased serum creatinine, decreased estimated creatinine clearance, and increased direct bilirubin (Table 4)
  - Creatinine results were confounded by identifiable risk factors for reduced renal function or renal tubular creatinine secretion, such as advanced HIV-1 disease, concomitant medications (eg, OBT with integrase inhibitors), and comorbidities
  - In most cases, increases in direct bilirubin were transient, without clinical signs or manifestations of liver disease, and all resolved without discontinuation of FTR

Table 4. Summary of Maximum Post-Baseline Emergent Grade 3 or 4 Clinical Chemistry Toxicities for Selected Laboratory Parameters Through Week 240[a,b]

Parameter, n (%)	Randomized Cohort (N=272)	Non-randomized Cohort (N=99)	Total (N=371)
Estimated creatinine clearance[c,d]	128 (48)	38 (39)	166 (45)
Creatinine[d]	93 (35)	24 (24)	117 (32)
Direct bilirubin	28 (10)	14 (14)	42 (11)
Triglycerides[e]	16 (7)	8 (11)	24 (8)
ALT	18 (7)	2 (2)	20 (5)
AST	13 (5)	4 (4)	17 (5)
Total cholesterol[e]	15 (7)	1 (1)	16 (5)
Total bilirubin	9 (3)	6 (6)	15 (4)
Creatine kinase	12 (4)	3 (3)	15 (4)
Urate	10 (4)	5 (5)	15 (4)

[a]Graded according to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.0 (Nov 2014). [b]Unless otherwise specified, N=268 for the Randomized Cohort, N=99 for the Non-randomized Cohort, and N=367 for the overall population. [c]N=98 for the Non-randomized Cohort and N=366 for the overall population. [d]All participants with emergent grade 3 or 4 change in creatinine or estimated creatinine clearance were able to continue treatment with FTR. [e]N=221 for the Randomized Cohort, N=73 for the Non-randomized Cohort, and N=294 for the overall population.

AEs of Special Interest

QTc Prolongation

- 11 (3%) participants were discontinued from the study for meeting protocol-specified QTc prolongation stopping criteria (QTcF >450 ms for male participants, QTcF >470 ms for female participants); 4 were discontinued between the Week 96 and 240 data cutoffs
  - 1 was receiving a concomitant medication of amiodarone for atrial fibrillation
  - 2 had QTc prolongation at baseline, and 7 had ECG abnormalities at baseline, which confound QT measurements (eg, sinus bradycardia, left or right bundle branch block, left axis deviation, and left anterior fascicular block); none had corresponding symptomatic cardiovascular events or evidence of ventricular tachyarrhythmia
  - Most (9/11 [82%]) continued FTR treatment after study discontinuation (enrolled in compassionate use program)
- An increase in QTcF ≥60 ms was seen in 5 (1%) participants; however, there were no reported cases of symptomatic cardiovascular disease or deaths attributable to QTc prolongation

Immune Reconstitution Inflammatory Syndrome (IRIS)

- IRIS was reported in 8 (2%) participants; 3 events were classified as SAEs (recurrent mycobacterial infection [fatal AE], n=1; neurotoxoplasmosis, n=1; central nervous system lesion, not otherwise specified, n=1)

Pregnancies

- Through the Week 240 data cutoff, 6 participants, all in the Randomized Cohort, became pregnant and were permitted to continue FTR (per protocol)
  - Of the 6 pregnancies, 3 led to normal births of healthy infants, 2 had complications (1 intrauterine growth restriction and 1 premature birth), and 1 ended in an elective abortion

Conclusions

- Cumulative safety findings through Week 240 in the BRIGHTE study are consistent with previous safety results
- Exposure-adjusted rates of all-cause AEs, infection and infestation PTSIs, and AIDS-defining events were lower in participants who achieved on-treatment CD4+ T-cell count ≥200 cells/mm³
- After Week 48, no new AIDS-defining events were reported among participants with any on-treatment CD4+ T-cell count ≥200 cells/mm³ at least once during the analysis period
- These long-term safety and tolerability results, coupled with robust virologic and immunologic responses, support FTR as an important treatment option for HTE individuals with multidrug-resistant HIV-1

Acknowledgments:

This study was funded by ViiV Healthcare. The authors thank all BRIGHTE clinical trial participants and their families and all BRIGHTE investigators. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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