ENTRANCE

Protocol 221794

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on behalf of the Entrance study team

N6LS and Fostemsavir

N6LS

- VH3810109 (N6LS) is a broadly neutralizing CD4-binding site antibody being developed for long-acting HIV-1 therapy
- N6LS was well tolerated and efficacious in participants with HIV-1 naive to ART when administered IV or SC in the proof-of-concept phase 2a BANNER study[1-4]
- In the phase 1 SPAN study, single-dose N6LS given IV (60 mg/kg) or SC (3000 mg) with rHuPH20 showed a good safety profile in adults without HIV[5]
- Using the same doses from SPAN, the EMBRACE study demonstrated the efficacy, safety, and tolerability of N6LS every 4 months + long-acting CAB IM monthly for maintenance of HIV-1 suppression[6]

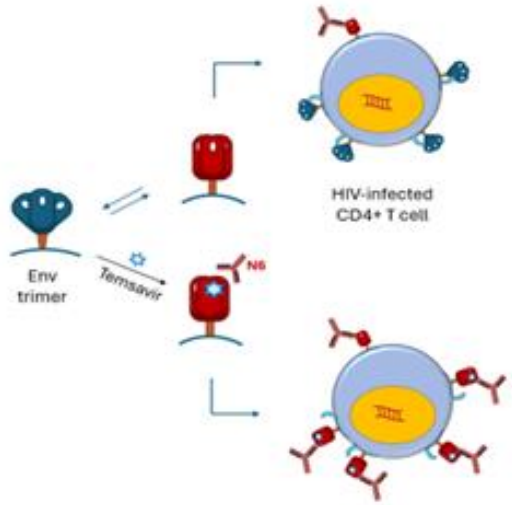
Fostemsavir

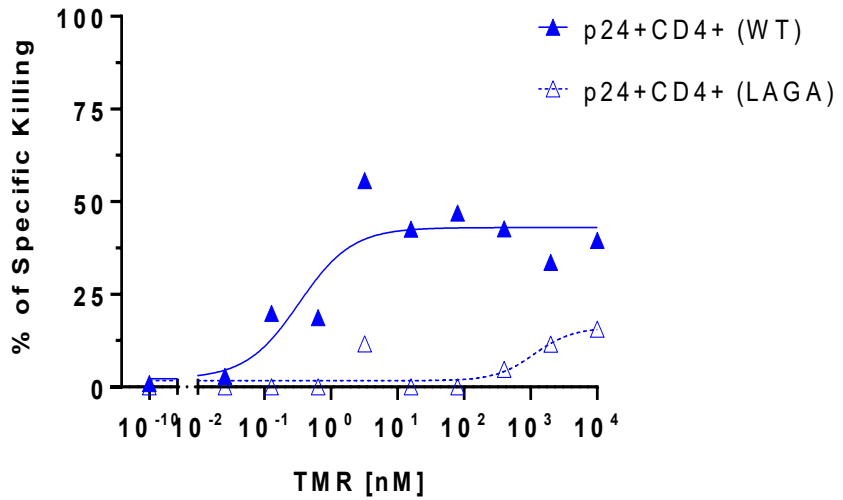
- FTR is a small molecule first-in-class HIV-1 attachment inhibitor.
- FTR is a prodrug that releases the active compound TMR, which binds to and stabilizes gp120 in a 'closed' conformation[7] and prevents interaction with the CD4 receptor
- TMR-enhances N6 binding and corresponds with increased N6-mediated ADCC activity[7]

. Leone et al. CROI 2024; Denver, CO. Oral presentation 117. 2. Leone et al. EACS 2023; Warsaw, Poland. Oral presentation PS8.O5. 3. Edwards et al. EACS 2023; Warsaw, Poland. Poster eP.A.099. 4. Edwards et al. PAGE 2024; Rome, Italy. Poster I-096. 5. Win et al. CROI 2024; Denver, CO. Poster 639. 6.Taiwo et al. CROI 2025;San Francisco, Oral presentation 203. .; 7. Munro, 2014 ; 8.Qi, CROI 2024 Poster 374

Strategy

Strategic Intent	• N6LS (± fostemsavir) as interventions that can potentially **REDUCE the viral reservoir** and **ENHANCE the host immune response** against HIV.
Target Populations	• Treatment-naïve people living with HIV. • Treatment-experienced virologically suppressed people living with HIV





ART = Antiretroviral therapy
SOC = standard of care
Fostemsavir = antiretroviral (attachment inhibitor)

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Virologic and Immunologic Biomarkers Of Remission/Cure

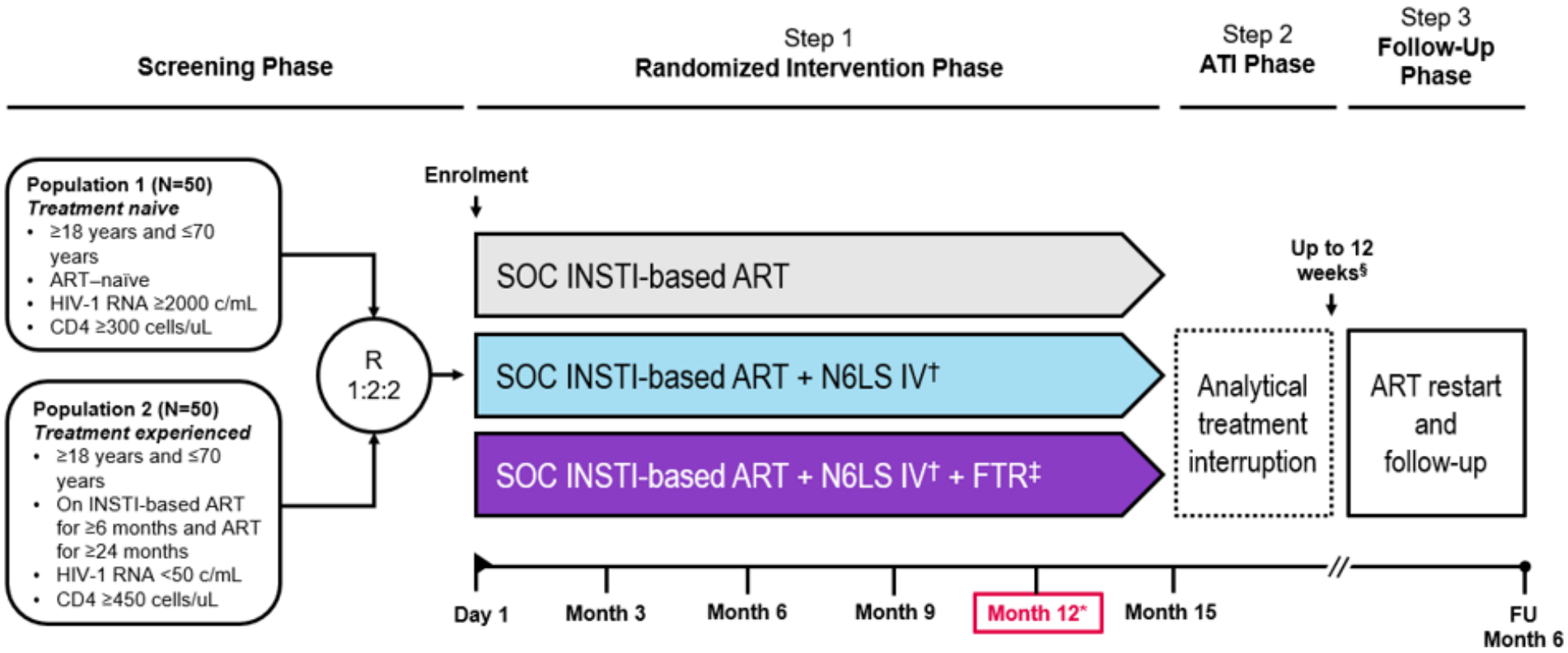
- Currently, there are no validated viral or host biomarker(s) that can predict the viral rebound kinetics or the probability of viral rebound/remission upon ART cessation.

- In ENTRANCE, we aim to determine whether N6LS and FTR can modulate and define biomarkers and models of these factors that can predict success of an intervention defined in part by delay in viral rebound as well as reduction is systemic markers of inflammation

- In ENTRANCE, we hope to define biomarkers associated with improved anti-HIV-1 immune function and viral rebound kinetics in both virologically-suppressed and unsuppressed PWH following administration of N6-LS ± FTR.
  - Innate immune activation/inflammation
  - HIV-specific CD4 and CD8 T cell responses
  - Autologous HIV-specific antibody responses
  - HIV reservoir size and composition

PMID: 35438384, 38979421

Study design



† N6LS (VH3810109) 4200 mg is dosed via IV infusion at Day 1 and Month 6.

‡ FTR 600 mg prolonged-release oral tablet is dosed once-daily from Day 1 to Month 12.

§ Participants will restart ART after 12 weeks, or upon meeting protocol-defined ART restart criteria.

ART = antiretroviral therapy; ATI = analytical treatment interruption; FTR = fostemsavir; FU = follow-up; INSTI = integrase strand transfer inhibitor; IV = intravenous; R = randomization; SOC = standard of care

*** 1^0 endpoint: Change in cell-associated RNA from baseline to month 12**

2^0/exploratory endpoints:

- Time to viral rebound/viral setpoint during ATI
- Innate immune activation/inflammation
- HIV-specific CD4 and CD8 T cell responses
- Autologous HIV-specific antibody responses
- HIV reservoir size and composition

Considerations/Questions

1. How will bnAbs be used in the treatment of HIV?

2. What are the clinically meaningful benefits of reducing the reservoir and other putative impacts of bnAbs?

3. What evidence/data is needed to support the clinical benefit/value proposition for bnAbs?