Project Brief: A5416/HVTN806/HPTN 108

Full Title of Study/Programme	A Phase I, Randomized, Placebo-Controlled Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in sub-Saharan Africa Living with HIV during a Monitored Analytical Treatment Interruption Short Title: Pausing Antiretroviral Treatment Under Structured Evaluation (PAUSE)
Technical Focus Area/Key Words	Broadly neutralizing antibodies, analytical treatment interruption
Rationale	Broadly neutralizing antibodies (bNAbs) have the potential to fill gaps in prevention, treatment, and cure, and analytical treatment interruption (ATI) trial designs facilitate simultaneous exploration of bNAbs' potential in all of these areas. Results from early phase clinical trials using different classes of bNAbs such as those targeting the CD4 binding site (VRC01 and 3BNC117) and the V3 loop (10-1074 and PGT121) have been encouraging, demonstrating the potential for and challenges of developing anti-HIV-1 bNAbs as preventive and therapeutic agents. Most bNAb studies completed to date in PWH were conducted in the US or Europe, where clade B is the predominant circulating strain. However, the African continent carries the greatest burden of the pandemic where non-clade B viruses are in circulation. It is therefore imperative that promising new therapeutic and cure strategies also be evaluated in PWH in sub-Saharan Africa, where clade-specific virologic features and population-specific immunologic characteristics may be at play. 3BNC117 and 10-1074 have not yet been tested clinically in non-clade B geographic areas, but as discussed above the combination maintained viral suppression in the absence of ART for a median of 28 weeks in 76% participants chronically living with HIV (13 out of 17; 15 with clade B viruses) who were not pre-selected for bNAb sensitivity. ATIs provide a direct measure of the antiviral potential of a bNAB combination, which can be used as an in vivo biomarker not only of the therapeutic or curative potential of an intervention but also of its prophylactic potential. Administration of bNAbs during ATI also allows safety evaluation of this strategy and provides information about candidate antibodies in an efficient manner.
Primary Objectives	To evaluate the safety and tolerability of intravenous infusions of 3BNC117-LS-J and 10-1074- LS-J in virally suppressed adults with HIV in sub-Saharan Africa. To evaluate the efficacy of the combination of 3BNC117-LS-J and 10-1074-LS-J versus placebo in preventing the return of sustained HIV-1 viremia (confirmed HIV-1 viral load >200 copies/mL) for 24 weeks after ART discontinuation in adults with HIV who have maintained viral suppression prior to the analytical treatment interruption (ATI) in sub-Saharan Africa.
Primary Endpoint/Outcome	Intravenous infusions of the combination of long-acting broadly neutralizing antibodies (bNAbs) 3BNC117-LS-J and 10-1074-LS-J will be safe and well tolerated; and compared to placebo, will maintain durable viral suppression in the absence of ART while levels are therapeutic in people living with HIV in sub-Saharan Africa.

Study Design	Is a Phase I, double-blind, randomized, placebo-controlled multi-step study
Study arms	Participants will be randomized in a 2:1 ratio to receive either the study investigational product (Arm A) or placebo (Arm B) and will discontinue ART 2 days later. Arm A: 32 participants will receive a single intravenous infusion of 3BNC117-LS-J (30 mg/kg) and a single intravenous infusion of 10-1074-LS-J (10 mg/kg). Arm B: 16 participants will receive a single intravenous infusion of Placebo for 3BNC117-LS-J (0.9% Sodium Chloride Injection) and a single intravenous infusion of Placebo for 10-1074-LS-J (0.9% Sodium Chloride Injection)
Study population	Individuals living with HIV, age ≥18 to ≤70 years, on stable ART who have a CD4+ count of >450 cells/µL, plasma viral load [VL] <50 copies/mL for at least 96 weeks prior to Step 1 entry, no history of receipt of any therapeutic HIV vaccine or HIV monoclonal antibody therapy.
Study sample size	48 participants will be enrolled into Step 1: Arm A (3BNC117-LS-J + 10-1074-LS-J): 32 participants Arm B (placebo): 16 participants
Follow up/duration	Up to 96 weeks (24 weeks in Step 1 [ATI], then if they have not met ART restart criteria, 48 weeks (week 25 to 72) in Step 2 [extended ATI], followed by 24 weeks in Step 3 [follow-up on ART])
Study/Programme sites	A5416/HVTN 806/HPTN 108 is a multicenter study open to selected ACTG, HVTN, and HPTN clinical research sites in sub-Saharan Africa.
Intervention	3BNC117-LS-J and 10-1074-LS-J
Investigators	Principal Investigator: Dr Carrie-Anne Mathew Sub Investigators: Prof Sinead Delany-Moretlwe; Dr Elizabeth Roos; Dr Monique Da Fonseca; Dr Juliet Vimbai Rundogo
Other Partners & Collaborators	HIV Vaccine Trials Network (HVTN) HIV Prevention Trials Network (HPTN) The Rockefeller University Bill and Melinda Gates Foundation (Collaboration for AIDS Vaccine Discovery)
Overall Study/Project Contact	Dr Carrie- Anne Mathew
Briefing owner and date	Tlhompho Gaoshebe-Mofolo 09 April 2024