A Subgroup Analysis of the Week 96 Efficacy and Safety Results Evaluating Fostemsavir in Heavily Treatment-Experienced HIV-1 Infected Participants in the Phase 3 BRIGHTE Study: Results From The Randomized Cohort

MOPEB234

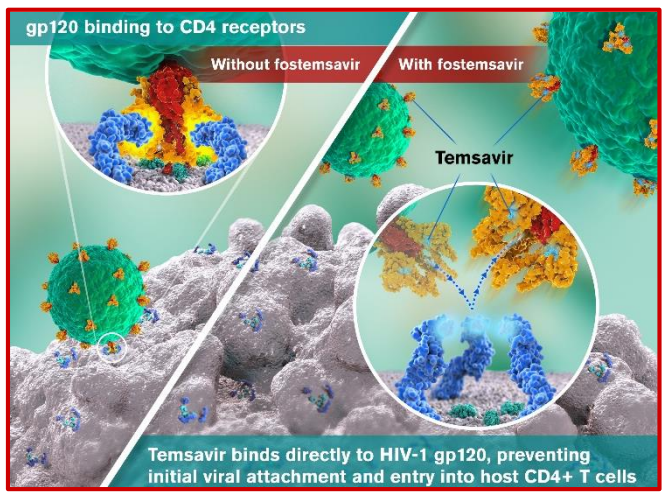
P. Ackerman[1], J. Aberg[2], J.-M. Molina[3], I. Cassetti[4], M. Kozal[5], S. Treviño-Pérez[6], A. Streinu-Cercel[7], G.H. Latiff[8], J. Lalezari[9], G. Pialoux[10], M. Gummel[11], S. Chabria[1], A. Pierce[12], C. Llamoso[1], M. Lataillade[1]

[1]ViiV Healthcare, Branford, United States, [2]Icahn School of Medicine at Mount Sinai, New York, United States, [3]Hospital Saint-Louis, Assistance Publique Hôpitaux de Paris, Paris, France, [4]Helios Salud, AIDS Care Center Infectious Diseases, Buenos Aires, Argentina, [5]Yale School of Medicine, New Haven, United States, [6]Mexico Centre for Clinical Research, Mexico City, Mexico, [7]National Institute of Infectious Diseases-Prof. Dr. Matei Balş, Bucharest, Romania, [8]Maxwell Centre, Durban, South Africa, [9]Quest Research, San Francisco, United States, [10]Hôpital Tenon, Assistance Publique Hôpitaux de Paris, Paris, France, [11]GlaxoSmithKline, Upper Providence, United States, [12]ViiV Healthcare, Research Triangle Park, United States

Introduction

- Fostemsavir (FTR) is a prodrug metabolized to temsavir (TMR), a first-in-class attachment inhibitor that binds to the HIV-1 envelope gp120, preventing attachment to CD4+ cell-surface receptors thereby preventing viral entry into and infection of host T-cells and other immune cells (**Figure 1**).[1,2]
- FTR has a unique resistance profile with no *in vitro* cross-resistance to other antiretroviral (ARV) classes[3,4] and is active regardless of HIV-1 tropism.[3–6]
- BRIGHTE is an ongoing Phase 3 study evaluating FTR in heavily treatment-experienced (HTE) adults with multi-drug–resistant HIV-1.
  - The primary endpoint of superior efficacy relative to placebo after 8 days of functional monotherapy was achieved.[7]
  - Virologic and immunologic response, as well as safety results, were favorable through Week 48.[8]
  - A subgroup analysis of virologic and immunologic outcomes at Week 48 in the Randomized Cohort was presented previously.[9]
- Overall efficacy and safety data at Week 96 will be presented in **Oral MOAB0102**.[10] Here we present subgroup analyses of virologic and immunologic response at Week 96 for the Randomized Cohort.

Figure 1. Mechanism of Action of Temsavir

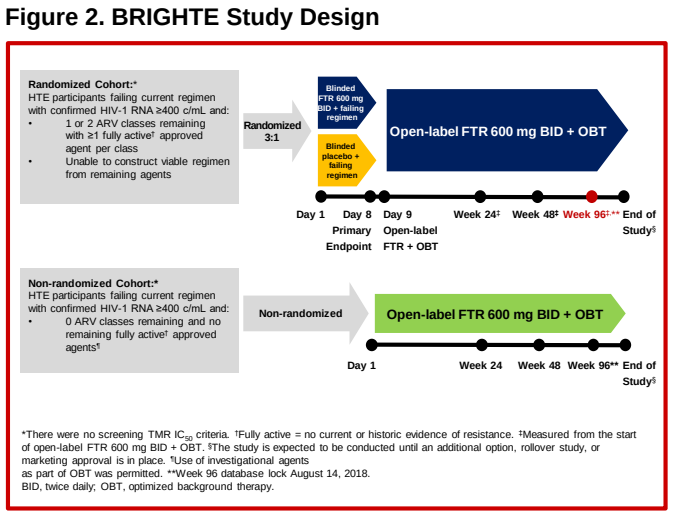


Methods

Eligibility Criteria, Study Design, and Statistical Methods

- HTE adults (≥18 years) with multi-drug–resistant HIV-1 failing their current ARV regimen (confirmed HIV-1 RNA ≥400 c/mL) and unable to form a viable alternative regimen from remaining fully active ARVs secondary to multi-drug resistance, prior intolerance, contraindication, or other safety concerns (**Figure 2**).
- No statistical test was performed between subgroups.

Figure 2. BRIGHTE Study Design



*There were no screening TMR IC_{50} criteria. †Fully active = no current or historic evidence of resistance. ‡Measured from the start of open-label FTR 600 mg BID + OBT. §The study is expected to be conducted until an additional option, rollover study, or marketing approval is in place. ¶Use of investigational agents as part of OBT was permitted. **Week 96 database lock August 14, 2018.
BID, twice daily; OBT, optimized background therapy.

Results

Baseline Demographics and Disease Characteristics

- Baseline demographics and disease characteristics for the Randomized Cohort are shown in **Table 1.**
  - 26% of participants were female, 22% were black, 40% were aged ≥50 years, and 85% had a history of AIDS*.
  - 67% of participants had been treated for HIV for a period of >15 years.
  - Median HIV-1 RNA $\log_{10}$ c/mL was 4.7, and 73% of participants had a CD4+ T-cell count <200 cells/µL (26% <20 cells/µL).
  - 52% of participants had one fully active ARV (FAA) in the initial OBT; 42% had two.

*AIDS history recorded if a participant has nadir CD4+ count <200 cells/µL, or prior history of AIDS-defining illness.

Table 1. Baseline Demographics and Disease Characteristics

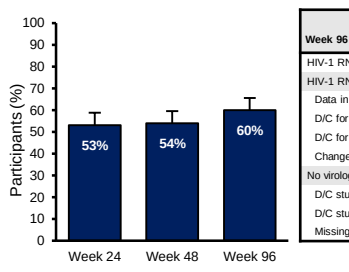
Parameter	Randomized Cohort (N=272)
Age, years	
Median (range)	48 (18–73)
≥50 years, n (%)	110 (40)
Sex, n (%)	
Female	72 (26)
Male	200 (74)
Race, n (%)	
White	185 (68)
Black/African-American	60 (22)
Median HIV-1 RNA $\log_{10}$ c/mL (range)	4.7 (1.6–6.9)
HIV-1 RNA c/mL, n (%)	
<400	21 (8)
400 to <1000	10 (4)
1000 to <100,000	161 (59)
100,000 to <500,000	59 (22)
≥500,000	21 (8)
Median CD4+ T-cells/µL (range)	99.5 (0–1160)
CD4+ T-cells/µL, n (%)	
<20	72 (26)
20 to <50	25 (9)
50 to <200	102 (38)
200 to <500	58 (21)
≥500	15 (6)
FAA in initial OBT, n (%)	
0*	16 (6)
1	142 (52)
2	114 (42)
Region, n (%)	
North America	108 (40)
South America	105 (39)
Europe	51 (19)
Rest of the World	8 (3)

*5 participants discontinued from the study during the double-blind period; 6 participants had at least 1 FAA at screening but had no FAAs in their initial OBT; 5 participants with no FAAs at screening, were assigned to the Randomized Cohort in error and were captured as a protocol deviation.

Virologic Response Overall and by Subgroups

- By Snapshot analysis, rates of HIV-1 RNA <40 c/mL increased from Week 24 to Week 96 (**Figure 3**).

Figure 3. HIV-1 RNA <40 c/mL Through Week 96; ITT-E Snapshot Analysis

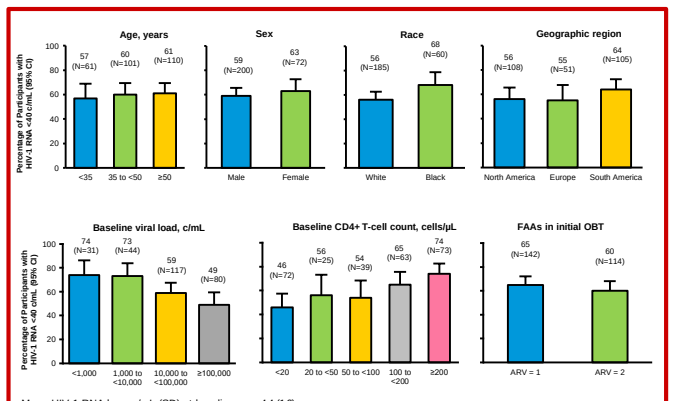


Week 96 outcome, n (%)	Randomized Cohort (N=272)
HIV-1 RNA <40 copies/mL	163 (60%)
HIV-1 RNA ≥40 copies/mL	81 (30%)
Data in window not below threshold	33 (12%)
D/C for lack of efficacy	10 (4%)
D/C for other reason while not below threshold	17 (6%)
Change in ART*	21 (8%)
No virologic data	28 (10%)
D/C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

*Change in OBT was counted as virologic failure in this analysis.
AE, adverse event; ART, antiretroviral therapy; D/C, discontinued; ITT-E, intent-to-treat exposed.

- At Week 96, rates of HIV-1 RNA <40 c/mL were similar across subgroups of age, sex, race, geographic region, and number of FAAs in initial OBT (**Figure 4**).
- At Week 96, rates of HIV-1 RNA <40 c/mL were lowest for those with baseline viral load >100,000 c/mL and those with baseline CD4+ cell counts <20 cells/µL; however, these same subgroups had the largest increase in rates over time. For participants with baseline viral load >100,000 c/mL, the proportion with HIV-1 RNA <40 c/mL at Week 48 was 28/80 (35%), increasing to 39/80 (49%) at Week 96. For participants with baseline CD4+ T-cell counts <20 cells/µL, the proportion with HIV-1 RNA <40 c/mL at Week 48 was 25/72 (35%), increasing to 33/72 (46%) at Week 96.

Figure 4. Snapshot Analysis of Virologic Response at Week 96, by Subgroups; ITT-E Population

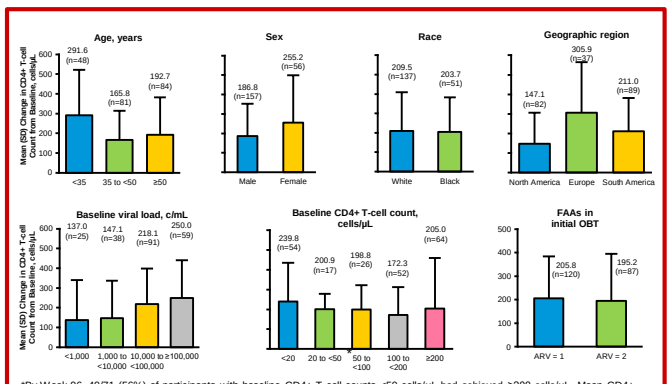


Mean HIV-1 RNA $\log_{10}$ c/mL (SD) at baseline was 4.4 (1.0)
The data presented in the figure are based on ad hoc analyses.
The following subgroups are excluded from this figure: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Mestizo, Mixed race, Hispanic, rest of world, 0 FAA.
SD, standard deviation.

Immunologic Responses Overall and by Subgroup

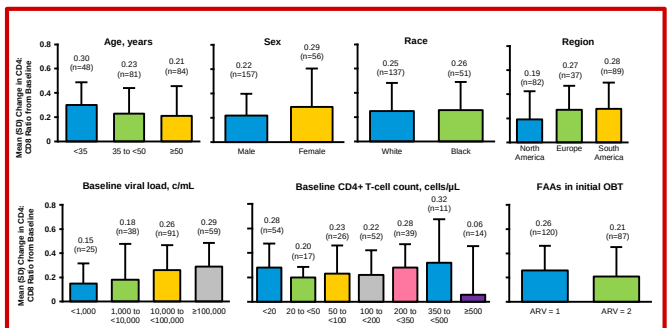
- Overall, the mean CD4 T-cell counts improved from baseline by 204.7 cells/µL at Week 96.
  - At Week 96, CD4+ T-cell response was similar across subgroups of age, sex, race, and FAA in initial OBT (**Figure 5**).
  - Increase in mean CD4+ T-cell count among those with baseline CD4+ <20 cells/µL was comparable to those with higher CD4+ counts at baseline. (**Figure 5**).
- Overall, mean (SD) CD4:CD8 ratio increased from 0.20 (0.24) at baseline to 0.44 (0.29) at Week 96.
  - Increase in CD4:CD8 ratio was observed across all subgroups (**Figure 6**).

Figure 5. Mean CD4+ T cell increase at Week 96, by Subgroups



*By Week 96, 40/71 (56%) of participants with baseline CD4+ T-cell counts <50 cells/µL had achieved ≥200 cells/µL. Mean CD4+ T-cells/µL (SD) at baseline was 152.5 (182.0). The following subgroups are excluded from this figure: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Mestizo, Mixed race, Hispanic, rest of world, 0 FAA.

Figure 6. CD4:CD8 ratio increase at Week 96, by Subgroups



The data presented in the figure are based on ad hoc analyses. The following subgroups are excluded from this figure: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Mestizo, Mixed race, Hispanic, rest of world, 0 FAA.

Week 96 Safety

- **Table 2** shows a safety summary by baseline CD4 categories.
  - Serious AEs (SAEs) and deaths occurred more frequently in the subgroup of participants with the lowest baseline CD4+ T-cell counts.
  - No clinically relevant differences were observed on the safety profile of FTR when assessed by sex, age, or racial subgroups.

Table 2. Week 96 Safety Summary by Subgroup

Parameter, n (%)	Randomized Cohort Baseline CD4+ T-cell count, cells/µL			
	<20 (n=72)	20 to <200 (n=127)	≥200 (n=73)	Total (N=272*)
Any AE	67 (93)	115 (91)	67 (92)	249 (92)
Grade 2–4 related AEs	18 (25)	19 (15)	20 (27)	57 (21)
AEs leading to discontinuation	4 (6)	5 (4)	5 (7)	14 (5)
SAEs	33 (46)	39 (31)	20 (27)	92 (34)
Related SAEs	3 (4)	1 (1)	5 (7)	9 (3)
Deaths§	6† (8)	4 (3)	2 (3)	12 (4)

*Includes all safety data from initiation of FTR dosing through Week 96 data cut-off. †1 death (immune reconstitution inflammatory syndrome; mycobacterial infection) was related to study treatment.
‡The median baseline CD4+ T-cell count for participants who died was 20.5 cells/µL.
The data presented in the table are based on ad hoc analyses.

Conclusions

- Virologic response in the ITT population continued to improve over time, including amongst participants with high baseline viral load and low baseline CD4+ count.
- Compared with their counterparts, comparable virologic outcomes were observed in older and Black participants, who are disproportionately represented within the HTE population.[11]
- Continued clinically meaningful improvement in CD4+ T-cell counts was seen across all subgroups, including those most immune suppressed at baseline.
- While FTR-containing regimens were well tolerated through Week 96, severe safety events (i.e. SAEs and deaths) were more frequent in the most immune compromised participants with the lowest baseline CD4+ T-cell counts.
- These results support the continued development of FTR as an important therapeutic option for a broad cross-section of the HTE population, including those who are most immune suppressed, have high baseline viral load, are older, female, and/or of Black race.

Acknowledgments

We would like to thank all of the BRIGHTE clinical trial participants and their families and all BRIGHTE investigators.

ViiV Healthcare and GSK personnel: Mark Krystal, Andrew Clark, Frank Mannino, Marcia Wang, Louise Garside, and Jill Slater.

Professional medical writing and editorial assistance was provided by Martha Hoque at Articulate Science and 3D graphics were developed by John Wong at Synaptik Digital, both funded by ViiV Healthcare.

References

1. Brown J, et al. *J Pharm Sci.* 2013;102(6):1742–1751.
2. Langley DR, et al. *Proteins*. 2015;83:331–350.
3. Nowicka-Sans B, et al. *Antimicrob Agents Chemother*. 2012;56(7):3498–3507.
4. Li Z, et al. *Antimicrob Agents Chemother*. 2013;57(9):4172–4180.
5. Ray N, et al. *J Acquir Immune Defic Syndr*. 2013;64(1):7–15.
6. Zhou N, et al. *J Antimicrob Chemother*. 2014;69(3):573–581.
7. Kozal M, et al. Abstract PS8/5. Presented at: *16th European AIDS Conference*; October 25–27, 2017; Milan, Italy.
8. Aberg J, et al. Poster 334A. Presented at: *HIV Glasgow Congress; October 28–31, 2018; Glasgow, United Kingdom.*
9. Molina J-M, et al. Poster O334B. Presented at: *HIV Glasgow Congress; October 28–31, 2018; Glasgow, United Kingdom.*
10. Lataillade M, et al. Oral presentation MOAB0102. Presented at: *IAS Congress; July 21–24, 2019. Mexico City, Mexico.*
11. Hsu R, et al. *Abstract #A-899-0141-05163*. Presented at: *AIDS Conference; July 23–27, 2018. Amsterdam, the Netherlands.*