Long-Term Safety and Efficacy of Fostemsavir in Treatment-Experienced Participants Living With HIV-1

Poster 483

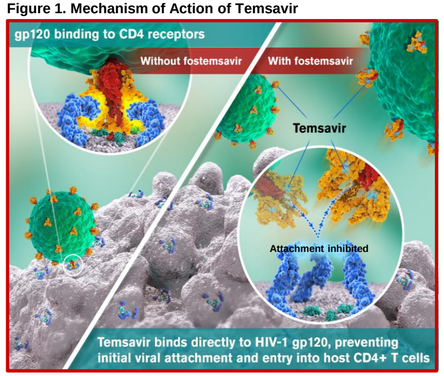
M. Thompson,[1] F. Mendo Urbina,[2] G. Latiff,[3] S. Treviño-Pérez,[4] E. DeJesus,[5] N. Zakharova,[6] M. Martins,[7] J. Bogner,[8] L. Ye,[9] A. Pierce,[10] S. Chabria,[11] P. Ackerman,[11] C. Llamoso,[11] M. Lataillade[11]

[1]AIDS Research Consortium of Atlanta, Atlanta, GA, USA; [2]Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru; [3]KwaZulu-Natal Research Institute for TB and HIV, Durban, South Africa; [4]Mexico Centre for Clinical Research, Mexico City, Mexico; [5]Orlando Clinical Research Center, Orlando, FL, USA; [6]Center of AIDS and Infectious Diseases Prevention and Treatment, St. Petersburg, Russian Federation; [7]Instituto Oulton, Córdoba, Argentina; [8]Internal Medicine IV, University Hospital of Munich, Munich, Germany; [9]GlaxoSmithKline, Collegeville, PA, USA; [10]ViiV Healthcare, Research Triangle Park, NC, USA; [11]ViiV Healthcare, Branford, CT, USA

Introduction

- Fostemsavir (FTR/GSK3684934, previously called BMS-663068) is a prodrug metabolized to temsavir (TMR), a first-in-class attachment inhibitor[1] (**Figure 1**).
- TMR binds directly to the viral envelope gp120, close to the CD4+ binding sites, locking gp120 into a closed state that prohibits the conformational change necessary for initial interaction between the virus and CD4 cell-surface receptors, thereby preventing viral attachment, and subsequent entry into and infection of host T-cells and other immune cells.[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]
- Study 205889 (AI438011, NCT01384734) is a Phase 2b dose-ranging study assessing FTR in treatment-experienced (TE) HIV-1-infected participants.[7,8]
  - In a 7-day lead-in monotherapy substudy, FTR resulted in median decreases in HIV-1 RNA of 0.7–1.5 $\log_{10}$ c/mL across the four studied doses. Through Week 48, there were comparable rates of virologic suppression (HIV-1 RNA <50 c/mL) across FTR arms and the atazanavir/ritonavir (ATV/r) reference group (61–82% vs 71%, respectively).
- Here, we present efficacy results through Week 192 (the latest time point achievable by all active study participants) and cumulative safety data through the conclusion of the study (May 12, 2017).

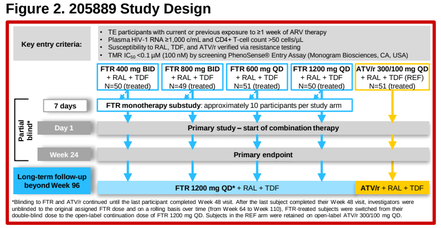
Figure 1. Mechanism of Action of Temsavir



Study Design and Eligibility Criteria

- Participants were randomized 1:1:1:1:1 to four FTR dosing arms (400 or 800 mg twice daily [BID]; 600 or 1200 mg once daily [QD]) or a reference (REF; ATV/r, 300/100 mg QD) arm; each with raltegravir (RAL, 400 mg BID) and tenofovir (TDF, 300 mg QD) as common background therapy (**Figure 2**).
- After the last subject completed their Week 48 visit, investigators were unblinded to the original assigned FTR dose, and on a rolling basis over time (from Week 64 to Week 110), FTR-treated subjects were switched from their double-blind dose to the open-label continuation dose of FTR 1200 mg QD. Subjects in the reference arm were retained on open-label ATV/r 300/100 mg QD.
  - Full study and background regimens were provided by the sponsor.

Figure 2. 205889 Study Design



Results

Study Disposition

- 581 participants were screened, 254 were randomly assigned, and 251 received treatment.
- The median time on FTR therapy for the combined FTR groups was 1645.5 days or 4.5 years (blinded and open-label phases) vs a median time of 1062.0 or 2.9 years on the REF regimen.

Participants at Baseline

- Baseline demographic and disease characteristics were broadly similar across all treatment groups (**Table 1**).
  - The median age was 39 years, 60% of the participants were male, and 66% had HIV-1 subtype B.
  - Median HIV-1 RNA viral load at baseline was 4.85 $\log_{10}$ c/mL and 43% of participants had a baseline viral load ≥100,000 c/mL.
  - Median CD4 T-cell count at baseline was 229.5 cells/μL and 38% of participants had <200 cells/μL.

Table 1. Baseline Characteristics

Baseline Parameter	FTR + RAL + TDF				REF
	400 mg BID (n=50)	800 mg BID (n=49)	600 mg QD (n=51)	1200 mg QD (n=50)	(n=51)
Sex, n (%)					
Female	19 (38)	21 (43)	22 (43)	16 (32)	22 (43)
Male	31 (62)	28 (57)	29 (57)	34 (68)	29 (57)
Median age, years (range)	38.5 (22–57)	37.0 (23–60)	40.0 (26–58)	40.0 (20–67)	39.0 (20–69)
Race, n (%)					
Black/African American	14 (28)	15 (31)	16 (31)	18 (36)	13 (25)
White	20 (40)	19 (39)	17 (33)	16 (32)	23 (45)
Other	16 (32)	15 (31)	18 (35)	16 (32)	15 (29)
HIV-1 RNA					
Median $\log_{10}$ c/mL (range)	4.97 (1.99–6.15)	5.01 (2.64–6.54)	4.88 (1.69–6.50)	4.78 (2.15–6.82)	4.78 (1.76–6.83)
>100,000 c/mL, n (%)	23 (46)	25 (51)	23 (45)	18 (36)	18 (35)
CD4 count					
Median cells/μL (range)	214.0 (43–640)	237.0 (47–744)	226.0 (41–771)	223.5 (32–586)	249.0 (37–729)
<200 cells/μL, n (%)	19 (38)	16 (33)	21 (41)	21 (42)	19 (37)
Median TMR IC_{90} nmol/L (range)	0.68 (0.08–65.2)	0.65 (0.09–61.7)	0.43 (0.05–160.6)	0.82 (0.09–94.5)	0.73 (0.12–75.8)

Virologic Response

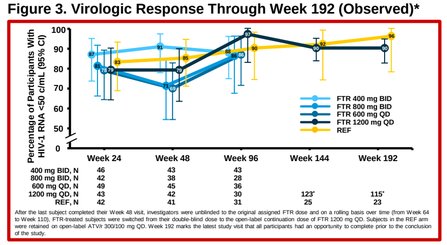
- Virologic response rates (HIV-1 RNA <50 c/mL) at Week 144 and Week 192 by FDA Snapshot algorithm and Observed analysis were comparable between the FTR arms and the REF arm (**Table 2** and **Figure 3**).

Table 2. Virologic Response Through Week 192 (Snapshot)

Week	FTR + RAL + TDF				REF
	400 mg BID (n=50)	800 mg BID (n=49)	600 mg QD (n=51)	1200 mg QD (n=50)*	(n=51)
	n (%), [95% CI]				
24	40 (80) [66.3–90.0]	34 (69) [54.6–81.7]	39 (76) [62.5–87.2]	36 (72) [57.5–83.8]	38 (75) [60.4–85.7]
48	41 (82) [68.6–91.4]	30 (61) [46.2–74.8]	35 (69) [54.1–80.9]	34 (68) [53.3–80.5]	36 (71) [56.2–82.5]
96	39 (78) [64.0–88.5]	24 (49) [34.4–63.7]	32 (63) [48.1–75.9]	29 (58) [43.2–71.8]	29 (57) [42.2–70.7]
144	–	–	–	116 (58) [50.8–64.9]	23 (45) [31.1–59.7]
192*	–	–	–	105 (53) [45.3–59.6]	22 (43) [29.3–57.8]

*After the last subject completed their Week 48 visit, investigators were unblinded to the original assigned FTR dose and on a rolling basis over time (from Week 64 to Week 110), FTR-treated subjects were switched from their double-blind dose to the open-label continuation dose of FTR 1200 mg QD. Subjects in the REF arm were retained on open-label ATV/r 300/100 mg QD. Week 192 marks the latest study visit that all participants had an opportunity to complete prior to the conclusion of the study.
CI, confidence interval.

Figure 3. Virologic Response Through Week 192 (Observed)*

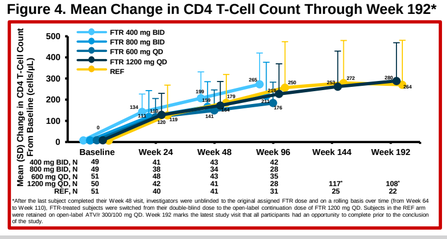


After the last subject completed their Week 48 visit, investigators were unblinded to the original assigned FTR dose and on a rolling basis over time (from Week 64 to Week 110), FTR-treated subjects were switched from their double-blind dose to the open-label continuation dose of FTR 1200 mg QD. Subjects in the REF arm were retained on open-label ATV/r 300/100 mg QD. Week 192 marks the latest study visit that all participants had an opportunity to complete prior to the conclusion of the study.

Change in CD4 T-Cell Counts

- Mean CD4 T-cell counts increased steadily through Week 192 in both the combined FTR arms and the REF arm (**Figure 4**).

Figure 4. Mean Change in CD4 T-Cell Count Through Week 192*



*After the last subject completed their Week 48 visit, investigators were unblinded to the original assigned FTR dose and on a rolling basis over time (from Week 64 to Week 110), FTR-treated subjects were switched from their double-blind dose to the open-label continuation dose of FTR 1200 mg QD. Subjects in the REF arm were retained on open-label ATV/r 300/100 mg QD. Week 192 marks the latest study visit that all participants had an opportunity to complete prior to the conclusion of the study.

Safety

- FTR-based therapy was well tolerated with no discontinuations related to the investigational agent throughout the study.
- The most common FTR-related adverse events (AEs; of any grade) were headache (6%) and nausea (5%), while the most common REF-related AEs were nausea, dizziness (8% each), and AEs related to bilirubin elevation (e.g. jaundice, scleral icterus; 8–18%).
- A greater percentage of REF participants experienced Grade 2–4-related AEs, Grade 3–4 AEs, and AEs leading to discontinuation (**Table 3**).

Table 3. Cumulative AE Summary

Parameter, n (%)	FTR Arms (N=200)	REF (N=51)	Total Treated Participants (N=251)
Any event	**186 (93)**	**50 (98)**	**236 (94)**
Grade 3–4 AEs	36 (18)	17 (33)	53 (21)
Grade 2–4-related AEs	23 (12)	20 (39)	43 (17)
AEs leading to discontinuation	7 (4)	6 (12)	13 (5)
SAEs*	35 (18)	8 (16)	43 (17)
Related SAEs	1 (<1)	2 (4)	3 (1)
Fatal SAEs	3 (2)	0	3 (1)

*None of the SAE events occurred in >2% of participants in each treatment arm. SAEs that occurred in >1 participant overall were: overdose (n=3 FTR arms, n=1 REF arm), and abdominal pain, accidental overdose, bone tuberculosis, and diarrhea (n=2 each, all in the FTR arms).
SAE, serious adverse event.

- A higher percentage of participants in the REF arm (12%), compared with the FTR arm (4%), experienced AEs leading to discontinuation (**Table 4**).

Table 4. AEs Leading to Discontinuation

Parameter, n (%)	FTR Arms (N=200)	REF (N=51)	Total Treated Participants (N=251)
Any event	**7 (4)**	**6 (12)**	**13 (5)**
Bone tuberculosis	2 (1)	0	2 (<1)
Abdominal distension	0	1 (2)	1 (<1)
Acute kidney injury	1 (<1)	0	1 (<1)
Blood bilirubin increased	0	1 (2)	1 (<1)
Completed suicide	1 (<1)	0	1 (<1)
Disseminated tuberculosis	1 (<1)	0	1 (<1)
Flatulence	0	1 (2)	1 (<1)
Hepatic steatosis	0	1 (2)	1 (<1)
Hyperbilirubinemia	0	1 (2)	1 (<1)
Hypertransaminasemia	0	1 (2)	1 (<1)
Ischemia	1 (<1)	0	1 (<1)
Jaundice	0	1 (2)	1 (<1)
Lymph node tuberculosis	1 (<1)	0	1 (<1)

- Lower cumulative rates of Grade 2–4 study drug-related AEs were seen with FTR (12%) when compared with REF (39%), primarily due to elevations in bilirubin (**Table 5**).

Table 5. Grade 2–4 Study Drug-Related AEs*

Parameter, n (%)	FTR Arms (N=200)	REF (N=51)	Total Treated Participants (N=251)
Any event	**23 (12)**	**20 (39)**	**43 (17)**
Hyperbilirubinemia	0	7 (14)	7 (3)
Abdominal pain	1 (<1)	2 (4)	3 (1)
Blood bilirubin increased	0	3 (6)	3 (1)
Blood creatine phosphokinase increased	2 (1)	1 (2)	3 (1)
Headache	1 (<1)	2 (4)	3 (1)
Proteinuria	3 (2)	0	3 (1)
Jaundice	0	2 (4)	2 (<1)
Nausea	0	2 (4)	2 (<1)

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

Conclusions

- FTR-based therapy resulted in rates of virologic and immunologic response comparable to an ATV/r-based regimen through 192 weeks in TE participants with HIV-1 infection across a range of FTR dosing arms.
- FTR demonstrated a favorable safety profile compared with ATV/r, with lower cumulative rates of Grade 2–4-related AEs, Grade 3–4 AEs, and AEs leading to discontinuation despite longer median exposure (4.5 vs 2.9 years).
- These results are supportive of the continued development of FTR as an important treatment option for HIV-1-infected heavily TE adults who have limited therapeutic options (≤2 ARV classes remaining) due to multi-drug resistance, prior intolerance, or other safety concerns (NCT02362503).

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