LONG-TERM (96-WEEK) SAFETY OF FOSTEMSAVIR (FTR) IN HEAVILY TREATMENT-EXPERIENCED (HTE) ADULTS INFECTED WITH MULTIDRUG-RESISTANT (MDR) HIV-1 (BRIGHTE PHASE 3 STUDY)

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Introduction

- Fostemsavir (Rukobia™), an oral prodrug of the first-in-class attachment inhibitor temsavir, is approved for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced (HTE) adults who are otherwise unable to form a suppressive antiretroviral regimen due to resistance, prior intolerance, or other safety concerns[1-4]
- In the phase 3 BRIGHTE study, in HTE adults with advanced HIV-1 disease and limited treatment options, fostemsavir plus optimized background therapy (OBT) was generally well tolerated and showed a trend of increasing virologic and immunologic response rates through 96 weeks[1-5]
- Safety and tolerability are particularly important for HTE individuals because prior intolerance, advanced HIV disease, immune compromise, and toxicity issues with antiretroviral drugs may have already played a role in limiting treatment options
- Fostemsavir has few drug–drug interactions and can be administered with most drugs prescribed for the management of HIV-1 and associated comorbidities without the need for dose adjustment[6]
- Fostemsavir was well tolerated in prior clinical studies conducted in participants with mild-to-severe renal impairment and in participants with mild-to-severe hepatic impairment[7]
- Since fostemsavir represents a novel class of antiretroviral agents, it is important to assess the long-term safety profile in the indicated population

Objectives

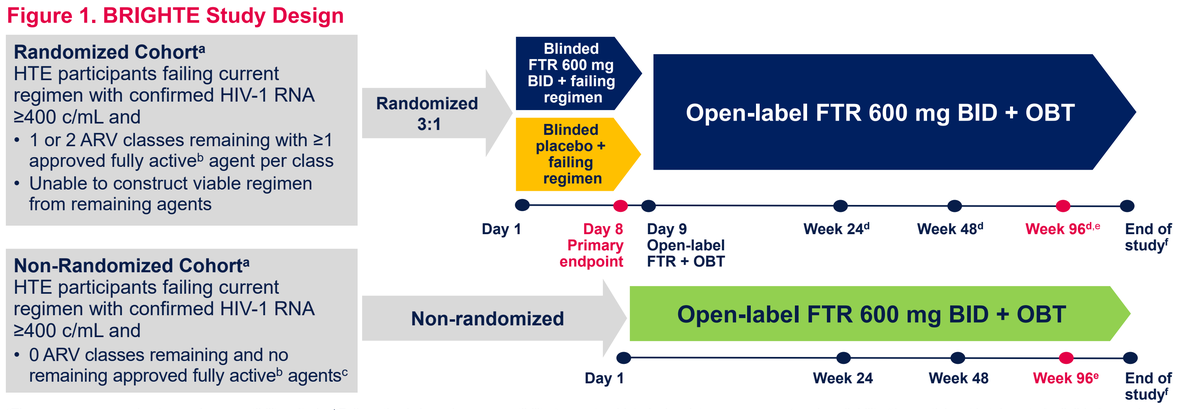
- To summarize the safety experience, through the Week 96 data cutoff, of HTE adults with HIV-1 who received fostemsavir-based antiretroviral therapy as participants in the phase 3 BRIGHTE trial

Methods

Study Design

- BRIGHTE is an ongoing phase 3 study evaluating twice-daily fostemsavir 600 mg plus OBT in HTE adults failing antiretroviral therapy with limited treatment options (Figure 1)
- All Week 96 safety data were obtained before the SARS-CoV-2 pandemic

Figure 1. BRIGHTE Study Design



[a]There were no screening temsavir susceptibility criteria. [b]Fully active is 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 antiretroviral). [c]Use of investigational agents as part of OBT was permitted in the Non-randomized Cohort only. [d]Measured from the start of open-label FTR 600 mg BID + OBT. [e]The Week 96 database lock was August 14, 2018 (first participant, first visit: February 23, 2015; last participant, first dose of study treatment: August 11, 2016; last participant, last visit for Week 96: June 22, 2018). [f]The study is expected to be conducted until participants can access FTR through other means (eg, rollover study or marketing approval).

Safety Analysis

- The safety population included all participants who received at least 1 dose of fostemsavir
- Cumulative safety data were collected through the Week 96 data cutoff (August 14, 2018)
- Safety assessments comprised monitoring of adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations
- AEs of special interest (AESIs) were selected on the basis of emerging nonclinical/clinical safety data for fostemsavir, disease and/or population events, and/or regulatory requirements

Results

Study Population

- 371 participants were enrolled and treated in BRIGHTE, 272 in the Randomized Cohort and 99 in the Non-randomized Cohort (Table 1)
  - 1 participant in the placebo group of the Randomized Cohort withdrew before starting fostemsavir treatment; therefore, the safety population included 370 participants

Table 1. Demographics and Baseline Characteristics (Safety Population)

Parameter, n (%)	Randomized Cohort (N=271)	Non-randomized Cohort (N=99)	Total (N=370)
Sex			
Female	72 (27)	10 (10)	82 (22)
Age			
≥50 years	110 (41)	55 (56)	165 (45)
Race			
African American/African heritage	60 (22)	23 (23)	83 (22)
White	184 (68)	74 (75)	258 (70)
History of AIDS	230 (85)	89 (90)	319 (86)
Baseline HIV-1 RNA[a]			
≥100,000 c/mL	76 (28)	15 (15)	91 (25)
Baseline CD4+ T-cell count[a]			
<200 cells/mm^3	195 (72)	79 (80)	274 (74)
<20 cells/mm^3	67 (25)	40 (40)	107 (29)

[a]Last observation before first fostemsavir dose.

Safety Overview

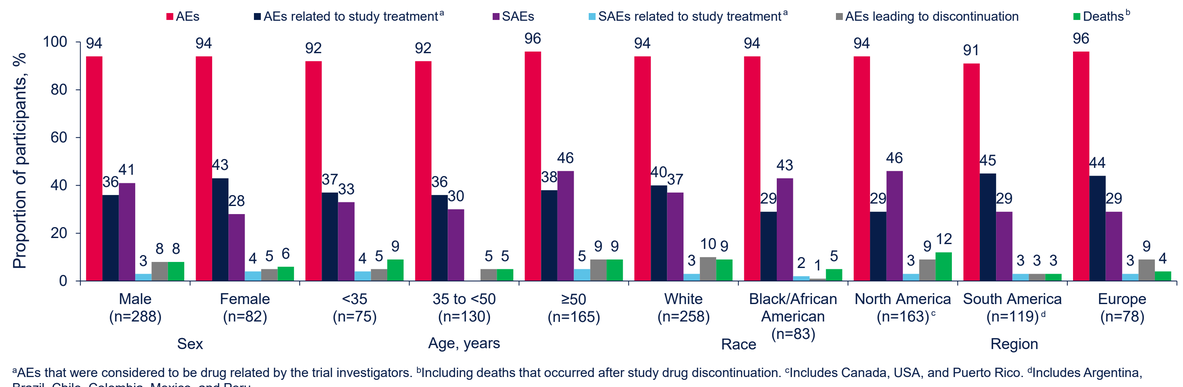
- Median duration of exposure to fostemsavir for the total population was 110.4 weeks (range, 1 day to 171.4 weeks)
- Across both cohorts, 94% of participants reported at least 1 AE (Table 2)
  - AEs classified as infections and infestations were most common (reported in 72% [268/370] of participants)
  - Grade 3 or 4 AEs reported in ≥2% of participants were pneumonia (10/370 [3%]) and diarrhea (7/370 [2%])
- Most drug-related AEs were grade 1 or 2 in severity; common drug-related AEs were nausea (9%), diarrhea (5%), headache (3%), and fatigue (3%)
  - Frequency of drug-related AEs was similar across baseline CD4+ T-cell count categories (Table 2)
- Severe AEs, including grade 3 or 4 AEs, serious AEs (SAEs), and deaths, occurred disproportionately in the Non-Randomized Cohort and those most immunosuppressed at baseline (Table 2)
  - SAEs reported in ≥2% of participants were pneumonia (15/370 [4%]), cellulitis (8/370 [2%]), and acute kidney injury (6/370 [2%])
  - Of the 28 deaths, 7 were AIDS related, 10 were acute infections, 6 were non–AIDS-related malignancies, and the remaining 5 were due to other conditions (acute kidney injury, cardiovascular disorder, cerebrovascular accident, 2 events of hepatic failure)
    - Median baseline CD4+ T-cell count among the 28 participants who died was 9 cells/mm^3
    - 22 of the 28 deaths (79%) occurred in participants with baseline CD4+ T-cell count <50 cells/mm^3
    - 1 death was considered related to study medication (immune reconstitution inflammatory syndrome [IRIS], related to recurrent atypical mycobacterial infection)
  - Among AEs leading to discontinuation, 38% (10/26) were related to infections
  - There were no clear differences in the safety profile across subgroups based on sex, age, race, or geographic region (Figure 2)

Table 2. Summary of Cumulative On-Treatment Adverse Events by Cohort and Baseline CD4+ T-cell Count

Safety parameter, n (%)	Total (N=370)	Cohort		Baseline CD4+ T-cell count (cells/mm^3)		
		Randomized (N=271)[a]	Non-randomized (N=99)	<20 (N=107)	20 to <200 (N=167)	≥200 (N=96)
Any AE	347 (94)	249 (92)	98 (99)	103 (96)	156 (93)	88 (92)
Any grade 3-4 AE	127 (34)	78 (29)	49 (49)	53 (50)	50 (30)	24 (25)
Any AE related to study treatment[b]	138 (37)	104 (38)	34 (34)	44 (41)	61 (37)	33 (34)
Any SAE	140 (38)	92 (34)	48 (48)	58 (54)	57 (34)	25 (26)
Any SAE related to study treatment[b,c]	12 (3)	9 (3)	3 (3)	5 (5)	2 (1)	5 (5)
Any AE leading to discontinuation of study treatment[d]	26 (7)	14 (5)	12 (12)	11 (10)	11 (7)	4 (4)
Any death[e]	28 (8)	11 (4)	17 (17)	16 (15)	10 (6)	2 (2)

[a]For participants randomized to placebo in the Randomized Cohort, only data from initiation of open-label fostemsavir dosing are presented. [b]AEs that were considered to be drug related by the trial investigator. [c]Drug-related SAEs included nephrolithiasis (n=2), IRIS (n=2), and 1 event each of acute kidney injury, CNS IRIS, disorientation, fetal growth restriction, hepatocellular injury, hyperglycemia, hyperkalemia, loss of consciousness, myocarditis, generalized rash, renal impairment, and rhabdomyolysis. [d]AEs leading to discontinuation in ≥2 participants were abdominal pain (n=2), QT prolonged (n=3), non-cardiac chest pain (n=2), and hepatic failure (n=2). [e]Including deaths that occurred after study drug discontinuation. Five deaths occurred after the participant discontinued (3 in the Randomized Cohort, 2 in the Non-randomized Cohort).

Figure 2. Summary of Cumulative On-Treatment Adverse Events by Subgroup



[a]AEs that were considered to be drug related by the trial investigators. [b]Including deaths that occurred after study drug discontinuation. [c]Includes Canada, USA, and Puerto Rico. [d]Includes Argentina, Brazil, Chile, Colombia, Mexico, and Peru.

Laboratory Parameters

- Incidence of grade 3 or 4 toxicities in ALT, AST, total bilirubin, total cholesterol, and triglycerides was low (Table 3)
- There were no grade 4 increases in direct bilirubin. Grade 3 toxicity was determined by any increase above the ULN, and the majority of increases were confounded by intercurrent serious comorbid events (eg, sepsis, cholangiocarcinoma, or other complications of viral coinfection). In the remaining cases, elevations in direct bilirubin were typically transient, occurred without changes in liver enzymes, and resolved on continued fostemsavir
- Clinically relevant increases in serum creatinine primarily occurred in participants with identifiable risk factors for reduced renal function including pre-existing medical history of renal disease and/or concomitant medications known to cause increases in creatinine

Table 3. Summary of Maximum Post-Baseline Emergent Grade 3 or 4 Clinical Chemistry Toxicities for Selected Laboratory Parameters

Participants with grade 3 or 4 increase, n (%)[a]	Total (N=370)	Cohort		Baseline CD4+ T-cell count (cells/mm^3)		
		Randomized (N=271)[b]	Non-randomized (N=99)	<20 (N=107)	20 to <200 (N=167)	≥200 (N=96)
ALT	15 (4)	14 (5)	1 (1)	3 (3)	7 (4)	5 (5)
AST	12 (3)	10 (4)	2 (2)	5 (5)	4 (2)	3 (3)
Direct bilirubin	38 (10)	22 (8)	16 (16)	16 (15)	12 (7)	10 (10)
Total bilirubin	14 (4)	8 (3)	6 (6)	4 (4)	5 (3)	5 (5)
Creatinine	85 (23)	58 (21)	27 (27)	36 (34)	33 (20)	16 (17)
Creatine kinase	9 (2)	6 (2)	3 (3)	4 (4)	4 (2)	1 (1)
Total cholesterol[c]	11 (4)	10 (5)	1 (1)	5 (6)	3 (2)	3 (4)
Triglycerides[c]	20 (7)	12 (5)	8 (11)	7 (9)	10 (7)	3 (4)

[a]Grading according to Division of Acquired Immune Deficiency Syndrome v2.0 (Nov 2014). [b]For participants randomized to placebo in the Randomized Cohort, only data from initiation of open-label fostemsavir dosing are presented. [c]N=293, 220, and 73 for the total, Randomized, and Non-randomized cohorts, respectively, and N=81, 142, and 80 for the <20, 20 to <200, and ≥200 cells/mm^3 groups, respectively, for lipid parameters.

Adverse Events of Special Interest

IRIS

- Events associated with IRIS included progressive multifocal leukoencephalopathy, atypical mycobacterial infection, CNS lesions, cryptococcal meningitis, pneumococcal pneumonia, immune reconstitution folliculitis, and cerebral toxoplasmosis
- All IRIS-related events occurred early after initiation of treatment, and the majority (5/8) occurred in participants with baseline CD4+ T-cell count <20 cells/mm^3 (Table 4)
  - 1 event of IRIS was fatal; none of the remaining 7 events resulted in discontinuation of study treatment

QT Prolongation

- In a thorough QT study in healthy participants, fostemsavir at 4 times the recommended daily dose prolonged QTc interval (mean increase of 11.2 ms [13.3 ms upper 95% CI])[8]; a therapeutic dose of fostemsavir does not prolong QT interval to a clinically relevant extent
- 7 participants were discontinued from the study for meeting protocol-specified QTc prolongation stopping criteria (Table 4); none experienced an increase in QTc >60 ms
  - There were no reported cases of symptomatic cardiovascular disease correlating with any of the episodes of QT prolongation
  - In 6 cases, the participants were transitioned to the fostemsavir early access program and continued dosing with fostemsavir

Tablet in Stool

- All participants with tablet in stool had an established history of chronic gastrointestinal condition and/or relevant intercurrent gastrointestinal illness with diarrhea
- None of these reports were associated with loss of virologic suppression in participants who were previously suppressed

Table 4. Summary of Time to Onset and Duration of AESIs (N=370)

AESI	Number of participants (%)	Median (range), weeks		
		Time to onset of first occurrence	Duration of first occurrence	Total duration
IRIS[a]	8 (2)	4.90 (0-16)	7.30 (1-26)	7.30 (1-26)
Rash[b]	24 (6)	15.4 (0.3-140.6)	2.95 (0.4-16.4)	4.35 (0.4-47.0)
Musculoskeletal[c]	56 (15)	25.5 (1-133.0)	3.40 (0-63.0)	4.10 (0-59.0)
Renal[d]	23 (6)	48.6 (1.1-144.1)	2.15 (0.3-86.1)	2.15 (0.3-86.1)
Electrocardiogram QT prolonged[e]	7 (2)	13.1 (0.1-49.6)	7.2 (3.4-25.1)	7.2 (3.4-25.1)
Tablet in stool	3 (<1)	61.7 (16.4-113.7)	0.1 (0.1-0.1)	0.5 (0.1-0.9)

[a]Includes IRIS and CNS IRIS. IRIS reports were based on treating clinician assessments and were not independently adjudicated. [b]Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular. [c]Includes myalgia, myositis, rhabdomyolysis, blood creatine phosphokinase increased, and preferred terms that contain "muscle" and "musculo." [d]Includes acute kidney injury, proteinuria, renal impairment, chronic kidney disease, glomerulonephritis, nephropathy, and renal tubular dysfunction. [e]Participants meeting stopping criteria of confirmed QTcF >450 ms for male participants and >470 ms for female participants. Duration of QT prolonged may partly reflect the interval between ECG recordings.

Pregnancy

- 4 pregnancies were reported in participants who received fostemsavir in BRIGHTE, and 1 pregnancy was reported in a partner of a male participant who received fostemsavir
  - 4 of these pregnancies resulted in live births (no congenital abnormalities; includes 1 report of intrauterine growth restriction in an otherwise healthy newborn) and 1 resulted in induced abortion
- Review of post-marketing data has not identified any new safety concerns. Pediatric studies with fostemsavir are planned

Conclusions

- Cumulative safety findings through the Week 96 interim analysis of the BRIGHTE trial are consistent with expectations for this HTE population with high rates of advanced HIV disease and multiple comorbidities
  - Fostemsavir was generally well tolerated, with low rates of discontinuations due to AEs and AEs related to study drug
  - Severe safety events (ie, grade 3 or 4 AEs, SAEs, and deaths) were mostly related to infections and infestations and were more frequent in the most immunocompromised participants with the lowest baseline CD4+ T-cell count
  - However, the frequency of drug-related AEs did not differ across baseline CD4+ T-cell count categories, suggesting immune status did not impact fostemsavir tolerability
- The safety and tolerability profile of fostemsavir is favorable in the intended-use population

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