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Title: **Assessing the safety and pharmacokinetics of the monoclonal antibodies, VRC07-523LS and PGT121 in HIV negative women in South Africa: Study protocol for the CAPRISA 012A randomised controlled Phase I trial**

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Running title

Phase 1 trial of the monoclonal antibodies VRC07-523LS and PGT121

Abstract

Introduction

Despite extensive prevention campaigns and scale-up of antiretroviral therapy, HIV incidence among young women in southern Africa remains high. While the development of an efficacious vaccine remains a challenge, the discovery of broadly neutralising monoclonal antibodies has created the opportunity to explore passive immunization as a long-acting injectable HIV prevention strategy. The purpose of this trial is to provide safety, pharmacokinetic (PK) and functional activity data of VRC07-523LS and PGT121 when administered subcutaneously to young South African women. Going forward, the aim is to select the ideal dose and/or monoclonal antibody for co-formulation and testing with CAP256-VRC26.25LS, a potent monoclonal antibody against subtype C virus, in an efficacy trial.

Methods and analysis

CAPRISA 012A is a randomized, double blinded, placebo-controlled phase I trial to assess the safety, PK profile of two monoclonal antibodies, VRC07-523.LS and PGT121 administered subcutaneously to 35 young HIV negative women at low risk for HIV infection. Women will be randomized into seven groups of five participants each. In each group, women will be randomized (4:1) to the active intervention, VRC07-523LS and/or PGT121, or placebo. Participants will be followed up for 24 weeks after the administration of the last dose of study product with a total study duration of 72 weeks. Safety in the study will be assessed by the number and percentage of reactogenicity and adverse events experienced by participants and the relatedness to study product. The PK study design was based on preliminary PK data for VRC07-523LS and PGT121.

Ethics and dissemination

Ethical approval has been granted by the South African Health Products Regulatory Authority and by the University of KwaZulu-Natal Biomedical Research Ethics Committee. Results will be presented at international conferences and published in academic peer-reviewed journals. Trial results will be uploaded on the clinical trial registry.

Registration details

Pan African Clinical Trials Registry: PACTR201808919297244.

Keywords

HIV prevention, monoclonal antibodies, VRC07-523LS, PGT121, South Africa

Article Summary

Strengths and limitations of this study

1. This trial will provide new safety, pharmacokinetic and functional activity data for two monoclonal antibodies, VRC07-523LS and PGT121, when administered subcutaneously alone or in combination to South African women.
2. The trial will inform the optimal dose and monoclonal antibody combination that will be selected for co-formulation and testing with the potent monoclonal antibody CAP256-VRC26.25LS, in an efficacy trial.
3. Data from this trial could inform the future development of an injectable HIV prevention method, with anticipated four- or six-monthly dosing, that offers implementation and adherence advantages over available antiretroviral pre-exposure prophylaxis options.
4. While the use of monoclonal antibodies are a promising HIV prevention strategy and high levels of protection have been demonstrated in animal studies, the efficacy in human clinical trials has not yet been established.

Introduction

Despite extensive prevention campaigns and scale-up of antiretroviral therapy (ART), South Africa remains an epicentre of the HIV pandemic[1]. In southern and eastern Africa, the incidence of HIV among young women below 25 years remains high[1 2]. While the HIV prevention landscape is changing rapidly, principally with the roll-out of pre-exposure prophylaxis (PrEP) and early antiretroviral therapy (ART) (Treatment as Prevention), current HIV prevention programmes have had limited impact on reducing HIV incidence in young women[3-5]. Clinical trials using daily oral tenofovir disoproxil fumarate alone and in combination with emtricitabine in African women demonstrated inconsistent results, most likely due to varying levels of medication adherence[6-8]. New approaches that overcome these adherence challenges, are being tested. While the development of an efficacious vaccine remains a major challenge, the discovery of potent monoclonal antibodies (mAbs) has created the opportunity to explore passive immunization as an HIV prevention strategy.

VRC07-523LS is a highly potent and broadly neutralizing mAb that targets the HIV-1 CD4 binding site. It was developed by the Vaccine Research Centre (VRC) at the National Institute of Health, United States. The antibody was engineered based on the VRC01 mAb, that was originally discovered in a subject infected with HIV-1, whose immune system controlled the virus without ART for more than 15 years [9 10]. The neutralization, potency and breadth of VRC01 was enhanced by next-generation sequencing and structure-guided design to create VRC07-523, which displayed 5- to 8-fold more potency than VRC01 and neutralized 96% of viruses tested [9]. A lysine-serine (LS) mutation was thereafter designed to extend the half-life and increase concentrations in mucosal tissue. This mutation was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor, resulting in increased recirculation of functional IgG, thus increasing plasma half-life [9]. Pharmacokinetic (PK) analyses in rhesus macaques demonstrated half-life values for VRC07-523LS ranging from 7-10 days, compared to 5 days for VRC07 and 5-6 days for VRC01. VRC07-523LS is approximately 10-fold more potent than VRC01 and active against 96% of diverse HIV-1 strains, including clade C[11]. This antibody is currently being evaluated in the HVTN 703/HPTN 081 Phase 2b clinical trial [ClinicalTrials.gov Identifier: NCT02568215].

PGT121, is a recombinant human IgG1 mAb, isolated from an African donor in 2011, that targets the V3 glycan-dependent epitope region of the HIV envelope protein [12]. PGT121 was

developed by the Centre for Virology and Vaccine Research at the Beth Israel Deaconess Medical Centre and the International AIDS Vaccine Initiative. This mAb has a long heavy chain complementarity determining region that forms an antibody binding site with two functional surfaces and does not bind simply to the GPGR region of V3. Structural studies have shown that although PGT121 does not engage the CD4 binding site, it inhibits CD4 binding to gp120. PGT121 disrupts the Env-receptor engagement by an allosteric mechanism which interferes with CD4 binding and viral entry[13]. Due to its mechanism of action, PGT121 has excellent potency and breadth, which is higher than that observed for VRC01[10].

In order to overcome the genetic diversity of HIV, combinations of mAbs targeting different epitopes on the viral envelope will likely be required [10]. To identify the optimal combination of mAbs, Wagh and colleagues assessed the neutralizing activity of 15 mAbs targeting four distinct epitopes of the envelope against a panel of 200 early/acute clade C HIV-1 Env-pseudoviruses and a mathematical model was developed to predict neutralization by mAb combinations [14] [15]. The analysis revealed that the neutralization profile of CAP256-VRC26.25LS (which targets the V2 loop) was particularly well suited as a complementary mAb with VRC07-523LS and PGT121. These two mAbs were found to be the best combinations in terms of neutralisation breadth and potency.

Currently there are two phase I trials assessing PGT121 and VRC07-523LS in the US. These are separate trials that are investigating the safety and tolerability of each mAb used alone, but not in combination (ClinicalTrials.gov Identifier: NCT03015181 and NCT02960581). Preliminary data from these trials have demonstrated no safety concerns. Neither mAb has been investigated in an African population, particularly young African women, who are at high risk of HIV acquisition. The purpose of this protocol is to provide safety, and functional activity data from a phase I trial assessing VRC07-523LS and PGT121 when administered subcutaneously (SC), alone and in combination to HIV negative women in South Africa. Data from this trial will inform the optimal dose and mAb combination that will be selected for co-formulation and testing with the potent mAb, CAP256-VRC26.25LS, in a proof-of-concept trial.

Methods and analysis (SPIRIT reporting guidelines used)

CAPRISA 012A is a randomized, double blinded, placebo-controlled phase I clinical trial.

Study setting

The study will be conducted at the CAPRISA eThekwini Clinical Research Site in Durban, KwaZulu-Natal, South Africa.

Study Population Selection

The study will include 35 HIV negative women. Enrolment will be based on the following eligibility criteria (Table1-3).

Table 1: Inclusion criteria

- 18 to 40 years of age
- Female sex at birth
- Able and willing to complete the informed consent process
- Has understood the information provided, including the potential impact and/or risks linked to SC administration of the study product, and is willing to comply with protocol procedures
- Has access to the clinical research site and is available for the duration of the study
- Based on clinical assessment must be in good general health
- Assessed by site staff to be at low risk for HIV infection
- If of reproductive potential, has evidence of effective contraceptive use in the previous 21 days, and agrees to continued use during the study period
- Willing to have blood and genital samples collected, stored, and used for research purposes.

Table 2: Screening laboratory parameters

- White Blood Cell Count within institutional normal range
- Haemoglobin > 10g/dL
- Creatinine ≤ upper limit of institutional normal range
- Alanine aminotransferase, aspartate aminotransferase ≤ upper limit of institutional normal range
- Negative for HIV infection by an FDA-approved method of detection in the last 30 days
- Negative β-HCG pregnancy test (urine or serum) within 21 days of enrolment

Table 3: Exclusion criteria

- Any clinically significant acute or chronic medical condition that makes the participant unsuitable for participation in the study, or jeopardizes the safety or rights of the volunteer
- If planning a pregnancy for the duration of the study, currently pregnant or breastfeeding

- Exceeding the weight of 90 kilograms (in order to restrict the amount of injections administered)
- A history of alcohol or substance use judged to potentially interfere with participant study compliance
- Prior participation in an investigational HIV vaccine trial, except if proof of allocation to the placebo arm is available
- Administration of a mAb or polyclonal immunoglobulin within 28 days prior to enrolment
- Any history of anaphylaxis and related symptoms such as hives, respiratory difficulty and angioedema
- Evidence of autoimmune disease, or receiving immunosuppressive therapy
- Participants in this study may not take part in other concurrent research studies that would interfere with the objectives of this study.

Study Schema

The 35 HIV negative participants at low risk for HIV infection will be randomised into seven groups of five participants each (Table 1). In each group (n=5), four women will be randomly assigned to the active intervention, VRC07-523LS and/or PGT121 and one participant randomly assigned to placebo. The safety and PK profile of one and two doses of VRC07-523LS and/or PGT121 mAbs administered SC will be evaluated. VRC07-523LS will be administered at a dose of 5mg/kg or 10mg/kg at one or two time points alone and in combination with PGT121. PGT121 will be administered SC at a dose of 3mg/kg at one or two time points and in combination with VRC07-523LS. Participants will be followed up for 24 weeks after the administration of the last dose of study product with a total study duration of 72 weeks.

Table 1: The distribution of study participants into individualised groups

Group	Regimen	N	Dose (mg/kg)
1	VRC07-523LS/Placebo	4/1	5 mg/kg SC one dose
2	VRC07-523LS/ Placebo	4/1	10 mg/kg SC one dose
3	VRC07-523LS/ Placebo	4/1	5 mg/kg SC with one repeat dose at 12 weeks
4	VRC07-523LS/ Placebo	4/1	10 mg/kg SC with one repeat dose at 24 weeks
5	PGT121/Placebo	4/1	3 mg/kg SC one dose

6	PGT121/Placebo	4/1	3 mg/kg SC with one repeat dose at 12 weeks
7	VRC07-523LS + PGT121/ Placebo	4/1	5 mg/kg SC + 3 mg/kg SC one dose

Study Objectives

Primary objective

- To evaluate the safety of one and two doses of VRC07-523LS and/or PGT121 mAbs administered SC.

Secondary objectives

- To characterize the PK profile of VRC07-523LS mAb (5 and 10 mg/kg) administered SC individually as a single dose or as two doses 12 and 24 weeks apart.
- To characterize the PK profile of PGT121 mAb (3 mg/kg) administered SC individually as a single dose or as two doses 12 weeks apart.
- To characterize the PK profile of VRC07-523LS and PGT121 mAbs administered in combination
- To assess the acceptability of VRC07-523LS and PGT121 mAbs SC injections.
- To evaluate the concentrations and functional activity of VRC07-523LS and/ or PGT121 mAb in plasma and genital samples following SC administration.
- To determine whether SC administration of VRC07-523LS and/or PGT121 mAbs induces anti-mAbs.

Primary sample

- Proportion of participants with mild, moderate and severe reactogenicity events within the first three days after SC administration.
- Proportion of participants with mild, moderate and severe adverse events (AEs) up to 24 weeks after the last SC administration.

Secondary outcomes

- Maximal concentration (Cmax), time of maximal concentration (tmax), area under the concentration vs time curve (AUC), apparent clearance (CL/F) and terminal half-life ($t_{1/2}$) of VRC07-523LS and PGT121 mAbs.
- Proportion of participants who report that the SC injections are acceptable.
- Concentration and function of mAbs in the systemic and genital tract compartments before and after SC mAb administration

- Changes in the concentration of serum anti-mAbs before and after SC mAb administration

Sample size calculation

The analysis of the CAPRISA 012A trial will be primarily descriptive and a pragmatic approach was taken when choosing the sample size, ensuring enough participants to obtain safety data. Currently, there is no safety data available to inform the true event rates that we might observe in the study. However, since the main objective of the study is to evaluate the safety of VRC07-523LS and PGT121 when administered SC, the ability of the study to detect serious adverse events (SAEs) was assessed for a range of hypothetical event rates. This was done by calculating the probability of detecting no SAE, at least one or two SAEs at a specified true event rate. These probabilities highlight the likelihood of the study to detect either rare or common AEs or SAEs as shown in Table 2 and 3. In addition, the 95% confidence interval for the true event rates were calculated.

Among the four participants receiving active product in each of the seven groups, there is a 34% chance of observing at least one event if the true event rate is 10%. When the true event rate is two to three-fold higher, this probability rises to 59% and 76% respectively (Table 2).

Table 2: Probability of observing no events, one or more events and two or more events for a range of hypothetical true event rates

True event rate (%)	Number of participants	No events	One or more events	Two or more events
5	4	0.81	0.19	0.01
10	4	0.66	0.34	0.05
20	4	0.41	0.59	0.18
30	4	0.24	0.76	0.35

Since the phase I assessment of SC administration includes eight participants receiving PGT121, 16 participants receiving VRC07-523LS and 28 participants receiving active study product, the probability of observing no events, one or more events, and two or more events for a range of true event rates is provided in Table 3. For example, among the eight participants receiving only PGT121 at enrolment there is an 8% chance of observing at least one event, if the true event is 1%, but 83% if the true event is 20%. However, if we combine all 16 women receiving only VRC07-523LS study product at enrolment these probabilities change to 15%

and 97% if the true event rates are 1% and 20%, respectively. As expected, an increase in sample size, increases the likelihood of detecting rare events.

Table 3: Probability of observing no events, at least 1 event or at least 2 events for a range of hypothetical true event rates

True event rate (%)	Number of participants	No events	At least 1 event	At least 2 events
1	4	0.96	0.04	<0.01
	8	0.92	0.08	<0.01
	12	0.89	0.11	0.01
	16	0.85	0.15	0.01
	28	0.75	0.25	0.03
5	4	0.81	0.19	0.01
	8	0.66	0.34	0.06
	12	0.54	0.46	0.12
	16	0.44	0.56	0.19
	28	0.24	0.76	0.41
10	4	0.66	0.34	0.05
	8	0.43	0.57	0.19
	12	0.28	0.72	0.34
	16	0.19	0.81	0.49
	28	0.05	0.95	0.78
20	4	0.41	0.59	0.18
	8	0.17	0.83	0.50
	12	0.07	0.93	0.73
	16	0.03	0.97	0.86
	28	<0.01	>0.99	0.98
30	4	0.24	0.76	0.35
	8	0.06	0.94	0.74
	12	0.01	0.99	0.91
	16	<0.01	>0.99	0.97
	28	<0.01	>0.99	>0.99

Study Procedures

Informed consent

In accordance with South African Good Clinical Practice guidelines, informed consent is obtained from each study participant in English or isiZulu (the local African language) prior to screening and enrolment. Consent for pharmacogenetic studies as well as specimen storage is also obtained. Participants are provided with copies of their forms if they wish to receive them. For illiterate participants, an impartial witness is required for the entire informed consent process.

Recruitment

The CAPRISA community programme will inform, educate and mobilise the community to enhance community input into the research process. The local community research support groups (CRSG) play an active role as an interface between the researchers and community members serving as advocates for the community's best interests and ensuring that the researchers are always aware of any concerns within the community about the research being conducted. The study concept is introduced to the CSRG and concerns are addressed, and feedback is given to the study team. The recruitment team will raise awareness of clinical trial opportunities and educate the community regarding eligibility, screening and enrolment. After enrolment into the study, study staff will make every reasonable effort to ensure retention by collecting adequate locator information for follow-up tracking, visit reminders and retention activities.

Screening and enrolment

Eligibility for the study is assessed in a step-wise manner at screening and enrolment. Potential participants will be invited to screen for the study and asked to provide informed consent for screening. Potential participants are checked for co-enrolment on the Biometric Co-Enrolment Prevention System (BCEPS) and are asked to provide proof of contraception, i.e. family planning card, as well as identity documents. Thereafter, they receive pre-test counselling and two rapid HIV tests are performed. Post-test counselling is provided and if required, referral to one of several HIV/AIDS care programs is facilitated. If both HIV test results are negative, the potential participant is asked to provide socio-demographic and behavioural information and undergoes a blood draw for screening bloods, as well as urine pregnancy testing. If potential participants remain eligible based on their screening blood results, they will undergo a complete physical examination. Screening blood tests include haematology, blood chemistry tests, liver function tests, serology, hepatitis B virus assays and serum and plasma storage. A genital specimen using the SoftCup collection device (SoftCup, EuroFemPro, Netherlands, or the SoftCup, Instead Inc., San Diego, CA) will also be obtained [16].

Randomisation

Participants will be randomized according to the randomization schedule prepared by the blinded study statistician prior to study start. In this study, the pharmacist will remain unblinded. Sequentially numbered, sealed, opaque envelopes containing the intervention allocation, participant identification number and a treatment code (for use by the unblinded pharmacist only) will be provided to the study coordinator, to be opened once a participant has been deemed eligible and is ready to be enrolled into the study. Group 1 (n=5) will be randomised first. After administration of the first dose to the first participant, the study team

will wait for three 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 will wait a further three days before enrolling the remaining participants into Group 1. Thereafter, the next 25 participants will be randomly allocated to Groups 2 – 6. Enrolment of the final five participants into Group 7 will only occur once 12-week safety data has been reviewed for the first eight participants who received product.

Laboratory investigations

Serum, plasma, and genital specimens will be taken at enrolment and designated follow-up visits and will be stored for PK analysis, detection of autoreactivity and assessments of markers of safety. The CAPRISA Research Laboratories will conduct specific laboratory testing required for this protocol. Sample processing and storage of specimens for possible future testing (blood and vaginal specimen) will also be undertaken. An accredited contract laboratory will perform all safety blood testing and provide a backup laboratory service when required.

Follow up visits

At each scheduled study visit, enrolled participants in the intervention and control arm will also be provided with HIV risk reduction counselling, contraception counselling and contraceptive methods of choice. Participants will receive advice on how to contact study staff with additional questions about the study, how to request additional counselling, and how to report possible AEs. In addition to the regular follow-up requirements, genital specimen collection and scheduled safety blood draws as well as samples for PK analysis and storage will be completed.

Safety Monitoring and Adverse Event Reporting

Reactogenicity assessments

A baseline local and systemic reactogenicity assessment will be conducted prior to study product administration. Once the study product has been administered, participants will be directly observed in the clinic for a minimum of one hour, after which an early reactogenicity assessment will be performed. The participant will be seen at the clinic on the day of product administration (enrolment visit) as well as Day one and Day three. Participants will be contacted telephonically on the evening of the enrolment visit and on Day two after product administration. In addition, all participants will keep a daily diary of local and systemic symptoms called a post-injection symptom log. This will aid to track and reconcile any local and systemic reactogenicity events that the participant experiences.

Adverse events and reporting requirements

Reporting of all AEs will occur during the period from the first study product administration through to the end of the study. After this period, only SAEs and AEs of special interest (potential immune-mediated diseases that include both autoimmune diseases and also other inflammatory and/or neurologic disorders that may or may not have an autoimmune aetiology), will be recorded. Each AE will be graded for severity using The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.1, July 2017. Attribution categories used will be either 'related' (a reasonable possibility that the AE may be related to the study product) or 'not related' (not a reasonable possibility that the AE is related to the study product). All AEs will be captured in the database regardless of attribution. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline or becomes non-gradable). Participants with unresolved AEs at study exit will be followed for up to 30 additional days and will be referred to a health care provider for further management, if required.

Data and safety monitoring

The trial will be audited by an external monitor prior to study start and during study conduct. Safety review decisions and the status of enrolment throughout the trial will be discussed as part of regular safety review meetings by a Protocol Safety Review Team (PSRT). In addition, a Data and Safety Monitoring Board (DSMB) consisting of three clinical trial specialists, a biostatistician and an ethicist, who are independent from the current study will review safety data during the trial. The study statisticians will prepare routine study progress reports which include reports of AEs experienced by study participants for review by the DSMB members. The members will meet in person and/or via teleconference during the study to conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and clinical and laboratory AEs. Any deaths of study participants or other SAEs will be reviewed immediately by the PSRT prior to DSMB review. Following review of the data during the trial, the DSMB may recommend that the study proceed as designed, proceed with design modifications or be discontinued. Enrollment and administration of study product will be stopped, and a safety review conducted by the DSMB for any of the following criteria:

- One or more participants experience an SAE that is related to the study product.
- There is a participant death, regardless of relationship to the study product.
- Two or more participants experience Grade 3 AEs in the same category System Organ Class that are considered to be related to the study product
- Any grade 4 AE that is considered to be related to the study product (Does not include

subjective reactogenicity symptoms)

Statistical analyses

Baseline characteristics including demographics and laboratory measurements will be summarized using descriptive statistics by group and overall. Summaries of the number and percentage of participants experiencing any AE or reactogenicity will be analysed and presented along with 95% confidence intervals. AEs and SAEs will be coded into Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The number and percentages of participants experiencing each specific AE will be tabulated by severity and relationship to study product. For the calculations in these tables, each participant's AE will be counted once under the maximum severity or strongest recorded causal relationship to study product. A complete listing of AEs for each participant will provide details including severity, relationship to study product, onset, duration and outcome.

Tolerability evaluation will be mostly descriptive and consist of solicited AEs that occur within one hour following study product administration and reasons for any withdrawal or discontinuation based upon subject discomfort. This early assessment of tolerability of the mAbs will inform which parameters should be solicited or routinely assessed to further characterize the tolerability profile in a larger number of subjects. Analysis will be carried out using either SAS version 9.4 or higher (SAS Institute, Cary, North Carolina) or R.

Pharmacokinetic analyses

PK disposition of PGT121 and VRC07-523LS administered SC alone and in combination will be evaluated in this study. The PK study design was based on preliminary mAb PK data [17]. Preliminary PK models have been constructed for VRC07-523LS and PGT121 and Monte Carlo simulation was performed to help design the sampling strategy and to predict overall distribution of mAb concentrations expected. The PK sampling design consists of 4 post-dose samples collected during the first week (Days 1,2,3 and 7) to capture C_{max} and T_{max} following SC administration. Sample collections will continue for 24 to 40 weeks depending on study group allocation to capture the concentration versus time profile. Predicted concentrations following single dose VRC07-523LS for Groups 1 and 2 are shown in Figure 1. VRC07-523LS concentrations are expected to be maintained > 1 mcg/mL for more than 24 weeks following 5 or 10 mg/kg. With repeat administration, predicted VRC07-523LS concentrations following 5 mg/kg at 0 and 12 weeks (Group 3) are around 10 mcg/mL; even with an extended interval to 24 weeks they are predicted to be maintained > 1 for more than 1 year with two doses (Figure 2). Simulated PGT121 concentrations following single dose (Group 5) are expected to be lower than VRC07-523LS due to the smaller dose and shorter

half-life. However, with repeat administration at 12 weeks (Group 6), PGT121 concentrations are expected to be maintained ≥ 1 mcg/mL as shown in Figure 3.

PK analysis will be calculated using standard non-compartmental methods using the program PKPlus. Additional compartmental population PK analysis will be performed using the computer program NONMEM. C_{max} and T_{max} will be derived directly from the observed data. AUC will be calculated using the trapezoidal method up to the last measured concentration ($AUC_{0\text{-}Clast}$) and $T_{1/2}$ from regression of the log-linear, terminal portion of the concentration versus time profile. If the final PK sample (Clast) has measurable mAb concentrations, the AUC after the final PK sample will be estimated as Clast/lz, where lz is the terminal slope of log-linear concentration versus time profile. The partial AUC over the first 12 and 24 weeks following the dose, $AUC_{0\text{-}12WK}$ and $AUC_{0\text{-}24WK}$, will also be calculated for assessment of accumulation in the repeat dose arms.

A two-compartment model will be used for the compartmental analysis. Either first order or zero order with or without lag time will be used for absorption input. Apparent clearance (CL/F) and apparent volume of distribution (Vdss/F) will be estimated for each mAb across the study arms. Due to the small sample size for the study, a limited covariate assessment will be performed looking at potential effects of dose level, repeat dosing and combination dosing. Overall results will be reported by subgroup and overall after the first dose by mAb. Correlation between PK parameters and reported safety and pharmacodynamics outcomes will also be explored in order to examine exposure-effect relationships. The frequency and levels of anti-mAb antibodies will also be calculated and tabulated.

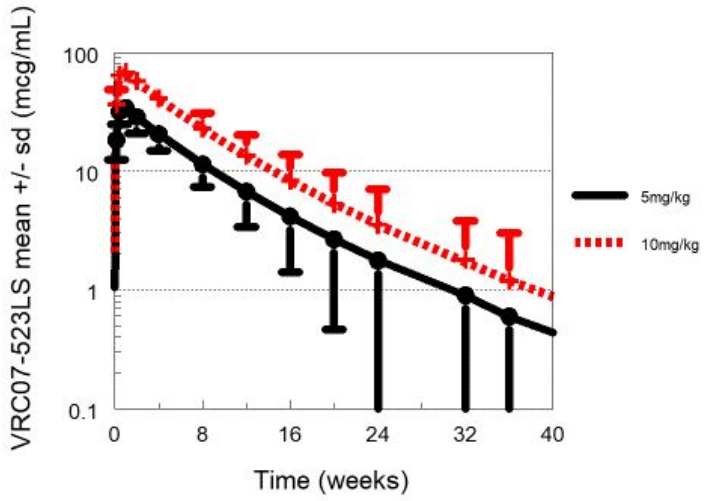

Figure 1: Predicted VRC07-523LS concentrations following single dose administration

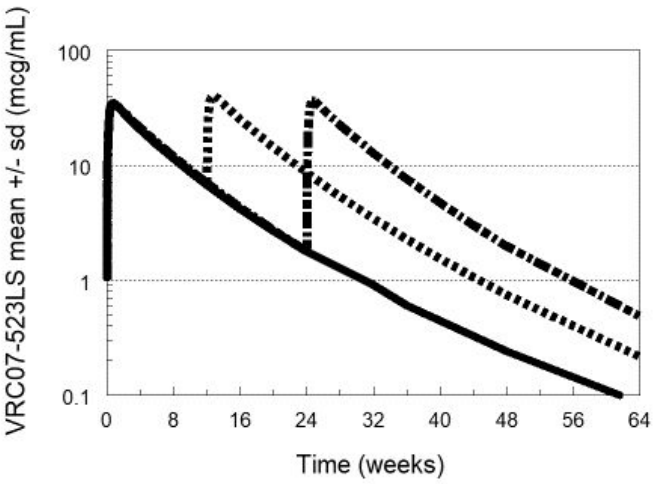

Figure 2: Predicted VRC07-523SL concentrations following repeat dose administration

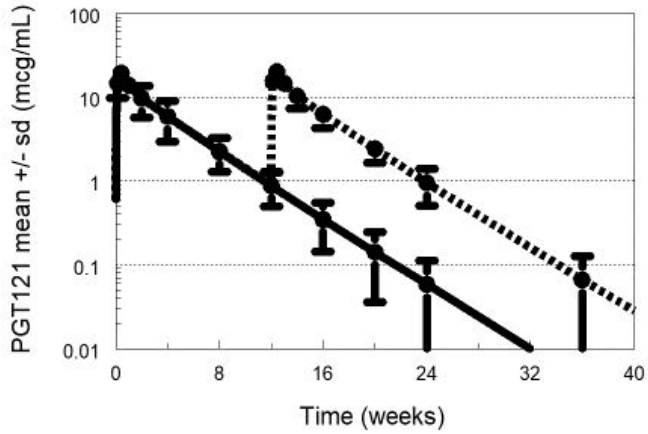

Figure 3: Simulated PGT121 concentrations following single dose administration

Data management

Data will be captured by study staff using standardised case report forms (CRFs). All source documents will be kept in the participants' study files and medical charts at the clinical research site. CRFs will be faxed to the central CAPRISA Data Management Server using the iDataFax system (DF/Net Research, Seattle, USA). All data entry will undergo three stages of quality control including immediate source document review, internal quality audits and weekly quality reports generated by iDataFax. Queries arising during validation of the data will be recorded in quality control reports sent to the sites on a regular basis. The original CRFs and study related documents will be securely stored at the site, during the study and after study completion.

Ethics and dissemination

Ethical approval has been granted by the South African Health Products Regulatory Authority (SAHPRA) (Trial reference number: 20180522) and University of KwaZulu-Natal Biomedical

Research Ethics Committee (Reference number: BFC108/18) for the study protocol (Version 1.1, Dated 01 June 2018). Any future protocol modifications will be communicated to the relevant regulatory authorities. Eligible patients will be asked to provide written informed consent for study procedures and sample storage. All participants will receive a small financial compensation for their time, transport and inconvenience after each study visit in accordance with South African National Health Research Ethics Council Guidelines[18]. Any breaches in confidentiality, study protocol or AEs attributable to this study will be reported to the above institutional review boards.

The study team will disseminate the trial results as broadly as possible. The research team will attend conferences periodically and present trial results to a multi-disciplinary scientific community. The results from this research may also be disseminated through presentations at scientific institutions/meetings, and/or publication in scientific journals. All publications will be uploaded to the University of KwaZulu-Natal publication repository. After sharing the results with study participants, they will be presented to communities from which participants are drawn, following Good Participatory Practice (GPP) guidelines. The results will also be shared with global and local policy makers. Summary results of the trial will be made publicly available through the clinical trial registry. Any datasets used for analysis in publications can be requested by investigators via an online request to the organisation. Measures will be taken to protect identifiable information in the datasets.

Trial status

The trial was registered on Pan African Clinical Trials Registry (PACTR 201808919297244) on www.pactr.org on 29 August 2018. Enrolment started in November 2018 and is predicted to be completed by June 2019.

References

1.UNAIDS. UNAIDS data 2017. Available from: http://www.unaids.org/en/resources/documents/2017/2017_data_book (Accessed: 28 February 2019). Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2017.

2. de Oliveira T, Kharsany AB, Graf T, et al. Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study. *Lancet HIV* 2017;4(1):e41-e50. doi: 10.1016/S2352-3018(16)30186-2

3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;365(6):493-505. doi: 10.1056/NEJMoa1105243

4. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012;367(5):399-410.

5. Van Damme L, Corneli A, Ahmed K, et al. Preexposure Prophylaxis for HIV Infection among African Women. *N Eng J Med* 2012;367:411-22.
6. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. *N Eng J Med* 2015;372(6):509-18.
7. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 2010;329:1168-74.
8. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis. *AIDS* 2016;30(12):1973-83.
9. Rudicell RS, Kwon YD, Ko SY, et al. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. *J Virol* 2014;88(21):12669-82.
10. Walker LM, Huber M, Doores KJ, et al. Broad neutralization coverage of HIV by multiple highly potent antibodies. *Nature* 2011;477(7365):466-70.
11. Gaudinski MR, Coates EE, Houser KV, et al. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: a phase 1 open-label clinical trial in healthy adults. *PLoS medicine* 2018;15(1):e1002493.
12. Stephenson KE, Barouch DH. Broadly Neutralizing Antibodies for HIV Eradication. *Curr HIV/AIDS Rep* 2016;13(1):31-7.
13. Julien JP, Sok D, Khayat R, et al. Broadly neutralizing antibody PGT121 allosterically modulates CD4 binding via recognition of the HIV-1 gp120 V3 base and multiple surrounding glycans. *PLoS pathogens* 2013;9(5):e1003342. doi: 10.1371/journal.ppat.1003342
14. Wagh K, Bhattacharya T, Williamson C, et al. Optimal Combinations of Broadly Neutralizing Antibodies for Prevention and Treatment of HIV-1 Clade C Infection. *PLoS pathogens* 2016;12(3):e1005520. doi: 10.1371/journal.ppat.1005520
15. Morris L, Mkhize NN. Prospects for passive immunity to prevent HIV infection. *PLoS Med* 2017;14(11):e1002436. doi: 10.1371/journal.pmed.1002436
16. Archary D, Liebenberg LJ, Werner L, et al. Randomized Cross-Sectional Study to Compare HIV-1 Specific Antibody and Cytokine Concentrations in Female Genital Secretions Obtained by Menstrual Cup and Cervicovaginal Lavage. *PLoS ONE* 2015;10(7):e0131906. doi: 10.1371/journal.pone.0131906
17. Gaudinski MR, Houser KV, Chen G, et al. A Phase I dose-escalation study of monoclonal antibody VRC07-523LS in healthy adults [Abstract: 1061]. Conference on Retroviruses and Opportunistic Infections; 2019 March 4-7; Boston, MA.
18. National Health Research Ethics Committee. Payment of Trial Participants in South Africa: Ethical Considerations for Research Ethics Committee (RECs). Available from: www.nhrec.org.za/index.php/grids-preview?download=11:guidelines-for-payment (accessed: 28 February 2019): National Health Research Ethics Committee, 2012.

Authors' contributions: state how each author was involved in writing the protocol.

SSAK conceived and designed the trial. SM and NG wrote the study protocol. EC will conduct PK simulations and analysis. NYZ performed sample size calculations and the statistical analysis strategy. All authors contributed to the manuscript and consented to final publication.

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Competing interests' statement

None declared

Word Count

3974/4000 words

Figures

Table 1

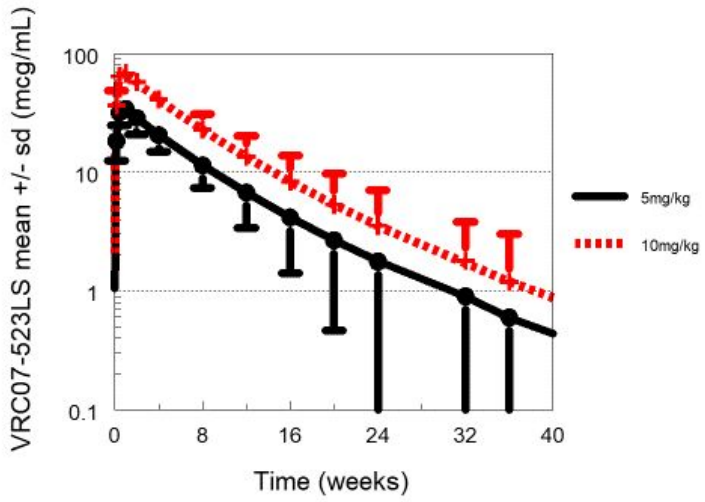

Figure 1: Predicted VRC07-523LS concentrations following single dose administration

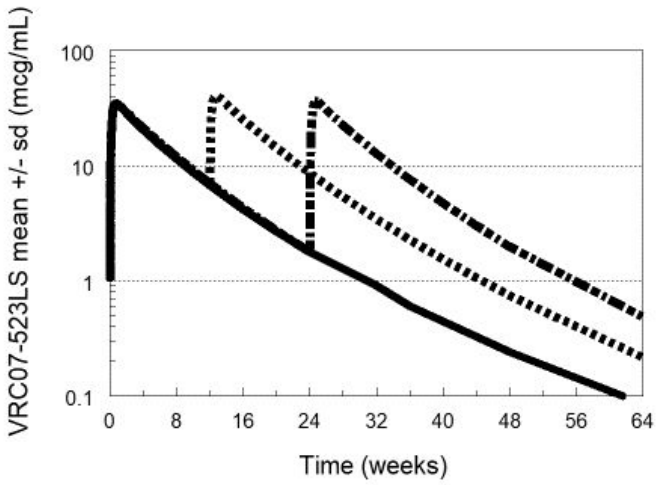

Figure 2: Predicted VRC07-523SL concentrations following repeat dose administration

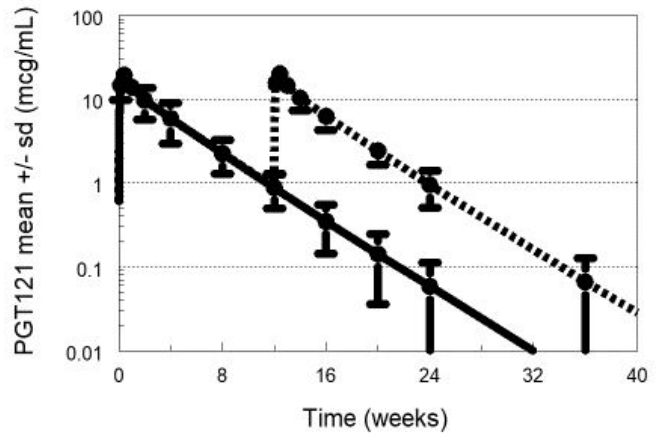

Figure 3: Simulated PGT121 concentrations following single dose administration

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	01
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	03,18

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	01-18
Protocol version	#3	Date and version identifier	03
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	01,20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	01
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A The applicant is the sponsor
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	01,05
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	05,06
Objectives	#7	Specific objectives or hypotheses	09,10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	06
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	06
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	07
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	08

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	09
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12,13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13, 14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	03,17

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11,12,17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11,12,17
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11,12,17
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17,18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14,15

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17,18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17,18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17,18
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11,12,17
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	11,12,17

BMJ Open

Assessing the safety and pharmacokinetics of the monoclonal antibodies, VRC07-523LS and PGT121 in HIV negative women in South Africa: Study protocol for the CAPRISA 012A randomised controlled Phase I trial

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Global health
Keywords:	HIV prevention, VRC07-523LS, PGT121, monoclonal antibodies

Title: **Assessing the safety and pharmacokinetics of the monoclonal antibodies, VRC07-523LS and PGT121 in HIV negative women in South Africa: Study protocol for the CAPRISA 012A randomised controlled Phase I trial**

Authors

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Running title

Phase 1 trial of the monoclonal antibodies VRC07-523LS and PGT121

Abstract

Introduction

Despite extensive prevention campaigns and scale-up of antiretroviral therapy, HIV incidence among young women in southern Africa remains high. While the development of an efficacious vaccine remains a challenge, the discovery of broadly neutralising monoclonal antibodies has created the opportunity to explore passive immunization as a long-acting injectable HIV prevention strategy. The purpose of this trial is to provide safety, pharmacokinetic (PK) and functional activity data of VRC07-523LS and PGT121 when administered subcutaneously to young South African women. Going forward, the aim is to select the ideal dose and/or monoclonal antibody for co-formulation and testing with CAP256-VRC26.25LS, a potent monoclonal antibody against subtype C virus, in an efficacy trial.

Methods and analysis

CAPRISA 012A is a randomized, double blinded, placebo-controlled phase I trial to assess the safety and PK profile of two monoclonal antibodies, VRC07-523LS and PGT121 administered subcutaneously to 35 young HIV negative women at low risk for HIV infection. Women will be randomized into seven groups of five participants each. In each group, women will be randomized (4:1) to the active intervention, VRC07-523LS and/or PGT121, or placebo. Participants will be followed up for 24 weeks after the administration of the last dose of study product with a total study duration of 72 weeks. Safety in the study will be assessed by the number and percentage of reactogenicity and adverse events experienced by participants and the relatedness to study product. The PK study design was based on preliminary PK data for VRC07-523LS and PGT121.

Ethics and dissemination

Ethical approval has been granted by the South African Health Products Regulatory Authority and by the University of KwaZulu-Natal Biomedical Research Ethics Committee. Results will be presented at international conferences and published in academic peer-reviewed journals. Trial results will be uploaded on the clinical trial registry.

Registration details

Pan African Clinical Trials Registry: PACTR201808919297244.

Keywords

HIV prevention, monoclonal antibodies, VRC07-523LS, PGT121, South Africa

Article Summary

Strengths and limitations of this study

1. This trial will provide new safety, pharmacokinetic and functional activity data for two monoclonal antibodies, VRC07-523LS and PGT121, when administered subcutaneously alone or in combination to South African women.
2. The trial will inform the optimal dose and monoclonal antibody combination that will be selected for co-formulation and testing with the potent monoclonal antibody CAP256-VRC26.25LS, in an efficacy trial.
3. Data from this trial could inform the future development of an injectable HIV prevention method, with anticipated four- or six-monthly dosing, that offers implementation and adherence advantages over available antiretroviral pre-exposure prophylaxis options.
4. While the use of monoclonal antibodies are a promising HIV prevention strategy and high levels of protection have been demonstrated in animal studies, the efficacy in human clinical trials has not yet been established.
5. The sample size in this study is small (typical of Phase 1 trials) and therefore all results and conclusions drawn must be prospectively validated. The potential clinical impact of these antibodies will depend on an efficacy signal established by Phase IIb efficacy trials

Introduction

Despite extensive prevention campaigns and scale-up of antiretroviral therapy (ART), South Africa remains an epicentre of the HIV pandemic[1]. In southern and eastern Africa, the incidence of HIV among young women below 25 years remains high[1 2]. While the HIV prevention landscape is changing rapidly, principally with the roll-out of pre-exposure prophylaxis (PrEP) and early antiretroviral therapy (ART) (Treatment as Prevention), current HIV prevention programmes have had limited impact on reducing HIV incidence in young women[3-5]. Clinical trials using daily oral tenofovir disoproxil fumarate alone and in combination with emtricitabine in African women demonstrated inconsistent results, most likely due to varying levels of medication adherence[6-8]. New approaches that overcome these adherence challenges, are being tested. While the development of an efficacious vaccine remains a major challenge, the discovery of potent monoclonal antibodies (mAbs) has created the opportunity to explore passive immunization as an HIV prevention strategy.

VRC07-523LS is a highly potent and broadly neutralising mAb that targets the HIV-1 CD4 binding site. It was developed by the Vaccine Research Center (VRC) at the National Institute of Health, United States. The antibody was engineered based on the VRC01 mAb, that was originally discovered in a subject infected with HIV-1, whose immune system controlled the virus without ART for more than 15 years [9 10]. The neutralization, potency and breadth of VRC01 was enhanced by next-generation sequencing and structure-guided design to create VRC07-523, which displayed 5- to 8-fold more potency than VRC01 and neutralized 96% of viruses tested [9]. Thereafter, a lysine-serine (LS) mutation was designed to extend the half-life and increase concentrations in mucosal tissue. The LS mutation is in the Fc region and was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor, resulting in increased recirculation of functional IgG, thus increasing plasma half-life [9]. Pharmacokinetic (PK) analyses in rhesus macaques demonstrated half-life values for VRC07-523LS ranging from 7-10 days, compared to 5 days for VRC07 and 5-6 days for VRC01. VRC07-523LS is approximately 10-fold more potent than VRC01 and active against 96% of diverse HIV-1 strains, including clade C[11]. The VRC01 antibody is currently being evaluated in the HVTN 703/HPTN 081 Phase 2b clinical trial [ClinicalTrials.gov Identifier: NCT02568215].

PGT121, is a recombinant human IgG1 mAb, isolated from an African donor in 2011, that targets the V3 glycan-dependent epitope region of the HIV envelope protein [12]. PGT121 was

developed by the Center for Virology and Vaccine Research at the Beth Israel Deaconess Medical Center and the International AIDS Vaccine Initiative. This mAb has a long heavy chain complementarity determining region that forms an antibody binding site with two functional surfaces and does not bind simply to the GPGR region of V3. Structural studies have shown that although PGT121 does not engage the CD4 binding site, it inhibits CD4 binding to gp120. PGT121 disrupts the Env-receptor engagement by an allosteric mechanism which interferes with CD4 binding and viral entry[13]. Due to its mechanism of action, PGT121 has excellent potency and breadth.

In order to overcome the genetic diversity of HIV, combinations of mAbs targeting different epitopes on the viral envelope will likely be required [10]. To identify the optimal combination of mAbs, Wagh and colleagues assessed the neutralising activity of 15 mAbs targeting four distinct epitopes of the envelope against a panel of 200 early/acute clade C HIV-1 Env-pseudoviruses and a mathematical model was developed to predict neutralization by mAb combinations [14] [15]. The analysis revealed that the neutralization profile of CAP256-VRC26.25LS (which targets the V2 loop) was particularly well suited as a complementary mAb with VRC07-523LS and PGT121. These two mAbs were found to be the best combinations in terms of neutralisation breadth and potency.

Results of preclinical and clinical studies have demonstrated promising results that support the clinical evaluation and development of mAbs for prevention[16-18].Currently there are two phase I trials assessing PGT121 and VRC07-523LS in the US. These are separate trials that are investigating the safety and tolerability of each mAb used alone, but not in combination (ClinicalTrials.gov Identifier: NCT03015181 and NCT02960581). Preliminary data from these trials have demonstrated no safety concerns. Neither mAb has been investigated in an African population, particularly young African women, who are at high risk of HIV acquisition. The purpose of this protocol is to provide safety, and functional activity data from a phase I trial assessing VRC07-523LS and PGT121 when administered subcutaneously (SC), alone and in combination to HIV negative women in South Africa. Data from this trial will inform the optimal dose and mAb combination that will be selected for co-formulation and testing with the potent mAb, CAP256-VRC26.25LS, in a proof-of-concept trial.

Methods and analysis (SPIRIT reporting guidelines used)

CAPRISA 012A is a randomized, double blinded, placebo-controlled phase I clinical trial.

Patient and Public Involvement

The CAPRISA community programme will inform, educate and mobilise the community to enhance community input into the research process. The local community research support groups (CRSG) play an active role as an interface between the researchers and community members serving as advocates for the community's best interests and ensuring that the researchers are always aware of any concerns within the community about the research being conducted. The study concept is introduced to the CSRG and concerns are addressed, and feedback is given to the study team. The recruitment team will raise awareness of clinical trial opportunities and educate the community regarding eligibility, screening and enrolment. After enrolment into the study, study staff will make every reasonable effort to ensure retention by collecting adequate locator information for follow-up tracking, visit reminders and retention activities.

Study setting

The study will be conducted at the CAPRISA eThekwini Clinical Research Site in Durban, KwaZulu-Natal, South Africa.

Study Population Selection

The study will include 35 HIV negative women. Enrolment will be based on the following eligibility criteria (Table1-3).

Inclusion criteria

- 18 to 40 years of age
- Female sex at birth
- Able and willing to complete the informed consent process
- Has understood the information provided, including the potential impact and/or risks linked to SC administration of the study product, and is willing to comply with protocol procedures
- Has access to the clinical research site and is available for the duration of the study
- Based on clinical assessment must be in good general health
- Assessed by site staff to be at low risk for HIV infection
- If of reproductive potential, has evidence of effective contraceptive use in the previous 21 days, and agrees to continued use during the study period
- Willing to have blood and genital samples collected, stored, and used for research purposes.

Screening laboratory parameters

- White Blood Cell Count within institutional normal range
- Haemoglobin > 10g/dL
- Creatinine ≤ upper limit of institutional normal range
- Alanine aminotransferase ≤ upper limit of institutional normal range
- Negative for HIV infection by an FDA-approved method of detection in the last 30 days
- Negative β-HCG pregnancy test (urine or serum) within 21 days of enrolment

Exclusion criteria

- Any clinically significant acute or chronic medical condition that makes the participant unsuitable for participation in the study, or jeopardizes the safety or rights of the volunteer
- If planning a pregnancy for the duration of the study, currently pregnant or breastfeeding
- Exceeding the weight of 90 kilograms (in order to restrict the amount of injections administered)
- A history of alcohol or substance use judged to potentially interfere with participant study compliance
- Prior participation in an investigational HIV vaccine trial, except if proof of allocation to the placebo arm is available
- Administration of a mAb or polyclonal immunoglobulin within 28 days prior to enrolment
- Any history of anaphylaxis and related symptoms such as hives, respiratory difficulty and angioedema
- Evidence of autoimmune disease, or receiving immunosuppressive therapy
- Participants in this study may not take part in other concurrent research studies that would interfere with the objectives of this study.

Study Schema

The 35 HIV negative participants at low risk for HIV infection will be randomised into seven groups of five participants each (Table 1). In each group (n=5), four women will be randomly assigned to the active intervention, VRC07-523LS and/or PGT121 and one participant randomly assigned to placebo. The safety and PK profile of one and two doses of VRC07-523LS and/or PGT121 mAbs administered SC will be evaluated. As per Table 1, VRC07-523LS will be administered alone at a dose of either 5mg/kg or 10mg/kg at one time point in Groups 1 and 2 respectively. VRC07-523LS will be administered alone at a dose of 5mg/kg

or 10mg/kg at two time points in Group 3 (repeat dose at 12 weeks) and Group 4 (repeat dose at 24 weeks).

PGT121 will be administered alone at a dose of 3mg/kg at one time point (Group 5) or at two time points in Group 6 (repeat dose at 12 weeks). VRC07-523LS and PGT121 will be administered in combination at one time point in Group 7. This mAb combination will not be administered as a single product containing two antibodies but rather as two separate injections, each containing a single mAb. Participants will be followed up for 24 weeks after the administration of the last dose of study product with a total study duration of 72 weeks.

Table 1: The distribution of study participants into individualised groups

Group	Regimen	N	Dose (mg/kg)
1	VRC07-523LS/Placebo	4/1	5 mg/kg SC one dose
2	VRC07-523LS/ Placebo	4/1	10 mg/kg SC one dose
3	VRC07-523LS/ Placebo	4/1	5 mg/kg SC with one repeat dose at 12 weeks
4	VRC07-523LS/ Placebo	4/1	10 mg/kg SC with one repeat dose at 24 weeks
5	PGT121/Placebo	4/1	3 mg/kg SC one dose
6	PGT121/Placebo	4/1	3 mg/kg SC with one repeat dose at 12 weeks
7	VRC07-523LS + PGT121/ Placebo	4/1	5 mg/kg SC + 3 mg/kg SC one dose

Study Objectives

Primary objective

- To evaluate the safety of one and two doses of VRC07-523LS and/or PGT121 mAbs administered SC.

Secondary objectives

- To characterize the PK profile of VRC07-523LS mAb (5 and 10 mg/kg) administered SC individually as a single dose or as two doses 12 and 24 weeks apart.

- To characterize the PK profile of PGT121 mAb (3 mg/kg) administered SC individually as a single dose or as two doses 12 weeks apart.
- To characterize the PK profile of VRC07-523LS and PGT121 mAbs administered in combination.
- To assess the acceptability of VRC07-523LS and PGT121 mAbs SC injections.
- To evaluate the concentrations and functional activity of VRC07-523LS and/ or PGT121 mAb in plasma and genital samples following SC administration.
- To determine whether SC administration of VRC07-523LS and/or PGT121 mAbs induces anti-mAbs.

Primary outcomes

- Proportion of participants with mild, moderate and severe reactogenicity events within the first three days after SC administration.
- Proportion of participants with mild, moderate and severe adverse events (AEs) up to 24 weeks after the last SC administration.
- Proportion of participants with serious adverse events (SAEs) related to SC administration

Secondary outcomes

- Maximal concentration (Cmax), time of maximal concentration (tmax), area under the concentration vs time curve (AUC), apparent clearance (CL/F) and terminal half-life ($t_{1/2}$) of VRC07-523LS and PGT121 mAbs.
- Proportion of participants who report that the SC injections are acceptable.
- Concentration and function of mAbs in the systemic and genital tract compartments before and after SC mAb administration.
- Changes in the concentration of serum anti-mAbs before and after SC mAb administration.

Sample size calculation

The analysis of the CAPRISA 012A trial will be primarily descriptive and a pragmatic approach was taken when choosing the sample size, ensuring enough participants to obtain safety data. Currently, there is no safety data available to inform the true event rates that we might observe in the study. However, since the main objective of the study is to evaluate the safety of VRC07-523LS and PGT121 when administered SC, the ability of the study to detect SAEs was assessed for a range of hypothetical event rates. This was done by calculating the probability

of detecting no SAE, at least one or two SAEs at a specified true event rate. These probabilities highlight the likelihood of the study to detect either rare or common AEs or SAEs as shown in Table 2 and 3. In addition, the 95% confidence interval for the true event rates were calculated. Amongst the four participants receiving active product in each of the seven groups, there is a 34% chance of observing at least one event if the true event rate is 10%. When the true event rate is two to three-fold higher, this probability rises to 59% and 76% respectively (Table 2).

Table 2: Probability of observing no events, one or more events and two or more events for a range of hypothetical true event rates

True event rate (%)	Number of participants	No events	One or more events	Two or more events
5	4	0.81	0.19	0.01
10	4	0.66	0.34	0.05
20	4	0.41	0.59	0.18
30	4	0.24	0.76	0.35

Since the phase I assessment of SC administration includes eight participants receiving PGT121, 16 participants receiving VRC07-523LS and 28 participants receiving active study product, the probability of observing no events, one or more events, and two or more events for a range of true event rates is provided in Table 3. For example, among the eight participants receiving only PGT121 at enrolment there is an 8% chance of observing at least one event, if the true event is 1%, but 83% if the true event is 20%. However, if we combine all 16 women receiving only VRC07-523LS study product at enrolment these probabilities change to 15% and 97% if the true event rates are 1% and 20%, respectively. As expected, an increase in sample size, increases the likelihood of detecting rare events.

Table 3: Probability of observing no events, at least 1 event or at least 2 events for a range of hypothetical true event rates

True event rate (%)	Number of participants	No events	At least 1 event	At least 2 events
1	4	0.96	0.04	<0.01
	8	0.92	0.08	<0.01
	12	0.89	0.11	0.01
	16	0.85	0.15	0.01
	28	0.75	0.25	0.03
5	4	0.81	0.19	0.01
	8	0.66	0.34	0.06
	12	0.54	0.46	0.12
	16	0.44	0.56	0.19
	28	0.24	0.76	0.41

True event rate (%)	Number of participants	No events	At least 1 event	At least 2 events
10	4	0.66	0.34	0.05
	8	0.43	0.57	0.19
	12	0.28	0.72	0.34
	16	0.19	0.81	0.49
	28	0.05	0.95	0.78
20	4	0.41	0.59	0.18
	8	0.17	0.83	0.50
	12	0.07	0.93	0.73
	16	0.03	0.97	0.86
	28	<0.01	>0.99	0.98
30	4	0.24	0.76	0.35
	8	0.06	0.94	0.74
	12	0.01	0.99	0.91
	16	<0.01	>0.99	0.97
	28	<0.01	>0.99	>0.99

Study Procedures

Informed consent

In accordance with South African Good Clinical Practice guidelines, informed consent is obtained from each study participant in English or isiZulu (the local African language) prior to screening and enrolment. Consent for pharmacogenetic studies as well as specimen storage is also obtained. Participants are provided with copies of their forms if they wish to receive them. For illiterate participants, an impartial witness is required for the entire informed consent process.

Screening and enrolment

Eligibility for the study is assessed in a stepwise manner at screening and enrolment. Potential participants will be invited to screen for the study and asked to provide informed consent for screening. Potential participants are checked for co-enrolment on the Biometric Co-Enrolment Prevention System (BCEPS) and are asked to provide proof of contraception, i.e. family planning card, as well as identity documents. Thereafter, they receive pre-test counselling and two rapid HIV tests are performed. Post-test counselling is provided and if required, referral to one of several HIV/AIDS care programs is facilitated. If both HIV test results are negative, the potential participant is asked to provide socio-demographic and behavioural information and undergoes a blood draw for screening bloods, as well as urine pregnancy testing. If potential participants remain eligible based on their screening blood results, they will undergo a complete physical examination. Screening blood tests include haematology, blood chemistry tests, liver function tests, serology, hepatitis B virus assays and serum and plasma storage. A

genital specimen using the SoftCup collection device (SoftCup, EuroFemPro, Netherlands, or the SoftCup, Instead Inc., San Diego, CA) will also be obtained[19].

Randomisation

Participants will be randomized according to the randomization schedule prepared by the blinded study statistician prior to study start. In this study, the pharmacist will remain unblinded. Sequentially numbered, sealed, opaque envelopes containing the intervention allocation, participant identification number and a treatment code (for use by the unblinded pharmacist only) will be provided to the study coordinator, to be opened once a participant has been deemed eligible and is ready to be enrolled into the study. Group 1 (n=5) will be randomised first. After administration of the first dose to the first participant, the study team will wait for three 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 will wait a further three days before enrolling the remaining participants into Group 1. Thereafter, the next 25 participants will be randomly allocated to Groups 2 – 6. Enrolment of the final five participants into Group 7 will only occur once 12-week safety data has been reviewed for the first eight participants who received product.

Laboratory investigations

Serum, plasma, and genital specimens will be taken at enrolment and designated follow-up visits and will be stored for PK analysis, detection of autoreactivity and assessments of markers of safety. The CAPRISA Research Laboratories will conduct specific laboratory testing required for this protocol. Sample processing and storage of specimens for possible future testing (blood and vaginal specimen) will also be undertaken. An accredited contract laboratory will perform all safety blood testing and provide a backup laboratory service when required.

Follow up visits

At each scheduled study visit, enrolled participants in the intervention and control arm will also be provided with HIV risk reduction counselling, contraception counselling and contraceptive methods of choice. Participants will receive advice on how to contact study staff with additional questions about the study, how to request additional counselling, and how to report possible AEs. In addition to the regular follow-up requirements, genital specimen collection and scheduled safety blood draws as well as samples for PK analysis and storage will be completed.

Safety Monitoring and Adverse Event Reporting

Reactogenicity assessments

A baseline local and systemic reactogenicity assessment will be conducted prior to study product administration. Once the study product has been administered, participants will be directly observed in the clinic for a minimum of one hour, after which an early reactogenicity assessment will be performed. The participant will be seen at the clinic on the day of product administration (enrolment visit) as well as Day one and Day three. Participants will be contacted telephonically on the evening of the enrolment visit and on Day two after product administration. In addition, all participants will keep a daily diary of local and systemic symptoms called a post-injection symptom log. This will aid to track and reconcile any local and systemic reactogenicity events that the participant experiences.

Adverse events and reporting requirements

Reporting of all AEs will occur during the period from the first study product administration through to the end of the study. After this period, only SAEs and AEs of special interest (potential immune-mediated diseases that include both autoimmune diseases and also other inflammatory and/or neurologic disorders that may or may not have an autoimmune aetiology), will be recorded. Each AE will be graded for severity using The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.1, July 2017. Attribution categories used will be either 'related' (a reasonable possibility that the AE may be related to the study product) or 'not related' (not a reasonable possibility that the AE is related to the study product). All AEs will be captured in the database regardless of attribution. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline or becomes non-gradable). Participants with unresolved AEs at study exit will be followed for up to 30 additional days and will be referred to a health care provider for further management, if required.

Data and safety monitoring

The trial will be audited by an external monitor prior to study start and during study conduct. Safety review decisions and the status of enrolment throughout the trial will be discussed as part of regular safety review meetings by a Protocol Safety Review Team (PSRT). In addition, a Data and Safety Monitoring Board (DSMB) consisting of three clinical trial specialists, a biostatistician and an ethicist, who are independent from the current study will review safety data during the trial. The study statisticians will prepare routine study progress reports which include reports of AEs experienced by study participants for review by the DSMB members. The members will meet in person and/or via teleconference during the study to conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and clinical and laboratory AEs. Any deaths of

study participants or other SAEs will be reviewed immediately by the PSRT prior to DSMB review. Following review of the data during the trial, the DSMB may recommend that the study proceed as designed, proceed with design modifications or be discontinued. Enrollment and administration of study product will be stopped, and a safety review conducted by the DSMB for any of the following criteria:

- One or more participants experience an SAE that is related to the study product.
- There is a participant death, regardless of relationship to the study product.
- Two or more participants experience Grade 3 AEs in the same category System Organ Class that are considered to be related to the study product
- Any grade 4 AE that is considered to be related to the study product (Does not include subjective reactogenicity symptoms)

Statistical analyses

Baseline characteristics including demographics and laboratory measurements will be summarized using descriptive statistics by group and overall. Summaries of the number and percentage of participants experiencing any AE or reactogenicity will be analysed and presented along with 95% confidence intervals. AEs and SAEs will be coded into Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The number and percentages of participants experiencing each specific AE will be tabulated by severity and relationship to study product. For the calculations in these tables, each participant's AE will be counted once under the maximum severity or strongest recorded causal relationship to study product. A complete listing of AEs for each participant will provide details including severity, relationship to study product, onset, duration and outcome.

Tolerability evaluation will be mostly descriptive and consist of solicited AEs that occur within one hour following study product administration and reasons for any withdrawal or discontinuation based upon subject discomfort. This early assessment of tolerability of the mAbs will inform which parameters should be solicited or routinely assessed to further characterize the tolerability profile in a larger number of subjects. Analysis will be carried out using either SAS version 9.4 or higher (SAS Institute, Cary, North Carolina) or R.

Pharmacokinetic analyses

PK disposition of PGT121 and VRC07-523LS administered SC alone and in combination will be evaluated in this study. The PK study design was based on preliminary mAb PK data [16]. Preliminary PK models have been constructed for VRC07-523LS and PGT121 and Monte Carlo simulation was performed to help design the sampling strategy and to predict overall

distribution of mAb concentrations expected. The PK sampling design consists of 3 post-dose samples collected during the first week at Days 1, 3 and 7 in order to capture C_{max} and T_{max} following SC administration. A PK sample will also be collected at Day 14. In the repeat dosing groups, PK samples are collected 7 days after the repeat dose; if the levels are different after the repeat dose, it will be important to know if it is due to changes in SC absorption or elimination.

Sample collections will continue for 24 to 40 weeks depending on study group allocation to capture the concentration versus time profile. Predicted concentrations following single dose VRC07-523LS for Groups 1 and 2 are shown in Figure 1. VRC07-523LS concentrations are expected to be maintained > 1 mcg/mL for more than 24 weeks following 5 or 10 mg/kg. With repeat administration, predicted VRC07-523LS concentrations following 5 mg/kg at 0 and 12 weeks (Group 3) are around 10 mcg/mL; even with an extended interval to 24 weeks they are predicted to be maintained > 1 for more than 1 year with two doses (Figure 2). Simulated PGT121 concentrations following single dose (Group 5) are expected to be lower than VRC07-523LS due to the smaller dose and shorter half-life. However, with repeat administration at 12 weeks (Group 6), PGT121 concentrations are expected to be maintained ≥ 1 mcg/mL as shown in Figure 3.

PK analysis will be calculated using standard non-compartmental methods using the program PKPlus. Additional compartmental population PK analysis will be performed using the computer program NONMEM. C_{max} and T_{max} will be derived directly from the observed data. AUC will be calculated using the trapezoidal method up to the last measured concentration ($AUC_{0\text{-}Clast}$) and $T_{1/2}$ from regression of the log-linear, terminal portion of the concentration versus time profile. If the final PK sample (Clast) has measurable mAb concentrations, the AUC after the final PK sample will be estimated as Clast/lz, where lz is the terminal slope of log-linear concentration versus time profile. The partial AUC over the first 12 and 24 weeks following the dose, $AUC_{0\text{-}12WK}$ and $AUC_{0\text{-}24WK}$, will also be calculated for assessment of accumulation in the repeat dose arms.

A two-compartment model will be used for the compartmental analysis. Either first order or zero order with or without lag time will be used for absorption input. Apparent clearance (CL/F) and apparent volume of distribution (Vdss/F) will be estimated for each mAb across the study arms. Due to the small sample size for the study, a limited covariate assessment will be performed looking at potential effects of dose level, repeat dosing and combination dosing. Overall results will be reported by subgroup and overall after the first dose by mAb. Correlation between PK parameters and reported safety and pharmacodynamics outcomes will also be

explored in order to examine exposure-effect relationships. The frequency and levels of anti-mAb antibodies will also be calculated and tabulated.

Data management

Data will be captured by study staff using standardised case report forms (CRFs). All source documents will be kept in the participants' study files and medical charts at the clinical research site. CRFs will be faxed to the central CAPRISA Data Management Server using the iDataFax system (DF/Net Research, Seattle, USA). All data entry will undergo three stages of quality control including immediate source document review, internal quality audits and weekly quality reports generated by iDataFax. Queries arising during validation of the data will be recorded in quality control reports sent to the sites on a regular basis. The original CRFs and study related documents will be securely stored at the site, during the study and after study completion.

Ethics and dissemination

Ethical approval has been granted by the South African Health Products Regulatory Authority (SAHPRA) (Trial reference number: 20180522) and University of KwaZulu-Natal Biomedical Research Ethics Committee (Reference number: BFC108/18) for the study protocol (Version 1.1, Dated 01 June 2018). Any future protocol modifications will be communicated to the relevant regulatory authorities. Eligible patients will be asked to provide written informed consent for study procedures and sample storage. All participants will receive a small financial compensation for their time, transport and inconvenience after each study visit in accordance with South African National Health Research Ethics Council Guidelines. Any breaches in confidentiality, study protocol or AEs attributable to this study will be reported to the above institutional review boards.

The study team will disseminate the trial results as broadly as possible. The research team will attend conferences periodically and present trial results to a multi-disciplinary scientific community. The results from this research may also be disseminated through presentations at scientific institutions/meetings, and/or publication in scientific journals. All publications will be uploaded to the University of KwaZulu-Natal publication repository. After sharing the results with study participants, they will be presented to communities from which participants are drawn, following Good Participatory Practice (GPP) guidelines. The results will also be shared with global and local policy makers. Summary results of the trial will be made publicly available through the clinical trial registry. Any datasets used for analysis in publications can be requested by investigators via an online request to the organisation. Measures will be taken to protect identifiable information in the datasets.

Trial status

The trial was registered on Pan African Clinical Trials Registry (PACTR 201808919297244) on www.pactr.org on 29 August 2018. Enrolment started in November 2018 and is predicted to be completed by June 2019.

References

1. UNAIDS. UNAIDS data 2017. Available from: http://www.unaids.org/en/resources/documents/2017/2017_data_book (Accessed: 28 February 2019). Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2017.
2. de Oliveira T, Kharsany AB, Graf T, et al. Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study. *Lancet HIV* 2017;4(1):e41-e50. doi: 10.1016/S2352-3018(16)30186-2
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;365(6):493-505. doi: 10.1056/NEJMoa1105243
4. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012;367(5):399-410.
5. Van Damme L, Corneli A, Ahmed K, et al. Preexposure Prophylaxis for HIV Infection among African Women. *N Eng J Med* 2012;367:411-22.
6. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. *N Eng J Med* 2015;372(6):509-18.
7. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 2010;329:1168-74.
8. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis. *AIDS* 2016;30(12):1973-83.
9. Rudicell RS, Kwon YD, Ko SY, et al. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. *J Virol* 2014;88(21):12669-82.
10. Walker LM, Huber M, Doores KJ, et al. Broad neutralization coverage of HIV by multiple highly potent antibodies. *Nature* 2011;477(7365):466-70.
11. Gaudinski MR, Coates EE, Houser KV, et al. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: a phase 1 open-label clinical trial in healthy adults. *PLoS medicine* 2018;15(1):e1002493.
12. Stephenson KE, Barouch DH. Broadly Neutralizing Antibodies for HIV Eradication. *Curr HIV/AIDS Rep* 2016;13(1):31-7.
13. Julien JP, Sok D, Khayat R, et al. Broadly neutralizing antibody PGT121 allosterically modulates CD4 binding via recognition of the HIV-1 gp120 V3 base and multiple surrounding glycans. *PLoS pathogens* 2013;9(5):e1003342. doi: 10.1371/journal.ppat.1003342
14. Wagh K, Bhattacharya T, Williamson C, et al. Optimal Combinations of Broadly Neutralizing Antibodies for Prevention and Treatment of HIV-1 Clade C Infection. *PLoS pathogens* 2016;12(3):e1005520. doi: 10.1371/journal.ppat.1005520
15. Morris L, Mkhize NN. Prospects for passive immunity to prevent HIV infection. *PLoS Med* 2017;14(11):e1002436. doi: 10.1371/journal.pmed.1002436

16. Gaudinski MR, Houser KV, Chen G, et al. A Phase I dose-escalation study of monoclonal antibody VRC07-523LS in healthy adults [Abstract: 1061]. Conference on Retroviruses and Opportunistic Infections; 2019 March 4-7; Boston, MA.
17. Julg B, Barouch DH. Neutralizing antibodies for HIV-1 prevention. *Current opinion in HIV and AIDS* 2019
18. Sok D, Burton DR. Recent progress in broadly neutralizing antibodies to HIV (vol 19, pg 1179, 2018). *NATURE IMMUNOLOGY* 2019;20(3):374-74.
19. Archary D, Liebenberg LJ, Werner L, et al. Randomized cross-sectional study to compare HIV-1 specific antibody and cytokine concentrations in female genital secretions obtained by menstrual cup and cervicovaginal lavage. *PloS one* 2015;10(7):e0131906.

Authors' contributions: state how each author was involved in writing the protocol.

SSAK conceived and designed the trial. SM and NG wrote the study protocol. EC will conduct pharmacokinetic (PK) simulations and analysis. NYZ performed sample size calculations and the statistical analysis strategy. CB, TG, DA, PM, NS,DHB,JM,JL,and LM contributed to the planning and conduct of the trial. All authors contributed to the write up of the manuscript. All authors consented to final publication.

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Competing interests' statement

None declared

Word Count

3974/4000 words

Figure Legends

Figure 1: Predicted VRC07-523LS concentrations following single dose administration

Figure 2: Predicted VRC07-523SL concentrations following repeat dose administration

Figure 3: Simulated PGT121 concentrations following single dose administration and repeat dose administration

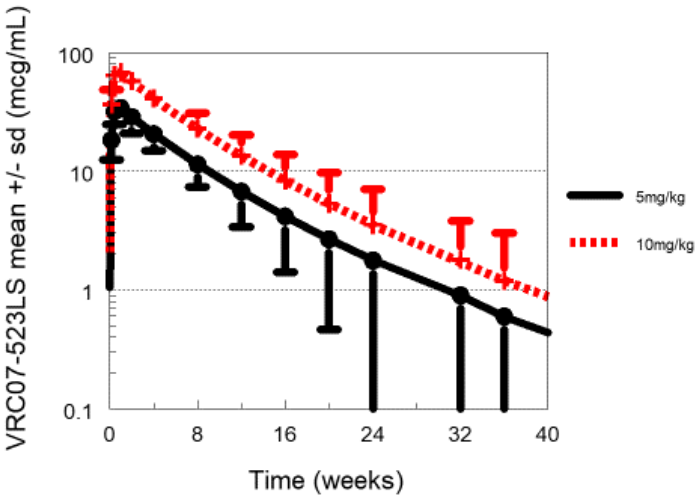

Figure 1: Predicted VRC07-523LS concentrations following single dose administration

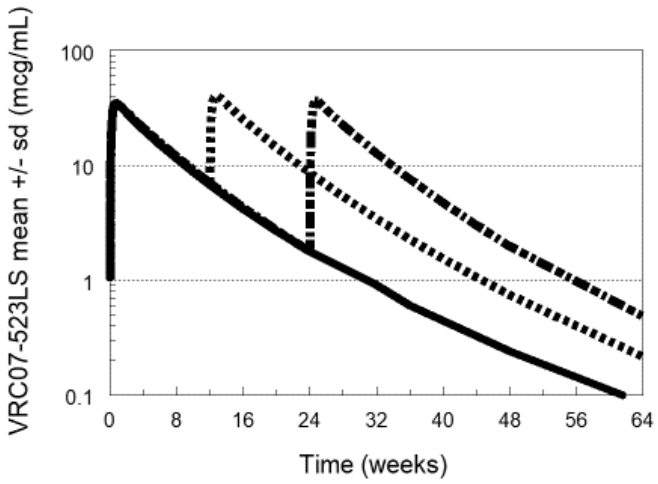

Figure 2: Predicted VRC07-523SL concentrations following repeat dose administration

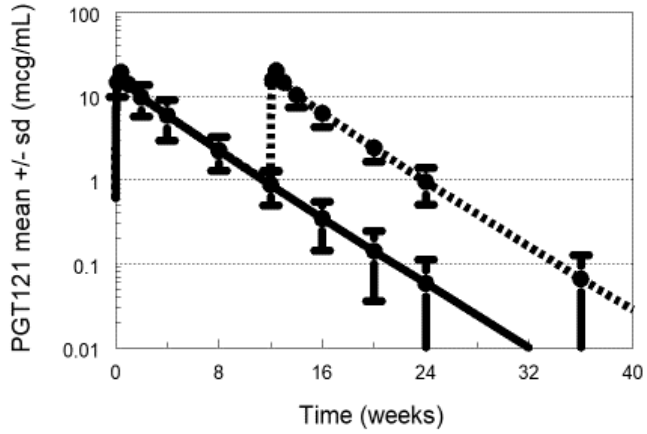

Figure 3: Simulated PGT121 concentrations following single dose administration and repeat dose administration

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	01
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	03,18

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	01-18
Protocol version	#3	Date and version identifier	03
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	01,20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	01
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A The applicant is the sponsor
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	01,05
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	05,06
Objectives	#7	Specific objectives or hypotheses	09,10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	06
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	06
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	07
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	08

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	09
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12,13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13, 14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	03,17

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11,12,17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11,12,17
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11,12,17
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17,18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14,15

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17,18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17,18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17,18
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11,12,17
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	11,12,17