

Safety and Pharmacokinetics of VRC07-523LS, PGDM1400LS, and PGT121.414.LS in combination among children in Botswana

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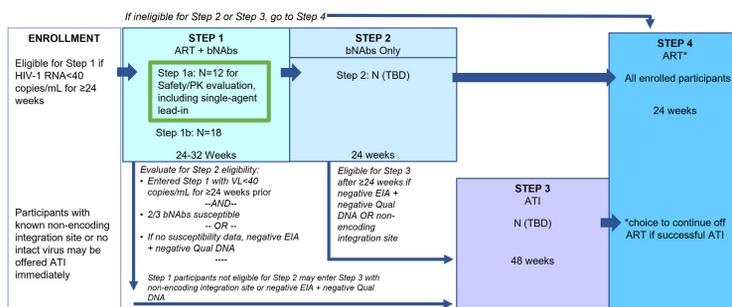
BACKGROUND

- Broadly neutralizing monoclonal antibodies (bNAbs) suppress HIV RNA and may promote HIV remission
- There are very limited safety and pharmacokinetic (PK) data for VRC07-523LS in children, and no currently published data for PGDM1400LS or PGT121.414.LS in children
- Tatelo Plus (IMPAACT 2042) is a multistep study designed to first evaluate the safety and PK of combination long-acting (LS) bNAbs in children on suppressive antiretroviral treatment (ART), followed by study steps using combination bNAbs alone, and an analytic treatment interruption (ATI), in selected children
- We report the safety and PK findings for the first study step, which evaluated intravenous VRC07-523LS, PGDM1400LS, and PGT121.414.LS with ongoing ART

METHODS

- The overall study consists of 4 Steps (Figure 1), with Step 1 split into **Step 1a** and **Step 1b**.
- Step 1a eligibility included:
 - ART initiated at <7 days of life
 - HIV RNA <40 copies/mL for ≥24 weeks prior to enrollment
- bNAb administration was staggered, starting with either PGDM1400LS (Group 1) or PGT121.414.LS (Group 2) given at Week 0. At Week 8, a second dose was administered, and VRC07-523LS was started with ongoing dosing every 4 weeks
- At Week 12, the 3rd bNAb was administered along with the second dose of VRC07-523LS, and the alternating pattern for PGDM1400LS/PGT121.414.LS was established (Table 1)
- In Step 1a, all bNAbs were dosed at 20mg/kg/dose
- Dolutegravir-based ART was used during Step 1a

FIGURE 1. Tatelo Plus / IMPAACT 2042 Study Design



VRC07-523LS, PGDM1400LS, and PGT121.414.LS were well tolerated and without serious adverse events when given in combination to children in Botswana. Steady-state troughs for VRC07-523LS and PGDM1400LS were lower than predicted based on adult PK data, requiring a dose increase in the next study steps.

Table 1. bNAb Administration Schedule

Step 1a Group	Day 0/Entry	Week 8	Week 12	Rotating bNAb Administration Every 4 Weeks for 32 Weeks		
	Single-agent Dose 1	Single agent Dose 2	Rotating Schedule with 3 rd bNAb Begins	Week 16, 24, 32	Week 20, 28	
Group 1 (N=6)	PGDM1400LS	PGDM1400LS	PGT121.414.LS	PGDM1400LS	PGT121.414.LS	PGDM1400LS
		VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS
Group 2 (N=6)	PGT121.414.LS	PGT121.414.LS	PGDM1400LS	PGT121.414.LS	PGDM1400LS	PGT121.414.LS
		VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS	VRC07-523LS

PHARMACOKINETIC METHODS

- Plasma samples for the three bNAb antibodies were collected prior to and 1hr post infusion at Week 0. Subsequent samples were obtained at Day 1, Weeks 1, 4, 8-pre-dose, 8-1hr and 1 day post-dose, 9, 12-pre-dose, 12-1 hr and 1 day post-dose, 13, 16-pre-dose and 16-1hr post-dose.
- Measured troughs at Week 16 (before the 3rd dose) for PGDM1400LS (Group 1) and PGT121.414.LS (Group 2) were evaluated.
- By Week 16 VRC07-523LS had only been administered for 8 weeks, so population PK (PopPK) analysis was performed using NONMEM (ver. 7.4) to predict steady-state trough concentrations.
- Week 16 bNAb target trough concentrations were extrapolated from PK in adults and were pre-specified as:
 - PGDM1400LS: >150 mcg/mL
 - PGT121.414.LS: >120 mcg/mL
 - VRC07-523LS: >140 mcg/mL
- PK samples were assayed by a validated multiplex pharmacokinetic assay: Binding Antibody Multiplex Assay (PK-BAMA; Wesley, et al. Front Immunol. 2021).

RESULTS

- Twelve participants were enrolled into Step 1a (6 Francistown, 6 Gaborone)
- Median age at enrollment 7.8 (range 1.5, 9.5) years; 75% female; median weight 18.9 (range 8.2, 36.5) kg; and median CD4 cell count 1238 (range 645, 2683) cells/mm³
- All infusions were well tolerated without any infusion reactions or grade 3 or 4 adverse events
- VRC07-523LS PK data well described by a 2-compartment model (Figure 2A/Figure 2B)
- Estimated VRC07-523LS population PK parameters:
 - Clearance (CL): 216 mL/d/70kg
 - Volume of distribution (Vss) 8.67 L/70kg
- Predicted VRC07-523LS accumulation shown in Figure 3
- The geometric mean of pre-dose Week 16 concentration are shown in Figure 4
 - PGDM1400LS -108.3 mcg/mL (95% CI 72.3-162.3) - below target
 - PGT121.414.LS - 194.4 mcg/mL (95% CI 113.8 - 254.0) - met target
 - VRC07-523LS - 108.8 mcg/mL (95% CI 68.4-173.1) - below target
- VRC07-523LS and PGDM1400LS trough concentrations were below target concentrations; doses therefore increased to 25mg/kg for subsequent Tatelo Plus steps

FIGURE 4. Geometric means concentrations for PGDM1400LS, PGT.121.414.LS, and VRC07-523LS

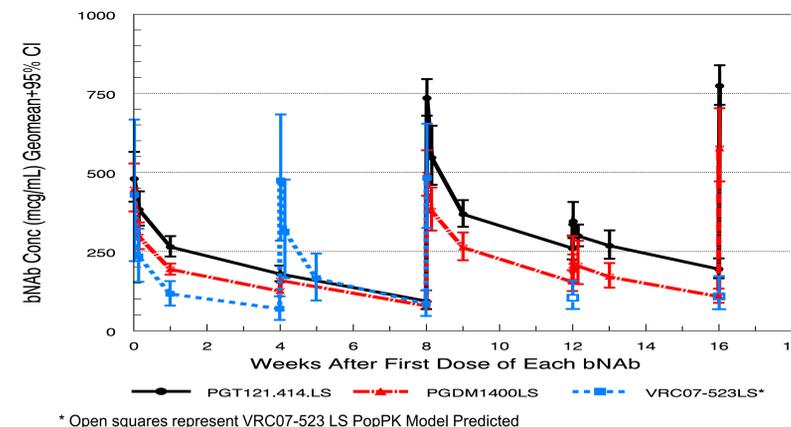


FIGURE 2A/2B. Goodness of Fit plots for VRC07-523LS PopPK Model

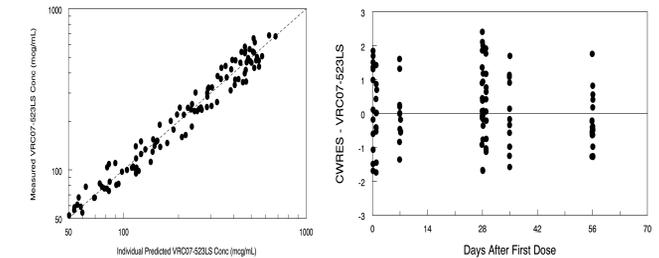
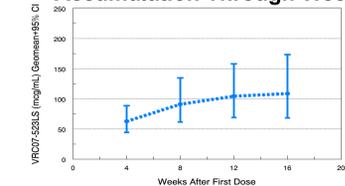


FIGURE 3. VRC07-523LS Model Predicted Trough Accumulation Through Week 16



CONCLUSIONS

- IV infusions of VRC07-523LS, PGDM1400LS, and PGT121.414.LS were well tolerated in children
- The alternating dosing schedule allowed two infusions per monthly visit rather than three, reducing the time and complexity of each visit
- Steady-state troughs were lower than predicted for VRC07-523LS and PGDM1400LS
- Protocol pre-specified dose increases to 25mg/kg/dose for these bNAbs were used in the next study steps, with ongoing PK monitoring of all three agents

PLAIN LANGUAGE SUMMARY

- Three antibodies against HIV were safe when given in combination to children living with HIV infection.
- Antibody blood concentrations were used to improve the antibody dosing.
- This antibody combination is now being tested to see if it can control HIV infection without drugs.

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