First-in-human evaluation of safety and pharmacokinetics of intravenous or subcutaneous infusions of PGT121.141.LS, an anti-V3 HIV-1 broadly neutralizing antibody in healthy adult volunteers without HIV

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Background

Multiple broadly neutralizing antibodies (bnAbs) targeting domains of gp120 are in development for prevention of HIV-1. PGT121.414.LS, a modification of the anti-V3 glycan bnAb PGT121, potently neutralizes multiple HIV-1 clades *in vitro*. In the HVTN 136/HPTN 092 trial, we are evaluating the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous (IV) or subcutaneous (SC) infusions in healthy, adult participants without HIV.

Methods

In Part A of the ongoing, phase 1 HVTN 136/HPTN 092 trial, we are assessing the safety, tolerability, and pharmacokinetics (PK) of PGT121.414.LS in 13 healthy adults without HIV (Table 1). We evaluated IV dose-escalation and SC infusion in four groups: 3 mg/kg IV (group T1, n=3), 10 mg/kg IV (T2, n=4), 30 mg/kg IV (T3, n=3) and 5 mg/kg SC (T4, n=3). In T2, 1 participant was discontinued later in the study due to ineligibility and an additional 4th participant was enrolled as a replacement. Serum concentrations of PGT121.414.LS were measured on Days 0, 1, 2, 3, 6, 14, 28, 56 and 112 after a single infusion. Non-compartmental PK analyses were performed. Part B data collection is in progress.

Table 1. HVTN 136/HPTN 092 trial study schema

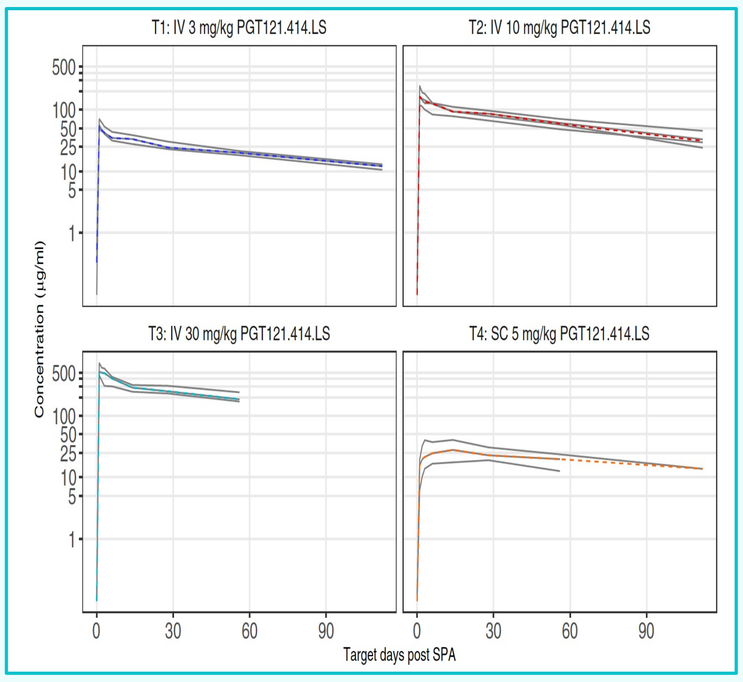
Treatment group	Number	Dose	Route	Study Product Administration Schedule		
				Month 0 (Day 0)	Month 4 (Day 112)	Month 8 (Day 224)
Part A						
Group T1	3	3 mg/kg	IV	PGT121.414.LS	—	—
Group T2	3	10 mg/kg	IV	PGT121.414.LS	—	—
Group T3	3	30 mg/kg	IV	PGT121.414.LS	—	—
Group T4	3	5 mg/kg	SC	PGT121.414.LS	—	—
Part B (data not yet available)						
Group T5	10	20 mg/kg + 20 mg/kg	IV	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS
Group T6	10	5 mg/kg + 5 mg/kg	SC	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS
Total	32					

Results

In part A of the study, the median participant age was 30 years; 77% of participants were assigned female sex at birth; 15% were Black and 85% White. IV and SC infusions were safe and well-tolerated, with no related serious adverse events or dose-limiting toxicities.

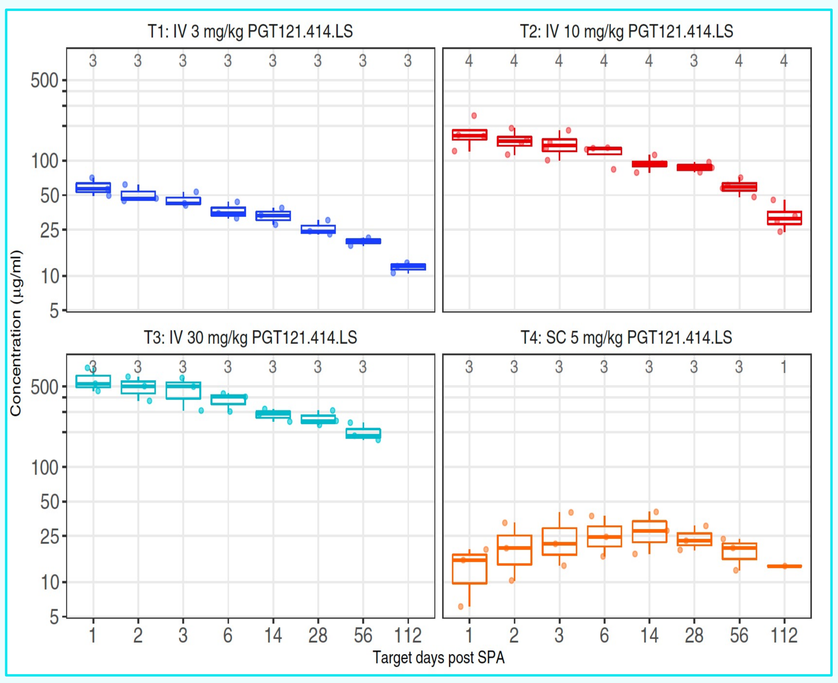
- Peak concentrations after IV infusions were observed on Day 1, increasing linearly with higher doses (median = 56.7 µg/mL in T1, 164.7 µg/mL in T2 and 525.8 in T3) [Fig 1]. Peak concentrations after SC infusion were observed on Day 14 (Fig 2). On Day 112, T1, T2 and T4 concentrations were 12.1 31.3, and 13.7 µg/mL, respectively; T3 data are in progress.
- The estimated clearance for PGT121.414.LS was 0.06-0.12 liter/day in T1-T4.
- The estimated elimination half-lives for PGT121.414.LS were 3 times longer than its precursor, PGT121, with medians of 53.6-74.3 days in T1-T4.

Fig 1. HVTN 136/HPTN 092 PGT121.414.LS serum concentrations, by participant



Color coded lines = medians; ——individual; --- group
SPA= study product administration

Fig 2. HVTN 136/HPTN 092 PGT121.414.LS serum concentrations, by treatment group and target day



Numbers at the top of the graph represent number of participants at each time point
SPA= study product administration

Conclusions

PGT121.414.LS was safe and well-tolerated following IV or SC infusion in healthy US adults without HIV. These preliminary safety and pharmacokinetic findings support further development of PGT121.414.LS in combination with other bnAbs for global HIV-1 prevention.

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