Week 48 Safety and Efficacy of the HIV-1 Attachment Inhibitor Prodrug Fostemsavir in Heavily Treatment-Experienced Participants (BRIGHTE Study)

O334A

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Introduction

- Fostemsavir (FTR, previously called BMS-663068/GSK3684934) 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] (TMR mode of action is shown in **Poster O334B**).
- 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 in the Randomised Cohort and 37% in the Non-randomised Cohort (81% of whom had FTR as the only fully active ARV) at Week 24.
- Here we present Week 48 efficacy and safety analysis from the ongoing Phase 3 BRIGHTE study. Efficacy by subgroups is presented in **Poster O334B**.

Eligibility Criteria and Study Design

- All BRIGHTE participants were HTE, failing their current regimen (confirmed HIV-1 RNA ≥400 c/mL) and unable to form a viable regimen with remaining fully active ARVs (FAAs).
- BRIGHTE study design shown in **Poster O334B**.
  - 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 and were permitted to us other investigational ARV therapies in their OBT.

Results

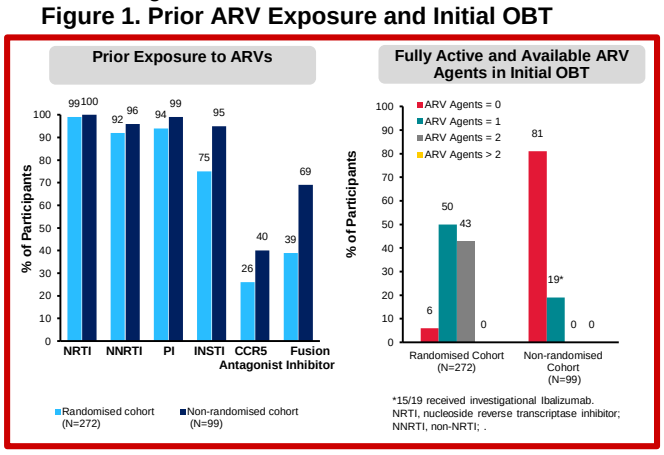
Demographics and Baseline Disease Characteristics

- Relative to the Randomised Cohort, a greater proportion of participants in the Non-randomised Cohort had a CD4+ T-cell count <20 cells/µL (**Table 1**).
- Overall, 71% (262/371) of participants were treated for HIV-1 infection for>15 years, 85% (316/371) had prior experience with ≥5 ARV regimens (80% and 96% were INSTI and PI-experienced, respectively), and 86% (320/371) had a history of AIDS (**Figure 1**).
- In the Randomised Cohort, 50% (137/272) and 43% had 1 or 2 FAAs in their initial OBT, respectively. Of the 99 Non-randomized participants, 81 had no approved FAAs or investigational ARVs in their initial OBT and 15 had investigational ibalizumab in their initial OBT **(Figure 1)**.

Study Disposition Through Week 48

- Through Week 48, 57/272 (21%, Randomised) and 32/99 (32%, Non-randomised) participants discontinued early; six participants (FTR n=5; placebo n=1) discontinued during the double-blind period. Primary reasons for discontinuation through Week 48 are shown in **Figure 2.**

Figure 1. Prior ARV Exposure and Initial OBT



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 Sharmin Bovill at Articulate Science, funded by ViiV Healthcare.

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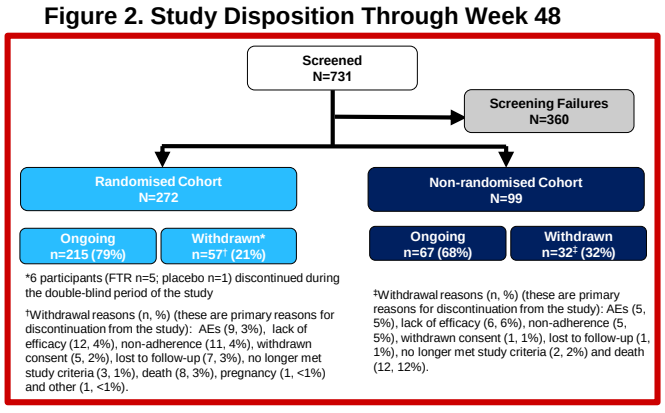
Table 1. Baseline Characteristics

Parameter	Randomised Cohort: Placebo BID (N=69)	Randomised Cohort: FTR 600 mg BID (N=203)	Non-randomised Cohort: FTR 600 mg BID (N=99)	Total Treated Participants (N=371)
Age years, median (range)	45 (19–66)	48 (18–73)	50 (17–72)	49 (17–73)
<50 years, n (%)	46 (67)	116 (57)	44 (44)	206 (56)
Sex, n (%)				
Male	57 (83)	143 (70)	89 (90)	289 (78)
Race, n (%)				
White	47 (68)	137 (67)	73 (74)	257 (69)
Black/African American	18 (26)	42 (21)	23 (23)	83 (22)
HIV-1 RNA $\log_{10}$ c/mL, median (IQR)	4.5 (3.6–5.2)	4.7 (4.0–5.1)	4.3 (3.6–4.8)	4.6 (3.9–5.33
HIV-1 RNA c/mL, n (%)				
<400	7 (10)	14 (7)	5 (5)	26 (7)
400 to <1000	3 (4)	7 (3)	4 (4)	14 (4)
1000 to <100,000	35 (51)	126 (62)	75 (76)	236 (64)
≥100,000	24 (35)	56 (28)	15 (15)	95 (26)
CD4+ T-cells/µL, median (IQR)	100 (23–244)	99 (15–203)	41 (6–161)	80 (11–202)
CD4+ T-cells/µL, n (%)				
<20	17 (25)	55 (27)	40 (40)	112 (30)
20 to <50	6 (9)	19 (9)	14 (14)	39 (11)
50 to <200	26 (38)	76 (37)	25 (25)	127 (34)
200 to <500	16 (23)	42 (21)	18 (18)	76 (20)
≥500	4 (6)	11 (5)	2 (2)	17 (5)

Figure 2. Study Disposition Through Week 48

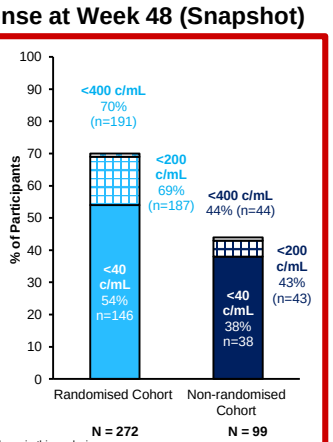


Virologic Response at Week 48

- Virologic response at Week 48 using the FDA Snapshot algorithm, is shown in **Figure 3.** Response rates were maintained from Week 24 despite ongoing attrition.
- Virologic response through Week 48 by observed analysis, is shown in **Figure 4.**

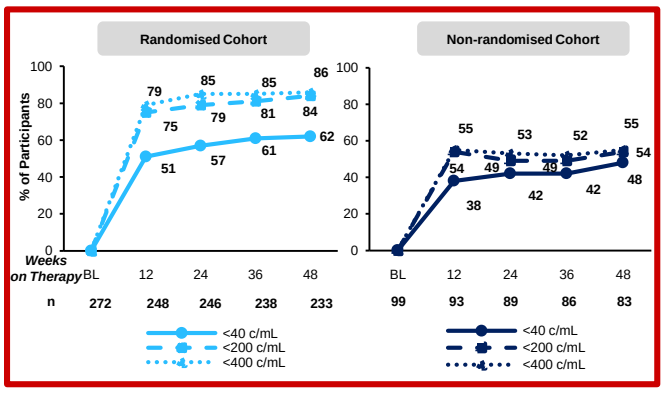
Figure 3. Virologic Response at Week 48 (Snapshot)

Outcome	Randomised Cohort (N=272)	Non-randomised Cohort (N=99)
Virologic Success (<40 c/mL), n (%)	146 (54)	38 (38)
Virologic Failure, (≥40 c/mL), n (%)	104 (38)	52 (53)
Data in window not below threshold	72 (26)	33 (33)
D/C for lack of efficacy	6 (2)	2 (2)
D/C for other reason while not below threshold	9 (3)	3 (3)
Change in OBT*	17 (6)	14 (14)
No Virologic Data	22 (8)	9 (9)
D/C study due to AE or Death	15 (6)	8 (8)
D/C study for Other Reasons	5 (2)	1 (1)
Missing data during window but on study	2 (<1)	0



*Change in OBT for efficacy reasons were considered virologic failures in this analysis.
D/C, discontinued.

Figure 4. Virologic Response through Week 48 (Observed)



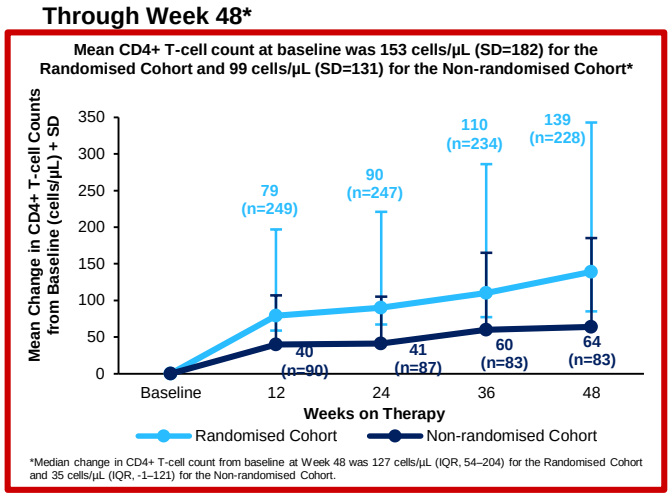
Change in CD4+ T-cell Counts

- Mean CD4+ T-cell counts continued to increase for both cohorts over time through Week 48 (**Figure 5**).

Week 48 Safety

- FTR was well tolerated through Week 48 with few discontinuations due to AEs (**Tables 2 and 3**).
- 92% (343/371) of participants had ≥1 AEs; most were Grade 1–2 in intensity and resolved without interruption of study drug.
- 35% of participants had ≥1 serious AE (SAE); most were related to infections.

Figure 5. CD4+ T-cell Counts Change from Baseline Through Week 48*



*Median change in CD4+ T-cell count from baseline at Week 48 was 127 cells/µL (IQR, 54–204) for the Randomised Cohort and 35 cells/µL (IQR, -1–121) for the Non-randomised Cohort.

- Compared with the Randomised Cohort, the Non-randomised Cohort experienced higher rates of SAEs (31% vs 44%), Grade 3–4 AEs (26% vs 47%) and deaths (4% vs 14%) (**Table 2**).
- Consistent with the results from Week 24, the most common Grade 2–4 treatment-related AEs were nausea (4%), diarrhea (3%) and headache (2%) (**Table 4**).

Table 2. Week 48* Safety Summary

Parameter, n (%)	Randomised Cohort (N=272)	Non-randomised Cohort (N=99)	Total Treated Participants (N=371)
Any event	**247 (91)**	**96 (97)**	**343 (92)**
Grade 3–4 AEs	70 (26)	47 (47)	117 (32)
Grade 2–4 related AEs	55 (20)	22 (22)	77 (21)
AEs leading to discontinuation	14 (5)	13 (13)	27 (7)
SAEs†	85 (31)	44 (44)	129 (35)
Related SAEs	7 (3)	3 (3)	10 (3)
Deaths‡	11 (4)	14 (14)	25 (7)

*All safety data reflect cumulative results collected through the data cutoff date of 4 March 2018. All treated participants had the opportunity to complete the Week 72 study assessment prior to the current data lock; †The majority (15%) of SAEs were from the infections/infestations system organ class; ‡17/25 deaths were due to AIDS-related events, immune reconstitution inflammatory syndrome (IRIS), or acute infection; estimated median baseline CD4 T-cell count among participants who died was 7 cells/µL.

Table 3. AEs Leading to Discontinuation*

Parameter, n (%)	Randomised Cohort (N=272)	Non-randomised Cohort (N=99)	Total Treated Participants (N= 371)
Any Event	**14 (5)**	**13 (13)**	**27 (7)**
Infections / Infestations†	4 (1)	5 (5)	9 (2)
Investigations‡	2 (<1)	2 (2)	4 (1)
QTcF Prolongation‡	2 (<1)	1 (1)	3 (<1)
Gastrointestinal disorders	2 (<1)	2 (2)	4 (1)
Abdominal pain	2 (<1)	0	2 (<1)
General disorders	1 (<1)	3 (3)	4 (1)
Non-cardiac chest pain	1 (<1)	1 (1)	2 (<1)
Neoplasms§	1 (<1)	3 (3)	4 (1)
Hepatobiliary disorders	1 (<1)	2 (2)	3 (<1)
Hepatic failure	0	2 (2)	2 (<1)
Skin and subcutaneous disorders	2 (<1)	0	2 (<1)

*AEs leading to discontinuation in ≥2 participants are reported; †Infections included: CMV colitis, Hepatitis B reactivation, viral meningoencephalitis, mycobacterial infection, pneumonia, sepsis, and sinusitis; all reported in 1 participant each; ‡Through the Week 48 data lock, 7 participants were discontinued from study due to confirmed QTcF prolongation beyond protocol-defined thresholds; not all 7 events were reported as AEs; §Kaposi sarcoma, squamous cell carcinoma, Hodgkin Disease and lymphoma were reported in 1 participant each.

Table 4. Grade 2–4 Related AEs*

Parameter, n (%)	Randomised Cohort (N=272)	Non-randomised Cohort (N=99)	Total Treated Participants (N= 371)
Any Event	**55 (20)**	**22 (22)**	**77 (21)**
Nausea	10 (4)	5 (5)	15 (4)
Diarrhea	7 (3)	3 (3)	10 (3)
Headache	7 (3)	1 (1)	8 (2)
Immune reconstitution inflammatory syndrome	5 (2)	1 (1)	6 (2)
Vomiting	4 (1)	2 (2)	6 (2)
Fatigue	3 (1)	2 (2)	5 (1)
Asthenia	2 (<1)	2 (2)	4 (1)

*Grade 2–4 related AEs occurring in ≥2% of participants in either arm.

Conclusions

- Rates of virologic suppression were maintained from Week 24 through Week 48, despite continued attrition in this active trial.
- There were continued, clinically meaningful, improvements in CD4+ T-cell count through Week 48, including among those who were most immune-compromised at baseline.
- FTR-containing regimens were well tolerated through Week 48 with few discontinuations due to AEs
  - Majority of significant safety events (Grade 3–4 AEs/SAEs/deaths) were related to infections or progression of AIDS and occurred in participants in the Non-randomised Cohort, who had lower baseline CD4 counts and no approved FAAs to pair with FTR at study start.
- Week 48 results from the ongoing BRIGHTE study support further development of FTR as a therapeutic option for HIV-1-infected HTE participants with multi-drug resistance and few remaining active therapies.