Week 96 Safety and Efficacy of the Novel HIV-1 Attachment Inhibitor Prodrug Fostemsavir in Heavily Treatment-Experienced Participants Infected With Multidrug-Resistant HIV-1 (BRIGHTE Study)

124

M Lataillade,[1] J Lalezari,[2] J Aberg,[3] J-M Molina,[4,5] M Kozal,[6,7] P Cahn,[8] M Thompson,[9] R Diaz,[10] A Castagna,[11] M Gummel,[12] M Gartland,[13] A Pierce,[13] P Ackerman,[1] C Llamoso,[1] A Carr[14,*]

[1]ViiV Healthcare, Branford, CT, USA; [2]Quest Clinical Research, San Francisco, CA, USA; [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris, Paris, France; [5]University of Paris Diderot Paris 7, Paris, France; [6]Yale University School of Medicine, New Haven, CT, USA; [7]VA Connecticut Healthcare System, New Haven, CT, USA; [8]Fundación Huésped, Buenos Aires, Argentina; [9]AIDS Research Consortium of Atlanta, Atlanta, GA, USA; [10]Federal University of São Paulo, Rio de Janeiro, Brazil; [11]Ospedale San Raffaele, Milan, Italy; [12]GlaxoSmithKline, Upper Providence, PA, USA; [13]ViiV Healthcare, Research Triangle Park, NC, USA; [14]St Vincent's Hospital Sydney, Darlinghurst, NSW, Australia

Presenting on behalf of the authors.

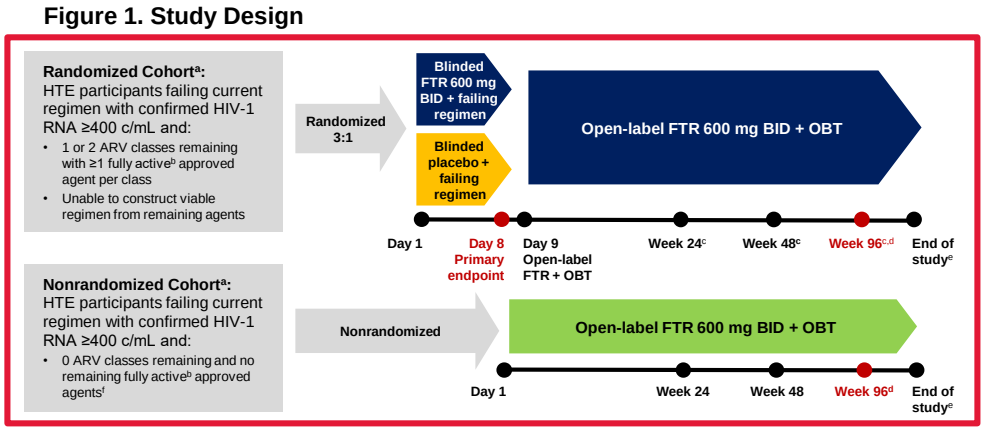
Introduction

- Fostemsavir (FTR), a prodrug metabolized to temsavir, is a first-in-class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into the host CD4+ T cell[1,2]
- Unique resistance profile with no in vitro cross-resistance to other antiretroviral (ARV) classes[3,4] and activity regardless of HIV-1 tropism[3-6]
- BRIGHTE (NCT02362503) is an ongoing phase III study evaluating FTR in heavily treatment-experienced (HTE) adults with multidrug-resistant HIV-1 who are unable to form a viable ARV regimen[7,8]
  - Primary endpoint achieved: superior efficacy vs placebo after 8 days of functional monotherapy
  - Clinically significant rates of virologic response were maintained between 24 and 48 weeks[8]
- Week 96 efficacy and safety results are presented here

Methods

- BRIGHTE is an ongoing phase III randomized, placebo-controlled, double-blind trial (Figure 1)

Figure 1. Study Design



OBT, optimized background therapy. [a]There were no screening TMR IC_{50} criteria. [b]No current or historical evidence of resistance and the participant is tolerant of, eligible for, and willing to take (in the case of enfuvirtide) the ARV. [c]Measured from the start of open-label FTR 600 mg BID + OBT. [d]Week 96 database lock August 14, 2018. [e]The study is expected to be conducted until an additional optional, rollover study or marketing approval is in place. [f]Use of investigational agents as part of OBT was permitted.

Results

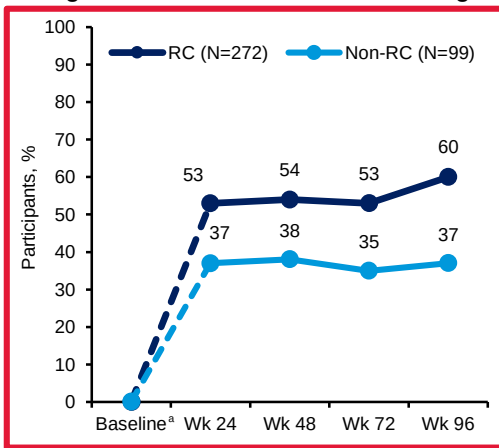
Demographics and Disposition

- Of the 371 participants who met eligibility criteria, 272 were assigned to the RC and 99 to the non-RC
- Overall demographics: median age, 49 years; 22% female; 22% black participants
- Median CD4+ T-cell count at baseline was 80 cells/µL (99 cells/µL and 41 cells/µL for the RC and non-RC, respectively), and 75% of participants had baseline CD4+ T-cell counts <200 cells/µL
- Through the Week 96 data cutoff, 59/272 (22%) and 38/99 (38%) participants discontinued from the RC and non-RC, respectively

Efficacy

- In the RC, rates of virologic response (HIV-1 RNA <40 c/mL) by Snapshot analysis increased from 53% (144/272) at Week 24 to 60% (163/272) at Week 96 (Figure 2)
- In the non-RC, rates remained consistent from Week 24 to Week 96 (37%, 37/99)

Figure 2. HIV-1 RNA <40 c/mL Through Week 96 Snapshot Analysis, ITT-E[a]



Week 96 outcome, n (%)	RC (N=272)	Non-RC (N=99)
HIV-1 RNA <40 c/mL	163 (60)	37 (37)
HIV-1 RNA ≥40 c/mL	81 (30)	43 (43)
Data in window not below threshold	33 (12)	15 (15)
D/C for lack of efficacy	10 (4)	3 (3)
D/C for other reason while not below threshold	17 (6)	6 (6)
Change in ART[b]	21 (8)	19 (19)
No virologic data	28 (10)	19 (19)
D/C study due to AE or death	15 (6)	14 (14)
D/C study for other reasons	8 (3)	4 (4)
Missing data during window	5 (2)	1 (1)

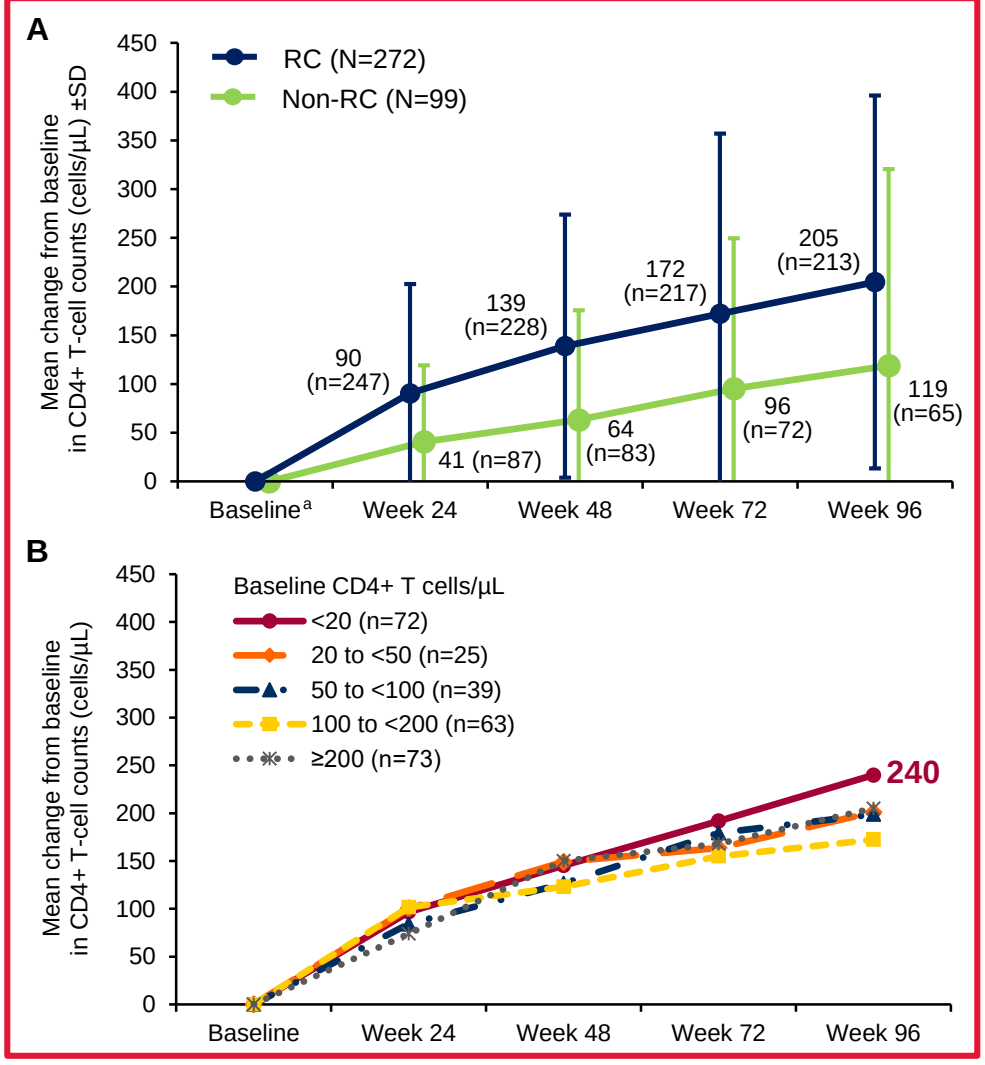
D/C, discontinued; non-RC, nonrandomized cohort; RC, randomized cohort. [a]Snapshot analysis did not include baseline. One participant had HIV-1 RNA <40 c/mL at baseline. [b]Changes in optimized background therapy for efficacy reasons were considered virologic failures in this analysis.

- CD4+ T-cell counts increased steadily over time, reaching a mean increase from baseline at Week 96 of 205 cells/µL (RC) and 119 cells/µL (non-RC; Figure 3)
- Of those in the RC with baseline CD4+ T-cell counts <50 cells/µL, 56% (40/71) increased to ≥200 cells/µL at Week 96

Safety

- Through Week 96, higher rates of serious adverse events (AEs), grade 3/4 AEs, and deaths were observed in the non-RC vs the RC (Table)
- Overall, 38% (140/371) of participants had a serious AE, 3% (12/371) had a drug-related SAE, and 7% (26/371) had an AE that led to discontinuation
- Most deaths were attributed to complications of advanced AIDS/acute infection (18/29; 62%)

Figure 3. Mean Change From Baseline in CD4+ T-Cell Count Through Week 96 by (A) RC and Non-RC and (B) Baseline CD4+ T-Cell Category in RC



Non-RC, nonrandomized cohort; RC, randomized cohort. [a]Mean baseline: RC = 153 cells/µL; non-RC = 99 cells/µL.

Table. Week 96 Safety Summary

Parameter, n (%)	RC (N=272)[a]	Non-RC (N=99)	Total (N=371)
Any event	249 (92)	98 (99)	347 (94)
Any grade 2-4 AE	216 (79)	87 (88)	303 (82)
Drug-related grade 2-4 AEs	57 (21)	22 (22)	79 (21)
Any grade 3-4 AE	78 (29)	49 (49)	127 (34)
Any SAE[b]	92 (34)	48 (48)	140 (38)
Drug-related SAE[c]	9 (3)	3 (3)	12 (3)
Any AE leading to discontinuation	14 (5)	12 (12)	26 (7)
Any CDC class C event	23 (8)	15 (15)	38 (10)
Death[d]	12 (4)	17 (17)	29 (8)

Non-RC, nonrandomized cohort; RC, randomized cohort. All safety data reflect cumulative results collected through the data cutoff date of August 14, 2018. [a]Includes participants randomized to the placebo group who received FTR 600 mg BID during the open-label phase; only data from initiation of open-label FTR dosing are presented. [b]The only SAEs occurring in ≥2% of participants were pneumonia (n=15), cellulitis (n=8), and acute kidney injury (n=6). [c]Drug-related SAEs (16 events in 12 participants) included: nephrolithiasis (n=2); immune reconstitution inflammatory syndrome (n=3); and one each of acute kidney injury, renal impairment, hyperglycemia, hyperkalemia, loss of consciousness, myocarditis, hepatocellular injury, rhabdomyolysis, fetal growth restriction, disorientation, and rash. [d]18/29 deaths were due to AIDS-related events or acute infections (one case was considered treatment-related: immune reconstitution inflammatory syndrome, related to recurrent atypical mycobacterial infection). 5/29 deaths occurred after the participant had discontinued from the study.

Conclusions

- Virologic response continued to improve over time despite continued attrition in this difficult-to-treat population
- Clinically significant and continuous improvements in CD4+ T-cell counts were observed through Week 96, including among those who were most immunocompromised at baseline
- FTR-containing regimens remained generally safe and well tolerated through Week 96 with no new safety signals and few AE-related discontinuations
- BRIGHTE results support continued development of FTR as an important treatment option for HTE people living with multidrug-resistant HIV-1

Acknowledgments: This study was funded by ViiV Healthcare. We would like to thank all of the BRIGHTE clinical trial participants and their families; Mark Krystal, Andrew Clark, Frank Mannino, Marcia Wang, Louise Garside, and Jill Slater (ViiV Healthcare and GlaxoSmithKline); and Carmeliza Santos (Monogram Biosciences). 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. Data included in this poster have been previously presented in full at the 10th IAS Conference on HIV Science; July 21-24, 2019; Mexico City, Mexico. Slides MOAB0102.

References: 1. Brown et al. *J Pharm Sci.* 2013;102:1742-1751. **2.** Langley et al. *Proteins.* 2015;83:331-350. **3.** Nowicka-Sans et al. *Antimicrob Agents Chemother.* 2012;56:3498-3507. **4.** Li et al. *Antimicrob Agents Chemother.* 2013;57:4172-4180. **5.** Ray et al. *J Acquir Immune Defic Syndr.* 2013;64:7-15. **6.** Zhou et al. *J Antimicrob Chemother.* 2014;69:573-581. **7.** Kozal et al. EACS 2017; Milan, Italy. Abstract PS8/5. **8.** Aberg et al. HIV Glasgow 2018; Glasgow, UK. Abstract O334A.

Australasian HIV&AIDS Conference; September 17-19, 2019; Perth, Australia