Phase 1 dose-escalation trial to evaluate the safety, tolerability, pharmacokinetics and neutralization activity of PGDM1400LS in combination with VRC07-523LS and PGT121.414.LS in healthy participants without HIV (HVTN 140/HPTN 101)

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BACKGROUND: Passive immunization with broadly neutralizing antibodies (bNAbs) presents a promising HIV prevention modality. Studies suggest that bNAb combinations targeting multiple HIV-1 epitopes and clades are necessary for effective prevention. HVTN140/HPTN101 evaluated the safety, tolerability, pharmacokinetics, and neutralization activity of PGDM1400LS (V2 apex) administered in combination with VRC07-523LS (CD4 binding site) and PGT121.414.LS (V3 glycan) in healthy adults, without HIV.

METHODS: The study was a multicenter, randomized, open-label study conducted in Africa and the United States. After establishing the safety of a single administration of PGDM1400LS in Part A (n=15), Part B (n=80) enrolled adults aged 18-50 years without HIV who received two doses of PGDM1400LS, VRC07-523LS and PGT121.414.LS four months apart. In the five bNAb combination groups, each bNAb was administered at weight-based doses of 20mg/kg or 40mg/kg intravenously, 20mg/kg subcutaneously or a fixed dose of 1.4g either intravenously or subcutaneously. Safety was evaluated through solicited and unsolicited adverse events. Pharmacokinetic parameters were estimated using a two-compartment population pharmacokinetic model. BNAb serum concentrations were measured by anti-idiotypic binding antibody assays. Serum neutralization was assessed against viruses sensitive to each of the three bNAbs administered and a panel of recently circulating HIV-1 strains.

RESULTS: Median age was 25.5 years, and 50.5% were assigned female sex at birth. Most participants reported mild-to-moderate solicited local and systemic symptoms. The median estimated elimination half-life of PGDM1400LS was 54 days, not significantly influenced by co-administration with VRC07-523LS and PGT121.414.LS. Compared to IV administration, the bioavailability of PGDM1400LS administered subcutaneously was 75.5%. The median estimated elimination half-life of PGT121.414.LS was 66 days, with subcutaneous bioavailability of 77.7%. The median estimated elimination half-life of VRC07-523LS was 45 days, with subcutaneous bioavailability of 80.1%. Weight-based and fixed-dose regimens showed similar pharmacokinetic patterns. ID80 neutralization titers aligned with predicted values, indicating sustained neutralization activity in vivo, with broad and potent neutralization against both bNAb-sensitive isolates and recently circulating HIV-1 strains. No treatment-induced anti-drug-antibody responses were observed.

CONCLUSIONS: The bNAb combination of PGDM1400LS, PGT121.414.LS, and VRC07-523LS was safe and well-tolerated, with no pharmacokinetic interactions or loss of complementary neutralization. These findings strongly support the evaluation of this triple combination in future efficacy trials.