Early and Durable Reductions in Soluble CD14 Concentrations Among Treatment-Experienced Persons With HIV-1 Through 96 Weeks of Fostemsavir Treatment in a Phase 2b Clinical Trial

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Presenter Disclosure Information

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discloses the following pertaining to this presentation:

Stock/Shareholder: GSK
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Introduction

- Elevated sCD14 concentrations reflect ongoing monocyte activation and are associated with higher mortality risk in people living with HIV[1,2]
- Cytokine bursts in monocytes may be induced by the binding of HIV-1 gp120 to monocyte-expressed CD4[3]
- Temsavir, the active agent of the prodrug FTR, binds directly to HIV-1 gp120 and locks it in a closed conformation, allosterically interfering with the ability of gp120 to attach to CD4 on target cells, which could prevent excess inflammatory responses and bystander CD4+ T-cell death[4,5]
- In a phase 2b study in treatment-experienced adults with HIV-1 who were viremic at baseline, participants treated with various doses of FTR in combination with RAL + TDF demonstrated similar virologic efficacy and increases in CD4+ T-cell count compared with those treated with ATV/r + RAL + TDF through Week 24[6]
  - FTR was generally well tolerated at all doses assessed, and no clinical or laboratory safety signals were identified
- Here, we present the changes in biomarkers, including sCD14, with FTR treatment through Week 96 from this phase 2b study

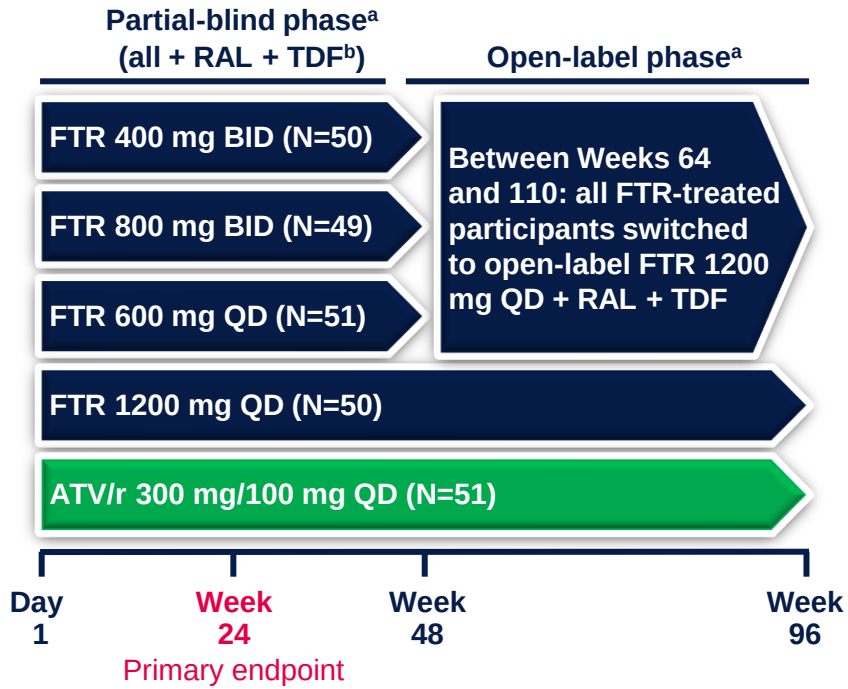
ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; RAL, raltegravir; sCD14, soluble CD14; TDF, tenofovir disoproxil fumarate.

1. Sandler et al. *J Infect Dis*. 2011;203:780-790. **2.** Shive et al. *AIDS*. 2015;29:1263-1265. **3.** Levast et al. *PLoS One*. 2017;12:e0174550. **4.** Pancera et al. *Nat Chem Biol*. 2017;13:1115-1122. **5.** Richard et al. *Cell Chem Biol*. 2023;30:540-552. **6.** Lalezari et al. *Lancet HIV*. 2015;2:e427-e437.

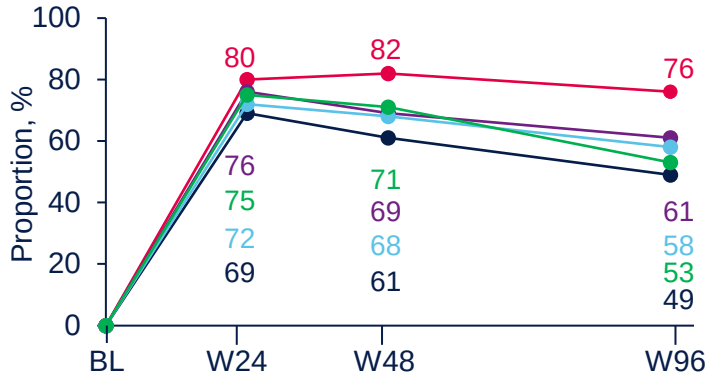
Study Design and Efficacy Analysis

Randomized, controlled, 5-arm, phase 2b study

Eligibility criteria:
- Adults aged ≥18 years
- HIV-1 RNA ≥1000 c/mL
- CD4+ T-cell count >50 cells/mm^3
- No prior treatment with any INI



Proportion with HIV-1 RNA <50 c/mL, all treated participants (mITT population)



Mean change in CD4+ T-cell count, all treated participants (observed population)

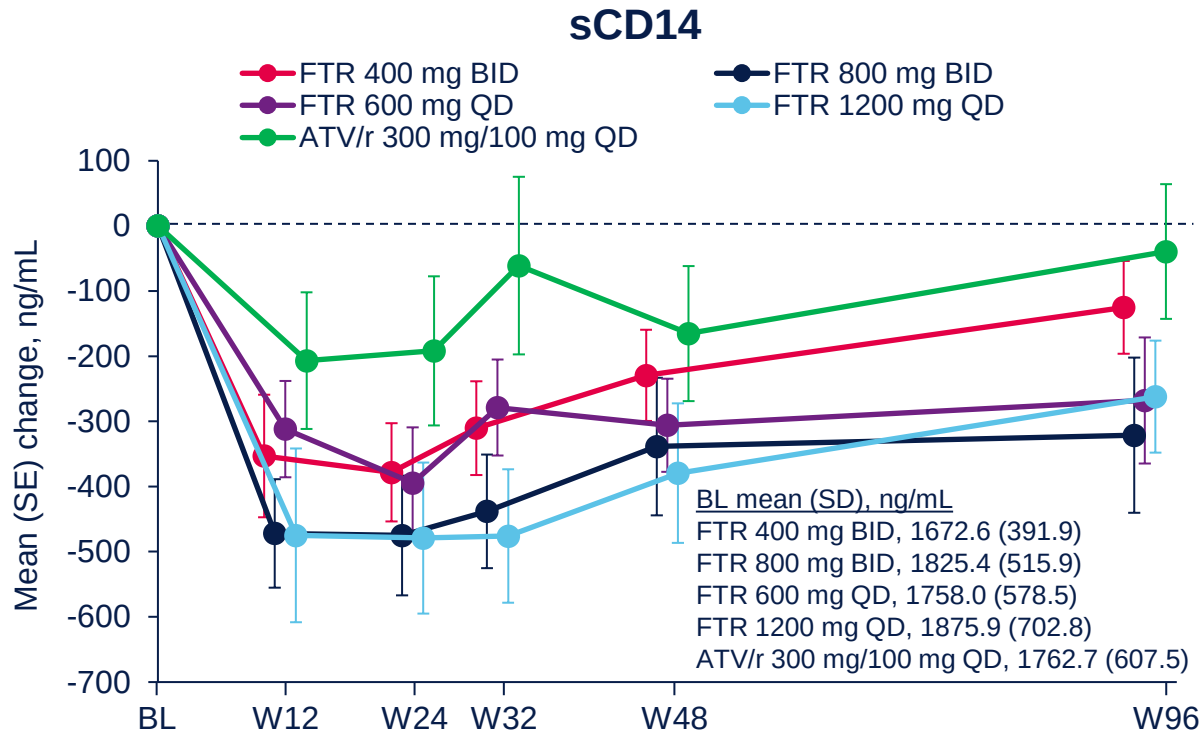
	BL mean (SD), cells/mm^3			
FTR 400 mg BID (N=50)	253 (151)	n= 49	42	44	43
FTR 800 mg BID (N=49)	264 (144)	n= 49	38	34	28
FTR 600 mg QD (N=51)	242 (128)	n= 51	48	43	35
FTR 1200 mg QD (N=50)	248 (142)	n= 50	42	41	28
ATV/r 300 mg/100 mg QD (N=51)	265 (165)	n= 51	40	41	31

ATV/r, ritonavir-boosted atazanavir; BID, twice daily; BL, baseline; FTR, fostemsavir; INI, integrase inhibitor; mITT, modified intention-to-treat; QD, once daily; RAL, raltegravir; TDF, tenofovir disoproxil fumarate; W, week.
[a]Unless unblinded at the Week 8 assessment, participants in the FTR groups remained blinded to study therapy until all participants had reached Week 24 and the optimal dose(s) had been selected. As a result, some participants were beyond Week 24 when unblinding occurred. [b]RAL 400 mg BID + TDF 300 mg QD.

Wonderlich et al. EACS 2023; Warsaw, Poland. Slides RA1.O4.

Mean Change From Baseline in sCD14 Over Time (All Treated Participants)

- Baseline mean (SD) sCD14 ranged from 1672.6 (391.9) to 1875.9 (702.8) ng/mL across FTR groups and was 1762.7 (607.5) ng/mL in the ATV/r group
- Mean decreases from baseline in sCD14 were observed among all groups through Week 96, reaching a maximum change of approximately −480 ng/mL with FTR 800 mg BID and FTR 1200 mg QD at Week 24
- Before dose optimization, participants treated with FTR 800 mg BID and FTR 1200 mg QD demonstrated greater decreases in sCD14 compared with those treated with FTR 400 mg BID and FTR 600 mg QD
- At all post-baseline measurements, every FTR group demonstrated greater mean decreases from baseline (Week 96 range, −125.2 to −321.4 ng/mL) compared with the ATV/r group (Week 96, −39.6 ng/mL)

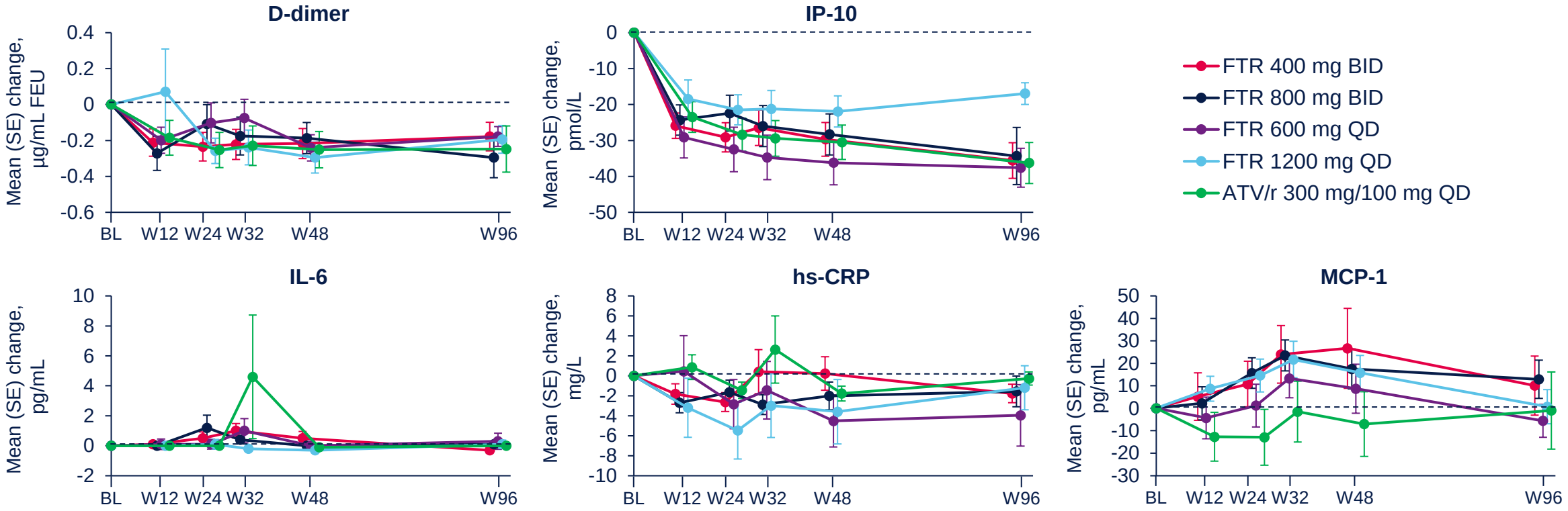


	BL	W12	W24	W32	W48	W96
FTR 400 mg BID n=	50	45	46	45	45	40
FTR 800 mg BID n=	48	45	41	38	38	28
FTR 600 mg QD n=	50	49	48	46	44	34
FTR 1200 mg QD n=	50	45	44	41	40	29
ATV/r 300 mg/100 mg QD n=	50	44	40	39	40	30

ATV/r, ritonavir-boosted atazanavir; BID, twice daily; BL, baseline; FTR, fostemsavir; QD, once daily; sCD14, soluble CD14; W, week.
Between Weeks 64 and 110, all FTR-treated participants switched to open-label FTR 1200 mg QD. Error bars represent SE. Per laboratory standards, reference range for sCD14 was 800-3200 ng/mL.

Mean Change From Baseline in Other Inflammation-Related Biomarkers Over Time (All Treated Participants)

- Through Week 96, no consistent differences were observed post-treatment between FTR groups and the ATV/r group in D-dimer, IP-10, IL-6, hs-CRP, or MCP-1 concentrations



ATV/r, ritonavir-boosted atazanavir; BID, twice daily; BL, baseline; FTR, fostemsavir; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IP-10, interferon gamma–inducible protein-10; MCP-1, monocyte chemotaxic protein-1; QD, once daily; W, week.
Between Weeks 64 and 110, all FTR-treated participants switched to open-label FTR 1200 mg QD. Error bars represent SE.

Conclusions

- FTR was well tolerated with a good safety profile and demonstrated virologic efficacy and improvements in CD4+ T-cell count comparable to those observed in the ATV/r reference group when administered with a RAL + TDF backbone
- These exploratory findings demonstrate that directly targeting gp120 with FTR treatment attenuated monocyte activation in people living with HIV-1, especially at higher doses
- Compared with ATV/r, treatment with FTR resulted in greater early and sustained decreases in sCD14 concentrations, a biomarker strongly associated with all-cause mortality in people living with HIV

Additional data on biomarkers of inflammation with FTR are presented in Poster eP.A.092[1]

ATV/r, ritonavir-boosted atazanavir; FTR, fostemsavir; RAL, raltegravir; sCD14, soluble CD14; TDF, tenofovir disoproxil fumarate.

1. Castagna et al. EACS 2023; Warsaw, Poland. Poster eP.A.092.

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