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Safety and Pharmacokinetics of Monoclonal Antibodies VRC07-523LS and PGT121 Administered Subcutaneously for Human Immunodeficiency Virus Prevention

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Background. Effective, long-acting prevention approaches are needed to reduce human immunodeficiency virus (HIV) incidence. We evaluated the safety and pharmacokinetics of VRC07-523LS and PGT121 administered subcutaneously alone and in combination as passive immunization for young women in South Africa.

Methods. CAPRISA 012A was a randomized, double-blinded, placebo-controlled, dose-escalation phase 1 trial. We enrolled 45 HIV-negative women into 9 groups and assessed safety, tolerability, pharmacokinetics, neutralization activity, and antidrug antibody levels. Pharmacokinetic modeling was conducted to predict steady-state concentrations for 12- and 24-weekly dosing intervals.

Results. VRC07-523LS and PGT121, administered subcutaneously, were safe and well tolerated. Most common reactogenicity events were injection site tenderness and headaches. Nine product-related adverse events were mild and transient. Median VRC07-523LS concentrations after 20 mg/kg doses were 9.65 μg/mL and 3.86 μg/mL at 16 and 24 weeks. The median week 8 concentration after the 10 mg/kg PGT121 dose was 8.26 μg/mL. Modeling of PGT121 at 20 mg/kg showed median concentrations of 1.37 μg/mL and 0.22 μg/mL at 16 and 24 weeks. Half-lives of VRC07-523LS and PGT121 were 29 and 20 days. Both antibodies retained neutralizing activity postadministration and no antidrug antibodies were detected.

Conclusions. Subcutaneous administration of VRC07-523LS in combination with optimized versions of PGT121 or other antibodies should be further assessed for HIV prevention.

Keywords. HIV; monoclonal; antibodies; PGT121; VRC07-523LS.

Despite extensive human immunodeficiency virus (HIV) prevention and treatment efforts, 1.5 million new infections and 690 000 HIV-related deaths were reported globally in 2020 [1]. In southern Africa, young women remain particularly vulnerable to new infections [2, 3] with reported incidence rates of up to 4 per 100 person-years [4, 5]. In the absence of an effective HIV vaccine, alternative biomedical prevention options need to be assessed.

Clinical trials of antiretrovirals (ARVs) as oral preexposure prophylaxis (PrEP) showed mixed results [6–9]. It is notable that 2 large trials in young African women reported no benefit [10, 11]. Low adherence and stigma associated with ARVs were major contributing factors [12–15]. Although intravaginal rings containing ARVs may overcome adherence challenges with daily oral PrEP [16, 17], they were not efficacious in young women, possibly due to the need for monthly replacements. Longer acting, injectable ARV formulations are a promising intervention [18], but the route of administration, adherence to dosing intervals, and emergence of resistance on treatment termination could remain drawbacks [19, 20].

Monoclonal antibodies are also being evaluated as long-acting biological agents for HIV prevention. Several phase 1/2a clinical trials evaluating broadly neutralizing antibodies (bnAbs) have demonstrated safety with favorable pharmacokinetic (PK) profiles [21]. Results from the Antibody Mediated Prevention (AMP) trials did not show an overall reduction in

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HIV-1 infections after intravenous administration of VRC01. However, infections with HIV strains sensitive to neutralization by VRC01 was 75% lower in the VRC01 recipients than placebo recipients [22]. These results provided evidence that bnAbs may prevent HIV infections. To overcome HIV genetic diversity, combinations of bnAbs targeting different epitopes on the viral envelope will likely be required [23]. For implementation, bnAbs with longer half-lives and higher potencies, which can be administered subcutaneously, could provide a long-acting option to overcome some of the current PrEP adherence challenges [24, 25].

The CAPRISA 012 series of 3 clinical trials aims to evaluate the subcutaneous administration of 3 bnAbs—VRC07-523LS, PGT121, and CAP256V2LS—among young African women [26, 27]. CAPRISA 012A was the first trial and evaluated the safety, tolerability, and PK of VRC07-523LS and PGT121 [26]. VRC07-523LS targets the CD4 binding site on the HIV-1 envelope glycoprotein and is an engineered heavy chain somatic variant of VRC01 [28]. Previous studies have shown that VRC07-523LS administered individually or in combination with other bnAbs was safe and well tolerated with a median half-life ($t_{1/2}$) of ~40 days across a range of doses and routes of administration [29, 30]. PGT121 targets the envelope V3 glycan supersite and was also safe and well tolerated with a $t_{1/2}$ of ~22 days, depending on dose and route [31]. The aim of CAPRISA 012A was to identify a subcutaneous dose of VRC07-523LS and/or PGT121 for 6-monthly dosing as long-acting PrEP in African women [21].

METHODS

Study Design and Participants

CAPRISA 012A was a randomized, double blinded, placebo-controlled, dose-escalation phase 1 trial conducted in Durban, South Africa. The primary endpoint was safety, which was defined as reactogenicity events and adverse events (AEs) up to 24 weeks after study product administration. The secondary endpoints were PK, the development of antidrug antibodies (ADA), and the acceptability of subcutaneous injections. The trial was approved by the South African Health Products Regulatory Authority and the University of KwaZulu-Natal Biomedical Research Ethics Committee and was conducted according to International Council for Harmonisation Good Clinical Practice guidelines.

Participants who provided informed consent and met eligibility criteria were enrolled [26]. Women who were 18–40 years, HIV-negative, at low risk for HIV infection, and of good general health with evidence of effective contraception were enrolled. Participants consented to have blood and genital samples collected and stored for research purposes. Volunteers who were pregnant, breastfeeding, weighed more than 90 kg, had a history of alcohol or substance use, received an investigational HIV vaccine previously, received a monoclonal antibody or polyclonal immunoglobulin within 28 days before enrollment, or had any history of anaphylaxis, autoimmune disease, or current use of immunosuppressive therapy were excluded. The study was registered with the Pan African Clinical Trial Registry (PACTR 201808919297244) on 29 August 2018.

Study Procedures

Forty-five HIV-negative participants were allocated to 9 groups of 5 participants each. In each group, 4 participants were randomly assigned to the intervention, VRC07-523LS and/or PGT121 and 1 to placebo [26]. The bnAbs were administered either alone or in combination. Enrollment into consecutive groups occurred in a stepwise, dose-escalation design following predetermined safety reviews (Figure 1). Repeat doses in Groups 3, 4, and 6 were administered at 12 or 24 weeks.

All study products were administered subcutaneously with a maximum volume of 2 mLs per injection site in the abdominal area using a needle and syringe. In combination groups, each antibody was administered separately at different areas of the abdomen. The concentrations of VRC07-523LS assessed were approximately twice those for PGT121 because the antibody concentration of VRC07-523LS was twice that of PGT121 for each dosing volume administered. VRC07-523LS is concentrated at 100 mg/mL and PGT121 is concentrated at 50 mg/mL. Reactogenicity assessments were conducted in person on the day of product administration, on day 1 and day 3, and telephonically on day 2. In addition, all participants kept a daily symptom diary for 3 days after each product administration.

The AEs were graded using the Medical Dictionary for Regulatory Activities system as per the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.1, July 2017. Participants had weekly follow-up visits in the first month, then monthly visits for 24 weeks after administration of the last dose of study product, with a total study duration of 72 weeks. Acceptability of the subcutaneous injections was assessed with a questionnaire at each injection visit and at study exit. Safety reviews were conducted by the Protocol Safety Review Team and the Data and Safety Monitoring Board at protocol specified intervals.

Laboratory Procedures

Plasma, serum, and peripheral blood mononuclear cells samples were collected at predetermined timepoints for endpoint analysis [27]. Human immunodeficiency virus testing was conducted using an algorithm, and HIV immunoassays were also evaluated for cross-reactivity.

Plasma samples for PK analysis were collected before and 1, 3, and 7 days and 2, 4, 8, 12, 16, and 24 weeks after the first dose. Participants who received a second bnAb dose had additional PK samples up to 24 weeks after the second dose. For VRC07-523LS, a quantitative electrochemiluminescence sandwich immunoassay technique was performed on the Meso

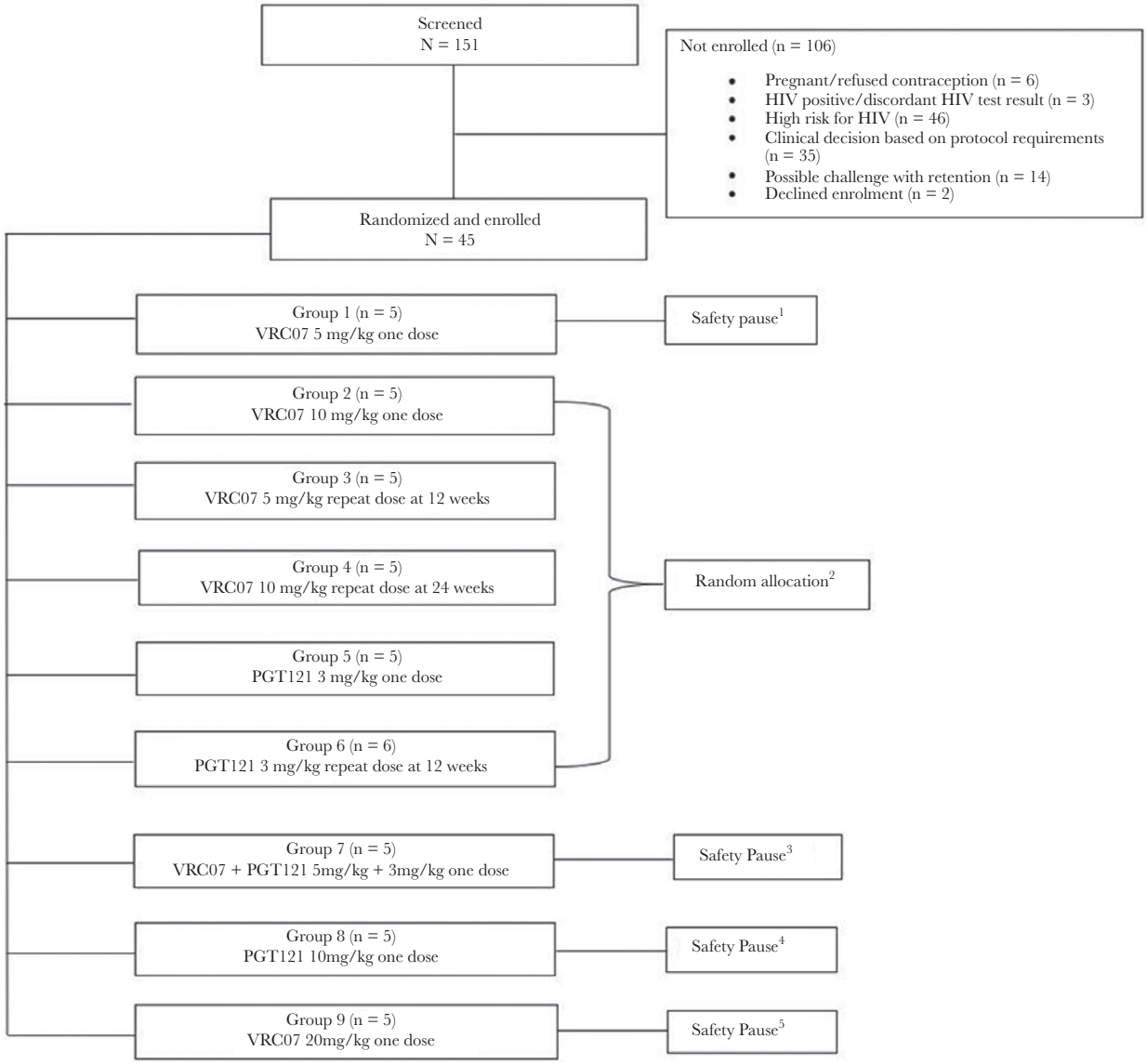


Figure 1. Screening and enrollment in the CAPRISA 012A trial. [1]After administration of the first dose to the first participant in Group 1, the study team waited 3 days before administering study product to the second participant in Group 1. After administration of the first dose to the second participant, the study team waited a further 3 days before enrolling the remaining participants into Group 1. [2]The next 25 participants were thereafter randomly allocated to Groups 2–6 and were randomized to receive study product or placebo at a 4:1 ratio. [3]Enrollment into Group 7 occurred once 12-week safety data were reviewed for the first 8 participants enrolled. [4]Dose escalation of PGT121 was assessed in group 8. After administration of study product to the first participant in Group 8, there was a safety pause of 3 days, under PSRT oversight, before administering study product to the second participant in the dose group. Once safety was established, the remaining participants were enrolled. [5]Dose escalation of VRC07-523LS was assessed in Group 9. After administration of study product to the first participant in Group 9, there was a safety pause of 3 days, under PSRT oversight, before administering study product to the second participant in the dose group. Once safety was established, the remaining participants were enrolled.

Scale Discovery platform. For PGT121, an enzyme-linked immunoassay platform was used [29, 31]. To determine neutralizing activity, a TZM-bl-neutralizing antibody assay using env-pseudotyped viruses was used [32] (Supplementary Text).

Pharmacokinetic Analysis

Pharmacokinetic analyses were performed using both compartmental and noncompartmental models. Results were reported overall and by subgroup. Summary descriptive results of PK parameters included the maximum concentration recorded (C_{max}), the time taken to reach C_{max} (T_{max}), and the area under the curve (AUC). Apparent clearance (CL/F), apparent volume of distribution (Vdss/F), and $t_{1/2}$ were estimated by compartmental methods. The PK data were fitted to a 1-compartment population PK model using NONMEM 7.3 software (ICON, Dublin, Ireland). Due to the limited participant numbers in each arm, a formal covariate analysis was not performed. Individual participant PK parameters were estimated by an empiric Bayesian method using post hoc subroutine. Parameters were normalized to 70 kg using standard

allometry, and linear PK was assumed with modeling assessed graphically.

Population PK modeling was used to conduct Monte Carlo simulations of subcutaneous 20 mg/kg VRC07-523LS and 10 mg/kg PGT121 and predict steady-state trough concentrations with every 16- or 24-week administration. Median Bayesian post hoc PK parameters values from the highest dose levels were used to generate simulation profiles. The PK profiles for VRC07-523LS were also compared with results from (1) the VRC605 trial and (2) the HVTN127/HPTN087 trial where 2.5–5.0 mg/kg VRC07-523LS was administered subcutaneously [30].

Target trough concentrations sufficient for protection have not been defined or selected for VRC07-523LS and PGT121. In rectal challenge model studies, infections occurred at VRC01 concentrations <10 μg/mL for viruses with a median infective dose (IC_{50}) of 2.06 and IC_{80} of 7.14 [33]. In the AMP trial, 8-weekly dosing of 10 and 30 mg/kg was selected to reach target concentrations of ~5 and 15 μg/mL. In the CAPRISA 012A trial, PK concentrations of >1 μg/mL were thus set as a benchmark. In AMP, VRC01 neutralized 72% of viruses with an IC_{50} <1 μg/mL. Thus, exceeding 1 μg/mL is a reasonable target, because VRC07-523LS and PGT121 are more potent.

Statistical Analysis

Baseline continuous variables were described with medians and upper and lower quartiles while categorical data were described with frequency counts and percentages. Summaries of the number and percentage of participants experiencing any AE or reactogenicity were analyzed. The number and percentages of participants experiencing each AE were tabulated by severity and relationship to study product. Each participant's adverse experience was counted once under the maximum severity or strongest recorded causal relationship. The number of reactogenicity events were summarized by severity and tabulated by study group. The acceptability of the injections was measured on a scale of 0–6 ranging from not acceptable to acceptable and was described by frequency counts and percentages. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

A total of 151 participants were screened and 45 were enrolled into the trial. One hundred four volunteers did not meet eligibility criteria and 2 decided not to enroll (Figure 1). Forty-four of the participants (98%) successfully completed the study, whereas 1 participant in Group 8 was lost to follow up after 58 weeks. Study participants were healthy women with a median age of 24 years (Table 1).

Table 1. Baseline Characteristics of the Women in the CAPRISA 012A Trial

[a]Characteristics	Group 1 (N = 4)	Group 2 (N = 4)	Group 3 (N = 4)	Group 4 (N = 4)	Group 5 (N = 4)	Group 6 (N = 4)	Group 7 (N = 4)	Group 8 (N = 4)	Group 9 (N = 4)	Placebo (N = 9)
Median age (IQR), years	23.0 (21.0–25.5)	24.5 (21.5–28.5)	22.5 (19.5–28.0)	24.0 (20.5–29.5)	22.5 (20.5–29.5)	25.5 (24.0–29.0)	23.0 (22.0–24.0)	29.5 (25.5–30.0)	26.5 (22.0–29.0)	26.0 (23.0–27.0)
Weight (kg) median (IQR)	68.1 (66.9–71.2)	49.3 (45.4–54.9)	62.6 (61.6–63.8)	57.8 (57.1–69.3)	69.9 (58.5–72.3)	68.6 (56.6–77.3)	66.4 (60.1–72.6)	64.2 (60.8–74.0)	62.7 (52.3–74.6)	68.5 (62.1–73.5)
Education level up to secondary school	2 (50.0)	3 (75.0)	3 (75.0)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	2 (50.0)	8 (88.9)
Education level up to tertiary institution	2 (50.0)	1 (25.0)	1 (25.0)						2 (50.0)	1 (11.1)
Employment status (Yes)		1 (25.0)		1 (25.0)						
Employment status (No)	4 (100.0)	3 (75.0)	4 (100.0)	3 (75.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	9 (100.0)

Abbreviations: IQR, interquartile range.

[a]Characteristics data are n (%) or median (IQR) unless otherwise specified.

Safety

Overall, product administrations were safe and well tolerated. All reported reactogenicity events were mild and resolved within the 3-day assessment period. There were no moderate or severe reactogenicity events reported. The most common events were injection site tenderness and headaches (Table 2).

A total of 161 AEs were reported. Of these, 9 were deemed related to study product and occurred within 7 days after product administration. These AEs included proteinuria in 7 participants: 4 received 5 mg/kg VRC07-523LS, 1 received 20 mg/kg VRC07-523LS, 1 received 3 mg/kg PGT121, and 1 received placebo. There were also 2 separate AEs of elevated alanine aminotransferase and aspartate aminotransferase in 2 participants who received 3 mg/kg PGT121. All related AEs were mild in severity and resolved in a median of 7 days (interquartile range, 7–21) (Supplementary Table 1). There was 1 reported unrelated serious AE of polytrauma due to a motor vehicle accident that occurred 50 days after study product administration.

Acceptability

All participants (45 of 45, 100%) reported that they were satisfied with the explanation of the injection procedure before administration and found subcutaneous administration acceptable. Most participants (39 of 45, 86.7%) found the injection schedule of 2 to 3 injections per year acceptable. Furthermore, 43 (96%) stated that, if effective, they were likely to recommend the injection to others, and 41 (91%) would be happy to disclose the receipt of the injection to their partners (Supplementary Table 2).

Human Immunodeficiency Virus Assay Cross-Reactivity

No participant had a positive HIV enzyme immunoassay response during the study, and no cases of cross-reactivity were observed when using the 2 HIV rapid antibody testing kits.

Pharmacokinetics Analysis

Although early concentrations including C_{max} and $AUC_{0\text{-}12WK}$ demonstrated less than proportional changes to dose, late VRC07-523LS concentrations increased nearly in proportion to dose. The median observed VRC07-523LS concentrations after 5, 10, and 20 mg/kg doses were 5.83, 10.05, and 15.06 µg/mL at 12 weeks; 2.52, 3.78, and 9.65 µg/mL at 16 weeks; and 0.96, 1.35, and 3.86 µg/mL at 24 weeks (Figure 2A and B). The median C_{max} after 5, 10, and 20 mg/kg doses were 42.14, 83.18, and 70.75 µg/mL. The median T_{max} after 5, 10, and 20 mg/kg doses were 4.8, 2.8, and 2.8 days. The AUC for the first 12 weeks after 5, 10, and 20 mg/kg doses were 1474.2, 3194.9, and 2010.9 µg/mL (Figure 2, Supplementary Table 3). A PopPK model pooled across dose levels for VRC07-523LS estimated the apparent total CL/F to be 288 mL/day, apparent volume of distribution (Vd/F) to be 12.4 liters, and $t_{1/2}$ to be 29.4 days. Although the median Bayesian CL/F for 5 and 10 mg/kg dose arms were in the same range, all 4 subjects that received 20 mg/kg had higher CL/F values (Figure 2). The estimated between-subject variabilities were 57% and 55% for CL/F and V/F (Supplementary Table 4).

Observed median PGT121 concentrations after 3 and 10 mg/kg doses were 3.90 and 25.35 µg/mL at 4 weeks and below the limit of quantitation for the 3 mg/kg dose beyond 8 weeks (Figure 3A). The percentage absorbed in the 4 participants that received 10 mg/kg appeared to be greater than with 3 mg/kg with greater than proportional increases in C_{max}, C_{8WK} and, $AUC_{0\text{-}12}$ (Figure 3D). The median week 8 concentration after the 10 mg/kg PGT121 dose was 8.26 µg/mL. For the 10 mg/kg dose, many of the week 12 and 16 samples were missed due to study interruption from the coronavirus disease 2019 pandemic and national lockdown. However, at week 24, PGT121 was detectable in 2 of 3 samples (Figure 3B). The median C_{max} after 3 and 10 mg/kg doses were 10.13 and 82.91 µg/mL. The median T_{max} after 3 and 10 mg/kg doses were 4.8 and 2.9 days. The AUC after 3 and 10 mg/kg doses were 9.1 and 78.6 µg/mL (Figure 3, Supplementary Table 3). A PopPK model pooled across dose levels estimated CL/F to be 720 mL/day, Vd/F to be 21.0L, and $t_{1/2}$ to be 20.2 days (Supplementary Table 4).

The PK modeling of 20 mg/kg VRC07-523LS showed that at 16 weeks the median concentration was 8.1 µg/mL, and 99.6% of concentrations were greater than 1 µg/mL, and 78% of concentrations greater than 5 µg/mL. At 24 weeks, the median concentration was 3.2 µg/mL, and 87% of concentrations were greater than 1 µg/mL, and 95% of concentrations were greater than 0.5 µg/mL (Figure 2C, Supplementary Figure 1). The PK modeling of 20 mg/kg PGT121 at 16 weeks showed a median concentration of 1.1 µg/mL and that 52% of concentrations were greater than 1 µg/mL and 66% of concentrations greater than 0.5 µg/mL. At 24 weeks, the median concentration was 0.13 µg/mL with 16% of concentrations greater than 1 µg/mL and 26% greater than 0.5 µg/mL (Figure 3C, Supplementary Figure 1).

The VRC07-523LS antibody concentrations were similar when given in combination with PGT121, and visa-versa. Repeat PK dosing resulted in similar profiles after the first and second dose. The VRC07-512LS PK profiles after administration of 5 mg/kg were similar to those previously reported after a 5 mg/kg subcutaneous dose in the VRC605 trial [29].

Antidrug Antibody Analysis

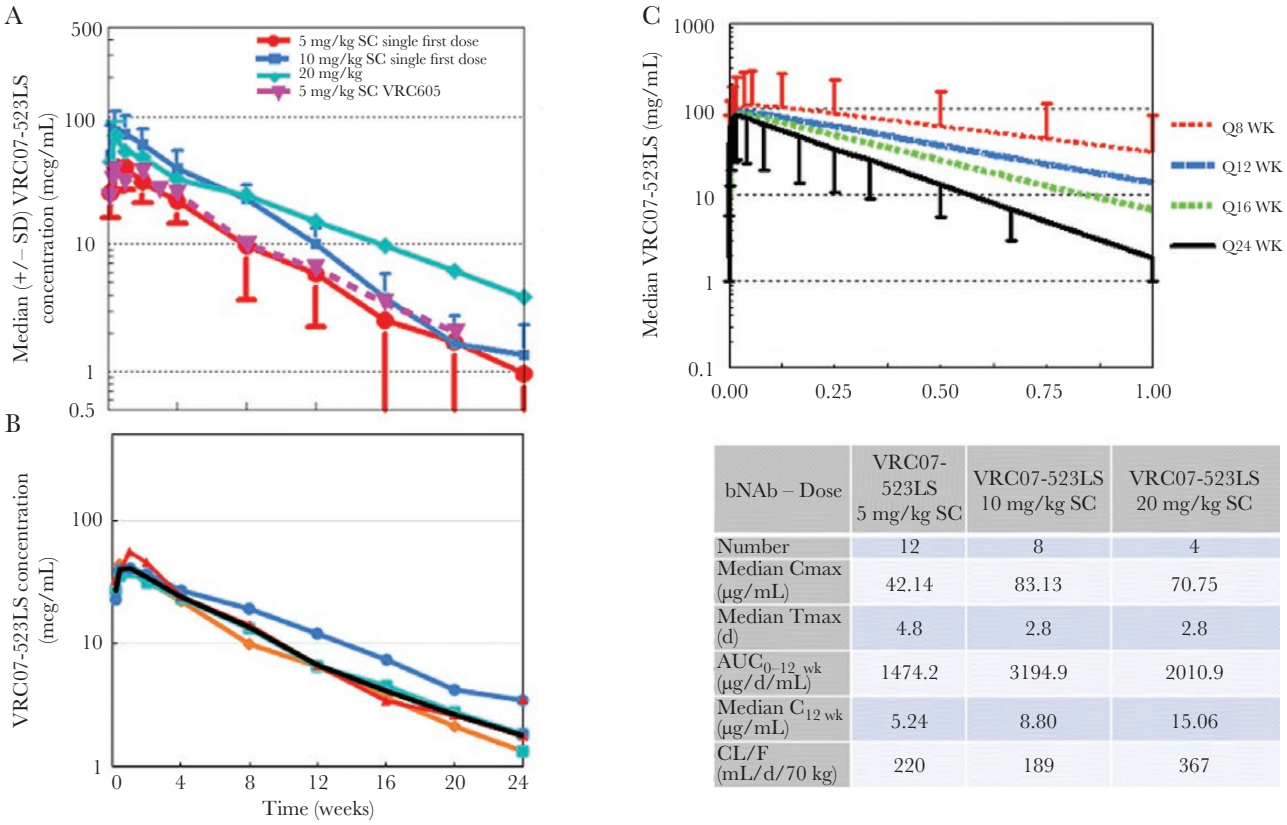
No ADA was detected at any timepoint, and participants who received repeat doses showed no evidence of diminished peak or trough concentrations.

Neutralizing Antibody Assays

Potent neutralization (ID_{50} >000) by VRC07-523LS and PGT121 was observed from Day 1 and peaked between Day 3 and 7 for all participants in both low- and high-dose groups. In general, the high-dose groups had higher titers at peak, but declined to

Table 2. Reactogenicity Events Reported in the CAPRISA 012A Trial

	VRC07-523LS 5 mg/kg (N = 8)		VRC07-523LS 10 mg/kg (N = 8)			PGT121 3 mg/kg (N = 8)				Placebo (N = 9)	
Severity	Dose 1 (N = 8/8)	Dose 2 (N = 4/8)	Dose 1 (N = 8/8)	Dose 2 (N = 4/8)	VRC07-523LS 20 mg/kg Single dose (N = 4)	Dose 1 (N = 8/8)	Dose 2 (N = 4/8)	PGT121 10 mg/kg Single dose (N = 4)	VRC07-523LS + PGT121 5 mg/kg + 3 mg/kg (N = 4)	Dose 1 (N = 9/9)	Dose 2 (N = 3/9)
Systemic Reactions											
Arthralgia											
None	8	4	8	4	4	8	3	4	4	9	3
Mild	0	0	0	0	0	0	1	0	0	0	0
Chills											
None	7	4	8	4	4	8	4	4	4	9	3
Mild	1	0	0	0	0	0	0	0	0	0	0
Headache											
None	7	3	6	3	3	8	4	4	4	7	3
Mild	1	1	2	1	1	0	0	0	0	2	0
Malaise/Fatigue											
None	7	3	7	4	4	8	3	4	4	9	3
Mild	1	1	1	0	0	0	1	0	0	0	0
Myalgia											
None	8	4	7	4	4	8	4	4	4	9	0
Mild	0	0	1	0	0	0	0	0	0	0	0
Nausea											
None	7	4	8	4	3	8	4	4	4	9	3
Mild	1	0	0	0	1	0	0	0	0	0	0
Local Reactions											
Erythema/Redness											
None	8	4	7	4	4	8	4	4	4	9	3
Not gradable	0	0	1	0	0	0	0	0	0	0	0
Induration/Swelling											
None	8	3	8	4	4	8	4	4	4	9	3
Mild	0	1	0	0	0	0	0	0	0	0	0
Pain											
None	8	4	6	4	4	8	3	4	4	9	3
Mild	0	0	2	0	0	0	1	0	0	0	0
Tenderness											
None	7	3	7	3	4	8	3	4	3	9	2
Mild	1	1	1	1	0	0	1	0	1	0	1



bNAb – Dose	VRC07-523LS 5 mg/kg SC	VRC07-523LS 10 mg/kg SC	VRC07-523LS 20 mg/kg SC
Number	12	8	4
Median Cmax (μg/mL)	42.14	83.13	70.75
Median Tmax (d)	4.8	2.8	2.8
$AUC_{0–12\ wk}$ (μg/d/mL)	1474.2	3194.9	2010.9
Median $C_{12\ wk}$ (μg/mL)	5.24	8.80	15.06
CL/F (mL/d/70 kg)	220	189	367

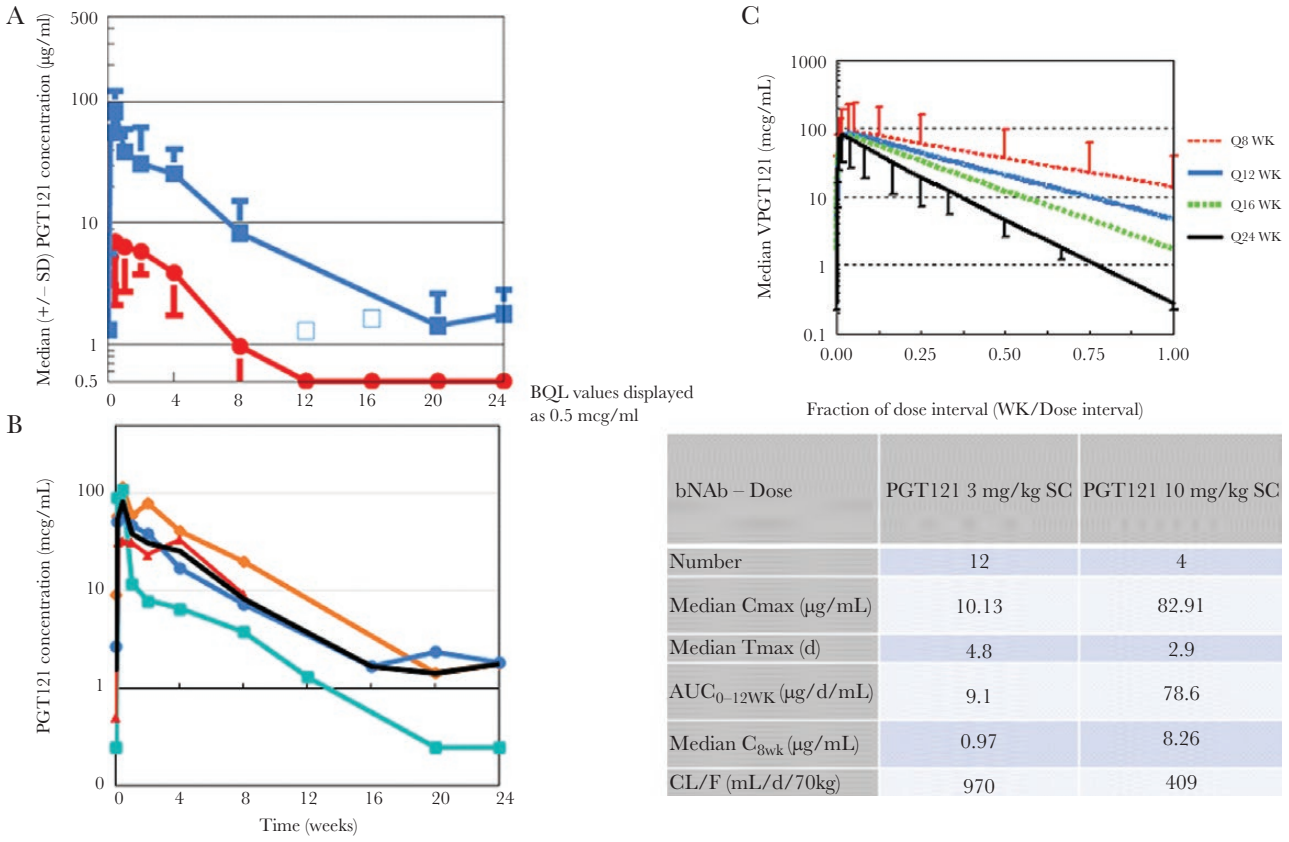
Figure 2. (A) Observed VRC07-523LS median concentrations after 5, 10, and 20 mg/kg subcutaneous (SC) administrations in the CAPRISA 012A trial and concentrations after 5 mg/kg subcutaneous administration in the VRC605 trial. (B) Observed VRC07-523LS concentrations after 20 mg/kg dosing in Group 9, each colored line represents concentrations for each participant, and the black line represents the median concentration. (C) VRC07-523LS pharmacokinetic simulations at 20 mg/kg showing median antibody concentrations at different dose intervals based on the PopPK model. Table insert shows pharmacokinetic parameters after subcutaneous administrations of VRC07-523LS at 5, 10, and 20 mg/kg. AUC, area under the curve; bnAbs, broadly neutralizing antibodies; CL/F, clearance; C_{max}, maximum concentration; SD, standard deviation; T_{max}, time taken to reach C_{max}.

almost the same levels as the lower dose groups (ID_{50}: 100–254) at week 24. The VRC07-523LS repeat dose at 12 and 24 weeks significantly increased neutralizing antibody titers, but then they decreased to undetectable levels at 12 and 24 weeks after the second dose, respectively. Due to fewer measurements being available in the PGT121 high-dose group, it was difficult to compare the effect of the additional dose in the low- and high-dose groups. However, an increase in neutralization titers with the second dose matching the first peak for the PGT121 low-dose group was observed. The changes in VRC07-523LS and PGT121 serum virus neutralization titers was consistent with serum PK concentrations, indicating that both antibodies retained functional activity after subcutaneous administration.

DISCUSSION

VRC07-523LS and PGT121 administered subcutaneously alone or in combination was safe and well tolerated. VRC07-523LS showed favorable pharmacokinetics over 24 weeks; PK modeling with 16- to 24-week dosing regimens showed acceptable concentrations of VRC07-523LS, and high-dose PGT121 simulations showed lower, but detectable concentrations. Overall, VRC07-523LS was found to be a suitable bnAb to take forward in developing combination bnAbs as a long-acting prevention technology to reduce HIV incidence among young women in southern Africa.

Our results align well and extend the data from the first-in-human VRC07-523LS trial (VRC605). In the CAPRISA 012A trial, VRC07-523LS subcutaneously administered at a dose of 20 mg/kg results in concentrations that persist above 1 μg/mL for more than 24 weeks. VRC605 evaluated intravenous administration of 1 to 40 mg/kg and subcutaneous administration at the dose of 5 mg/kg, demonstrating safety and tolerability with a favorable PK profile and $t_{1/2}$ of 33 days, similar to our finding of 29 days [29]. In the VRC605 subcutaneous arm, the reported C_{max} of 50 μg/mL is comparable to our value of 42 μg/mL. The 12-week antibody concentrations were approximately 20% lower than reported in VRC605. In this study, the absorption after the highest dose of 20 mg/kg of VRC07-523LS appeared to be less complete and slower than lower doses. Mean VRC07-523LS concentrations at week 24 were 1.27, 1.68, and 3.60 μg/mL after doses of 5, 10, and 20 mg/kg, respectively (Supplementary Table 3). Absorption may have been limited at the highest dose,



bNAb – Dose	PGT121 3 mg/kg SC	PGT121 10 mg/kg SC
Number	12	4
Median Cmax (µg/mL)	10.13	82.91
Median Tmax (d)	4.8	2.9
$AUC_{0–12WK}$ (µg/d/mL)	9.1	78.6
Median C_{8wk} (µg/mL)	0.97	8.26
CL/F (mL/d/70kg)	970	409

Figure 3. (A) Observed PGT121 median concentrations after 3 and 10 mg/kg subcutaneous (SC) administrations in the CAPRISA 012A trial. (B) Observed PGT121 concentrations after 10 mg/kg dosing in Group 8, each colored line represents concentrations for each participant, and the black line represents the median concentration. (C) PGT121 pharmacokinetic simulations at 20 mg/kg showing median antibody concentrations at different dose intervals based on the PopPK model. Table insert shows pharmacokinetic parameters after 3 and 10 mg/kg subcutaneous administrations of PGT121. AUC, area under the curve; bnAbs, broadly neutralizing antibodies; CL/F, clearance; C_{max}, maximum concentration; SD, standard deviation; T_{max}, time taken to reach C_{max}.

but the small sample size in the 20 mg/kg study arm precluded any robust subgroup analyses. The HIV Vaccine and Prevention Trials Networks assessment of intravenous, intramuscular, and subcutaneous administrations of VRC07-523LS demonstrated that VRC07-523LS was safe and well tolerated with a $t_{1/2}$ of approximately 40 days and concentrations at 16 weeks similar to our study [30].

PGT121 plasma concentrations were low 8 weeks after administration of a low dose of 3 mg/kg. The rate of PGT121 absorption seemed to be greater in the 4 subjects that received 10 mg/kg compared with the lower dose. Preliminary data from another phase 1 trial of PGT121 administered intravenously at 3, 10, and 30 mg/kg and subcutaneously at 3 mg/kg was safe and well tolerated with a $t_{1/2}$ of 23 days, which ranged from 19 to 26 days depending on dose and route of administration, in keeping with this trial [31]. PGT121 had a lower $t_{1/2}$ compared with VRC07-523LS (29 vs 20 days), which was expected considering it is not an LS version [34, 35].

Both antibodies maintained their neutralizing activity postadministration as measured in the TZM-bl neutralization assay using differentially sensitive pseudoviruses. The ID_{50} titers were dependent on the choice of virus used and do not represent a protective titer or relative concentrations of the antibodies. The neutralization profiles of individual antibodies in the combination group matched those who received single antibodies, indicating that there was no interference between the 2 antibodies. There were no antidrug antibodies found during the study even after the second dose, in line with other studies. The retention of neutralizing activity suggests that neither VRC07-523LS nor PGT121 was adversely affected by the subcutaneous route of administration.

The CAPRISA 012B trial will be evaluating the safety and PK of 2 LS version antibodies, CAP256V2LS and VRC07-523LS, as an antibody combination for HIV prevention [27]. VRC07-523LS has already been advanced in other clinical trials alone and in combination with other bnAbs. Studies are ongoing to assess the improved PGT121.414.LS version in both double and triple combinations [21]. Several other monoclonal antibodies have also been evaluated in clinical trials [21, 36]. Preliminary data of N6LS showed that it was safe and well tolerated with a $t_{1/2}$ exceeding 30 days [37]. The initial trials of 3BNC117 and 10-1074 demonstrated safety and tolerability with $t_{1/2}$ of 17.2

and 24 days [38–40]. To improve the PK profile of this intravenous combination, LS versions of the bnAbs were engineered and are currently being evaluated alone and in combination via both intravenous and subcutaneous routes [38].

The CAPRISA 012A trial had some strengths. It was the first assessment of both these monoclonal antibodies in combination. The study focused specifically on young African women, who bear the greatest burden of new HIV infections. Furthermore, doses administered subcutaneously were substantially higher than in previous trials, which only evaluated low subcutaneous doses of 3–5 mg/kg. This study also evaluated a wider range of doses than other studies.

Limitations of the trial included the small sample size in each study arm, which is typical of phase I trials. The confidence in PGT121 modeling results was lower than the VRC07-523LS modeling, especially at later time points. This was due to the relative lack of PGT121 concentrations and high variability beyond 8 weeks and no administration of a higher PGT121 dose of 20 mg/kg.

The relatively large number of injections (up to 9) used to deliver the higher doses, despite being well tolerated by the participants, highlights the need for improved delivery methods that would also allow an extension of dosing intervals. One such method under investigation in the CAPRISA 012B trial [27] is the use of dispersing agents, such as hyaluronidase containing products to allow an increase in the administered volume, thereby improving practicality [21, 41]. In addition, coformulation of higher concentrations of antibodies as a single subcutaneous injection is also being explored [42].

CONCLUSIONS

In the absence of an effective HIV vaccine, the development of an injectable passive immunization as a prevention technology, which can be administered 4- or 6-monthly to young women, may provide an adherence advantage over existing HIV prevention modalities. Results from the AMP trial demonstrated that to effectively prevent HIV-1 infection, the optimal selection of complementary bnAbs with strong neutralization potency and extended serum persistence is required. In the CAPRISA 012A trial, antibody levels suggest that subcutaneous administration of VRC07-523LS at a dose of 20 mg/kg is appropriate for dosing intervals up to 24 weeks, whereas shorter intervals (<8 weeks) are appropriate for low-dose PGT121. These findings are supportive of continued evaluation of VRC07-523LS and optimized version of PGT121 as interventions for HIV prevention.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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