Phase 3 Study of Fostemsavir in Heavily Treatment-Experienced HIV-1-Infected Participants: BRIGHTE Week 48 Subgroup Analysis in Randomised Cohort Participants

O334B

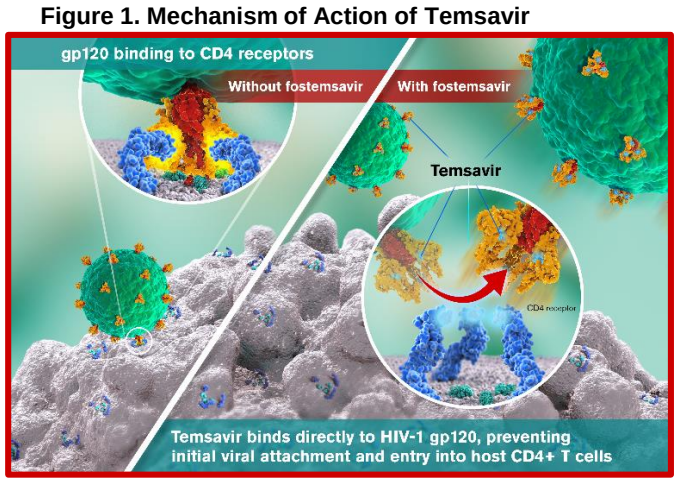
J.-M. Molina,[1] J. Aberg,[2] I. Cassetti,[3] M. Kozal,[4] G. Latiff,[5] J. Lalezari,[6] G. Pialoux,[7] A. Streinu-Cercel,[8] M. Gummel,[9] A. Pierce,[10] P. Ackerman,[11] C. Llamoso,[11] M. Lataillade[11]

[1]Hôpital Saint-Louis, APHP and University of Paris Diderot Paris, Infectious Diseases, Paris, France; [2]Icahn School of Medicine at Mount Sinai, Infectious Diseases, New York, NY, USA; [3]Helios Salud, Ambulatory AIDS Care Center, Infectious Diseases, Buenos Aires, Argentina; [4]Yale University School of Medicine, Infectious Diseases, New Haven, CT, USA; [5]Maxwell Centre, Infectious Diseases, Durban, South Africa; [6]Quest Research, Internal Medicine, San Francisco, CA, USA; [7]Hôpital Tenon, Infectious Diseases, Paris, France; [8]Carol Davila University of Medicine and Pharmacy, Infectious Diseases, Bucharest, Romania; [9]GlaxoSmithKline Statistics, Upper Providence, Philadelphia, PA, USA; [10]ViiV Healthcare Clinical Development, Research Triangle Park, NC, USA; [11]ViiV Healthcare Clinical Development Branford, CT, USA

Introduction

- Fostemsavir (FTR, previously called BMS-663068/ GSK 3684934) is a first-in-class attachment inhibitor prodrug that is metabolised to its active moiety, temsavir (TMR)[1] which binds to the viral envelope glycoprotein 120 (gp120), locking it in a conformational state that inhibits initial interaction between the virus and host immune cells. This prevents viral attachment and entry into the host CD4+ T-cells[2] (**Figure 1**).
- FTR is being evaluated in heavily treatment-experienced (HTE), HIV-1-infected participants.
- 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]
- At the Week 24 interim analysis for the ongoing Phase 3 BRIGHTE study (formerly 205888/AI438-047), FTR demonstrated :[7]
  - Superior efficacy relative to placebo (0.8 $\log_{10}$ c/mL decrease for FTR vs 0.2 $\log_{10}$ c/mL for placebo; treatment difference = 0.625, *P*<0.0001) after 8 days of functional monotherapy (Primary Endpoint).
  - A median decrease in HIV-1 RNA of 1.0 $\log_{10}$ c/mL in participants with baseline HIV-1 RNA >1,000 c/mL in the Randomised Cohort at Day 8.
  - Virologic suppression (HIV-1 RNA <40 c/mL) in 53% of participants and mean increase in CD4+ T-cell count by 90 cells/µL from baseline at Week 24 in the Randomised Cohort.
- Here we present a pre-specified subgroup analysis of virologic efficacy and immunologic response at Week 48 for the Randomised Cohort. See **Poster O334A** for Week 48 safety and efficacy.

Figure 1. Mechanism of Action of Temsavir



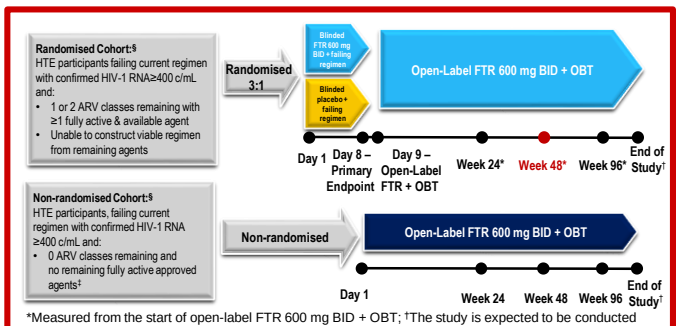
Methods

- The following subgroup analyses are presented here:
  - Virologic response by proportion of participants achieving <40 c/mL at Week 48.
  - Immunologic response by mean change from baseline in CD4+ T-cell count at Week 48.
- Point estimates and associated 95% confidence intervals (CI) are provided by subgroup and no statistical test was performed between subgroups.

Eligibility Criteria and Study Design

- HTE participants failing their current regimen (confirmed HIV-1 RNA ≥400 c/mL) and unable to form a viable regimen with remaining fully active ARVs (FAA) were eligible for this study (**Figure 2**).
  - Participants with 1–2 remaining ARV classes (Randomised Cohort) were randomised 3:1 to blinded FTR 600 mg or placebo twice daily (BID) + current failing regimen for 8 days, followed by open-label FTR + OBT.
  - Participants with 0 remaining approved FAAs (Non-randomised Cohort) started open-label FTR + OBT on Day 1.

Figure 2. BRIGHTE Study Design



*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; §There were no screening FTR IC_{50}criteria.

Results

Demographics and Baseline Disease Characteristics

- Demographics and baseline disease characteristics were well balanced between the placebo and FTR groups (**Table 1**).
- Sixty-seven percent of participants had been treated for HIV-1 infection for >15 years, 85% had a history of AIDS at entry and 73% had a CD4+ T-cell count of <200 cells/µL at baseline.
- Eighty-three percent (226/272) of participants were exposed to ≥5 ARV regimens, which included prior INSTI (75%) and PI (94%) exposure.
- Participant disposition through the Week 48 data lock is presented in **Poster O334A.**

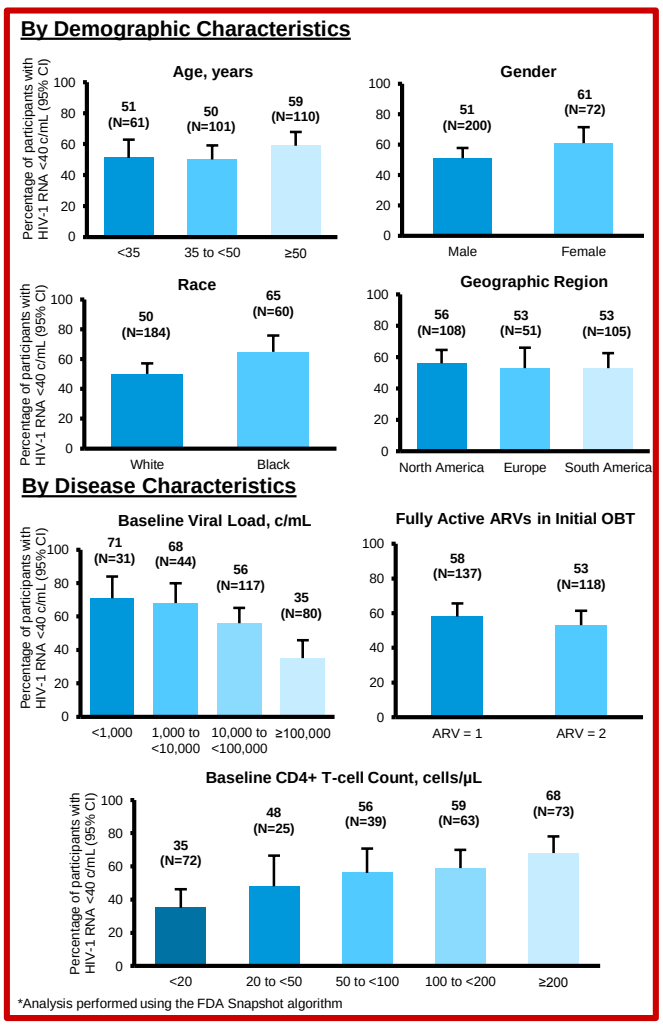
Table 1. Demographics and Baseline Disease Characteristics

Parameter	Placebo BID (N=69)	FTR 600 mg BID (N=203)	Total Treated Participants, Randomised Cohort (N=272)
Age years, median (range)	45 (19–66)	48 (18–73)	48 (18–73)
<50 years, n (%)	46 (67)	116 (57)	162 (60)
Gender, n (%)			
Male	57 (83)	143 (70)	200 (74)
Race, n (%)			
White	47 (68)	137 (67)	184 (68)
Black/African American	18 (26)	42 (21)	60 (22)
HIV-1 RNA $\log_{10}$ c/mL, median (IQR)	4.5 (3.6–5.2)	4.7 (4.0–5.1)	4.7 (3.9–5.1)
HIV-1 RNA c/mL, n (%)			
<400	7 (10)	14 (7)	21 (8)
400 to <1000	3 (4)	7 (3)	10 (4)
1000 to <100,000	35 (51)	126 (62)	161 (59)
≥100,000	24 (35)	56 (28)	80 (29)
CD4+ T-cells/µL, median (IQR)	100 (23–244)	99 (15–203)	99.5 (15–207)
CD4+ T-cells/µL, n (%)			
<20	17 (25)	55 (27)	72 (26)
20 to <50	6 (9)	19 (9)	25 (9)
50 to <200	26 (38)	76 (37)	102 (38)
200 to <500	16 (23)	42 (21)	58 (21)
≥500	4 (6)	11 (5)	15 (6)
No. of fully-active and available ARV agents in initial OBT, n (%)			
ARVs = 0	1 (1)	16 (8)	17 (6)
ARVs = 1	31 (45)	106 (52)	137 (50)
ARVs = 2	37 (54)	81 (40)	118 (43)

Snapshot Analysis of Virologic Response Rate by Subgroups at Week 48 (Figure 3)

- Virologic response was similar across subgroups of age, gender, race, region and FAA in initial OBT with numerically higher response rates for participants who were ≥50 years old, female, Black, or had 1 FAA in their initial OBT.

Figure 3. Snapshot* Analysis of Virologic Response (HIV-1 RNA <40 c/mL) at Week 48, by Subgroups



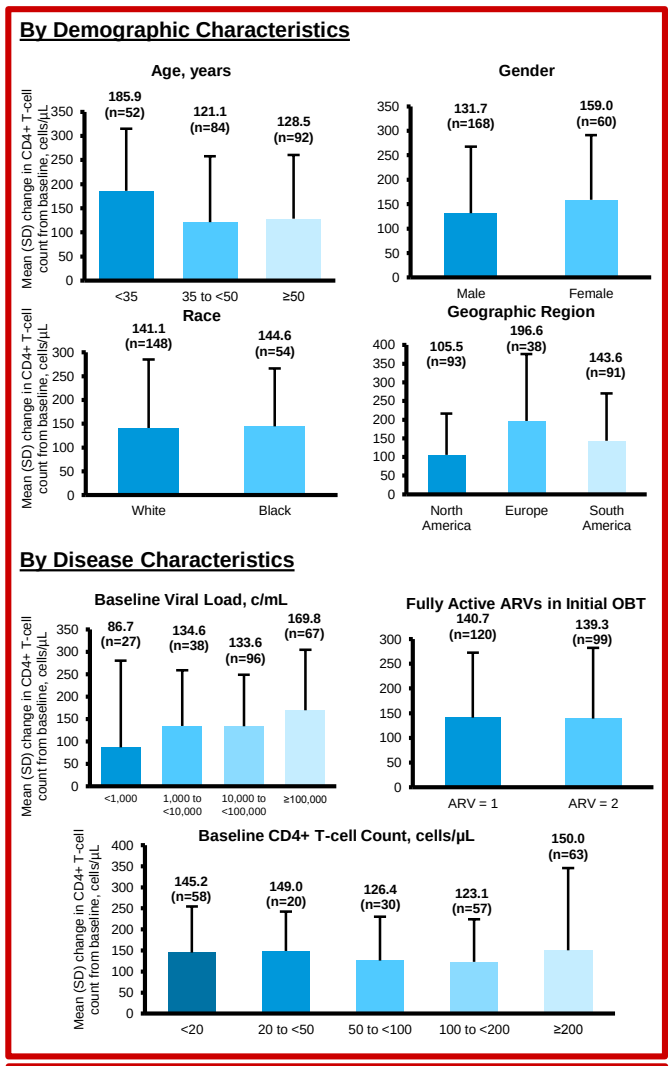
*Analysis performed using the FDA Snapshot algorithm

- Virologic response rates were lower for participants with either low baseline CD4+ T-cell count of <20 cell/µL (35%) and/or with a baseline viral load of ≥100,000 c/mL (35%).

Mean Change From Baseline in CD4+ T-cell Count by Subgroups at Week 48 (Figure 4)

- Increase in mean CD4+ T-cell count at Week 48 was similar across subgroups and regardless of baseline CD4+ T-cell count category, including those with a baseline CD4+ T-cell count of <20 cells/µL.

Figure 4. Mean Change From Baseline in CD4+ T-cell Count at Week 48, by Subgroups



Conclusions

- Treatment with FTR + OBT demonstrated durability of virologic response across most key subgroups, particularly in Black participants and older participants. These populations are generally disproportionately represented within the HTE population.[8]
- Virologic response was lower for those with high baseline viral load (≥100,000 c/mL) and low baseline CD4+ T-cell count (<20 cells/µL); two well-recognised determinants of virologic response.
- Treatment with FTR + OBT provided notable and clinically relevant improvement in CD4+ T-cell counts for all subgroups, including participants with very low baseline CD4+ T-cell counts (<20 cells/µL).

Acknowledgements

- We would like to thank all of the BRIGHTE clinical trial participants and their families and all BRIGHTE investigators.
- ViiV Healthcare: S Chabria, A Clark, M Gartland, C Henegar, K Moore, J Plummer, J Slater, C Trezza. GSK: S Anderson, K Barker, A Bonwick, K Davis, M Drapeau, F Du, M Fairfax, L Garvey, M Gunshenan, C Ham, J Lim, M Magee, F Mannino, B McCaughey, B Shepherd, M Wang, K Zhai. PPD: M Benoffi, A Boswell, A-C Daussat, K D'Orsi, S Edwards, M Enslen, A Escheverria, C Fernando de Oliveria, S Fuentes, S Greenawald, E Gould, S Gunturu, J King, T Jackson, H Jones, B Scafe, A Sousa, W Teets, P Vemula. Paraxel: B Gilbert, S Nair, M Padmanabhan, B Wellbourn
- Professional medical writing and editorial assistance was provided by Nicole Ogbonnaya at Articulate Science and 3D graphics were developed by John Wong at Nucleus Central, both funded by ViiVHealthcare.

References

1. Brown J, et al. *J Pharm Sci*. 2013;102(6):1742-1751; 2. Langley DR, et al. *Proteins*. 2015; 83:331-50; 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. Hsu R, et al. Poster THPEB044. Presented at: *22nd International AIDS Conference*; July 23–27, 2018.