Extended safety and tolerability of subcutaneous CAP256V2LS and VRC07-523LS in HIV-negative women: study protocol for the randomised, placebo-controlled double-blinded, phase 2 CAPRISA 012C trial


ABSTRACT

Introduction Women-controlled HIV prevention technologies that overcome adherence challenges of available daily oral pre-exposure prophylaxis and give women a choice of options are urgently needed. Broadly neutralising monoclonal antibodies (bnAbs) administered passively may offer a valuable non-antiretroviral biological intervention for HIV prevention. Animal and human studies have demonstrated that bnAbs which neutralise HIV can prevent infection. The optimal plasma antibody concentrations to confer protection against HIV infection in humans is under intense study. The Centre for the AIDS Programme of Research in South Africa (CAPRISA) 012C trial will evaluate extended safety and pharmacokinetics of CAP256V2LS and VRC07-523LS among young HIV-negative South African and Zambian women. The study design also allows for an evaluation of a signal of HIV prevention efficacy.

Methods and analysis CAPRISA 012 is a series of trials with three distinct protocols. The completed CAPRISA 012A and 012B phase 1 trials provided critical data for the CAPRISA 012C trial, which is divided into parts A and B. In part A, 90 participants will be randomised to receive both CAP256V2LS and VRC07-523LS at 20mg/kg or placebo, subcutaneously every 16 or 24 weeks. Part B will enrol 900 participants in South Africa and Zambia who will be randomised in a 1:1 ratio and receive an initial loading dose of 1.2g of CAP256V2LS and VRC07-523LS or placebo followed by 600mg of CAP256V2LS and 1.2g of VRC07-523LS or placebo subcutaneously every 6 months. Safety will be assessed by frequency and severity of reactogenicity and other related adverse events. Pharmacokinetics of both antibodies will be measured in systemic and mucosal compartments over time, while participants will be monitored for breakthrough HIV infections.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial will provide comprehensive safety and pharmacokinetic data on the subcutaneous administration of CAP256V2LS and VRC07-523LS for HIV prevention among South African and Zambian women.
⇒ The trial will provide detailed pharmacokinetic data for two promising bnAbs administered at a fixed dose and with a loading dose for potential ease of future implementation.
⇒ Although the primary goal of this study is extended safety, the study has adequate statistical power to provide a signal of efficacy of CAP256V2LS and VRC07-523LS against HIV and could provide supportive data for a larger efficacy trial.
⇒ Data from this trial will inform planning of future prevention trials using combinations of bnAbs, as well as vaccine design, if shown to be efficacious.
⇒ An inherent limitation of the phase 2 trial design is that the sample size may not provide sufficient statistical power for a comprehensive HIV endpoint analysis.

Ethics and dissemination of study findings The University of KwaZulu-Natal Biomedical Research Ethics Committee and South African Health Products Regulatory Authority have approved the trial (BREC/00002492/2021, SAHPRA20210317). Results will be disseminated through conference presentations, peer-reviewed publications and the clinical trial registry.

Trial registration number PACTR202112683307570.
INTRODUCTION

Despite significant progress in HIV treatment and prevention, there were 1.5 million new HIV infections and 680,000 deaths from AIDS-related disease globally in 2021.1 In South Africa, young women, between the ages of 15 and 24 years, carry a large HIV burden with persistently high HIV incidence rates contributing to 38% of new infections globally.2,3 Similarly, in Zambia, young women and adolescent girls are disproportionately affected compared with their male peers. Studies have demonstrated that the use of pre-exposure prophylaxis (PrEP) decreases HIV acquisition, and antiretroviral therapy (ART) decreases HIV transmission.4,5 However, challenges with access, adherence, low-risk perception, side effects, implementation costs and access to treatment remain a barrier to the successful elimination of HIV.6 Thus, women-controlled HIV prevention technologies that expand women’s choices of effective prevention options and that overcome adherence challenges of available daily oral PrEP are urgently needed.7–9

Newer long-acting PrEP options including antiretroviral (ARV)-containing intravaginal rings and long-acting ARV injectables have become available or are currently being evaluated. Two clinical trials assessing dapivirine-containing vaginal rings showed an overall HIV risk reduction of 27%–31%.10,11 In 2021, the HIV Prevention Trials Network 085 and 084 trials demonstrated that the long-acting injectable integrase inhibitor cabotegravir was superior to daily oral tenofovir disoproxil fumarate/ emtricitabine for HIV prevention among cisgender men, cisgender women and transgender women who have sex with men in sub-Saharan Africa.12 Cabotegravir administered every 2 months, and the dapivirine-containing ring has been licensed in most countries including South Africa and Zambia, but access remains a challenge. Lenacapavir, a promising long-acting HIV capsid inhibitor, is currently being evaluated as a 6-monthly injectable in clinical trials for HIV prevention.13 These agents may overcome barriers to adherence. However, long-acting agents have challenges including the route of administration, potential injection site reactions, contraindication with other medications, dosing intervals and a pharmacokinetic (PK) tail when injections are stopped, which can lead to the emergence of resistant viruses, if breakthrough infections occur.

Broadly neutralising monoclonal antibodies (bnAbs) administered passively may address some of the challenges faced with other long-acting and small molecule PrEP choices. Half-life-extension mutations for bnAbs, including the LS (lysine-serine) mutation, have demonstrated increased half-lives enabling longer dosing intervals and less frequent administration. Thus, bnAbs may not require adherence to the same extent as daily pill-taking or vaginal applications and administration would be unrelated to sexual intercourse. The mechanism of action of bnAbs is different to ARV drugs, with a reduced side effect profile expected. The binding targets of bnAbs that are currently in clinical testing, do not overlap with those of approved ART for PrEP use or treatment, which removes the concern about drug resistance. Furthermore, a fixed dose of subcutaneously administered bnAbs, as tested in this trial, may offer an advantage for future implementation, if found effective.

In animal studies, bnAbs protected rhesus macaques from simian-HIV (SHIV) infection.14–17 In vitro studies have also demonstrated that combinations of bnAbs result in improved neutralisation breadth and potency.18 To date several new potent bnAbs, assessed alone and in combination in early phase 1 trials, have demonstrated safety and favourable PK profiles.19,20 Data from the Antibody Mediated Prevention (AMP) proof of concept trials showed protection against HIV acquisition if the transmitted virus was sensitive to VRC01 with an IC50 of less than 1 µg/mL.21,22

Combinations of bnAbs that target multiple sites on the virus are needed to protect against high HIV diversity in circulating strains; however, plasma antibody concentration correlates of protection for combinations of bnAbs have yet to be defined. Gilbert et al analysed data from the AMP trial and proposed that the predicted serum neutralisation 80% inhibitory dilution titre (PT80) biomarker could be used as a surrogate endpoint for evaluating bnAb regimens.23 This PT80 biomarker quantifies the neutralisation potency as measured by the TZM-bl pseudovirus assay of bnAbs against an HIV-1 isolate and can be used to predict prevention efficacy. A PT80 value above 200 is potentially effective against 90% of circulating viruses.24,25 In this analysis, a single bnAb VRC01 was not sufficiently potent against most viral strains. The need for combinations of potent bnAbs that will produce superior neutralisation for HIV prevention is clear.

CAP256-VRC26.25 targets the V2 region of the HIV-1 envelope glycoprotein and is a member of the CAP256-VRC26 antibody lineage.24 This bnAb was isolated from a South African volunteer in the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 002 Acute Infection study conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA), in KwaZulu-Natal.25–27 This antibody is notable for its exceptional potency, particularly against clade C, with 70% breadth and a median IC50 of 0.007 µg/mL against a panel of 100 acute/transmitted clade C Env-pseudoviruses.26,28 In the macaque model, all animals were protected from SHIV challenges by CAP256-VRC26.25-LS at a dose as low as 0.08 µg/kg, corresponding to plasma concentrations lower than 0.75 µg/mL, which correlated with its greater in vitro neutralisation potency against the challenge virus.16 The native antibody, CAP256VRC26.25, was modified to an LS version and engineered to prevent proteolytic clipping of the heavy chain in the CDRH3 region.28,29 The non-clipped variant is referred to as CAP256V2LS. VRC07-523LS, a variant of VRC07 and clonal relative of VRC01, targets the CD4 binding site of the HIV-1 Env protein. VRC07-523LS was engineered to improve the half-life, potency and breadth of the antibody.17,30,31 VRC07-523LS showed a >5-fold increase in protection
in neutralisation potency in vitro compared with the VRC01 antibody,\textsuperscript{17} which was also reflected in the plasma of subjects who received it intravenously or subcutaneously.\textsuperscript{31} Complete protection from a mucosal SHIV challenge was demonstrated at a 20 mg/kg intravenous dose of VRC07-523LS, with an average plasma concentration of 114.2 µg/mL on the day of the first challenge.

The CAPRISA 012C trial will evaluate subcutaneous administration of CAP256V2LS and VRC07-523LS in young HIV-negative South African and Zambian women. It is the third trial of the CAPRISA 012 Subcutaneous Administration of Monoclonal Broadly neutralising Antibodies clinical trial programme. CAPRISA 012A evaluated the safety and PK of VRC07-523LS and PGT121 individually and in combination.\textsuperscript{32} CAPRISA 012B evaluated the safety and PK of CAP256V2LS administered intravenously to HIV-negative and HIV-positive women and subcutaneously alone and in combination with VRC07-523LS to HIV-negative women in South Africa.\textsuperscript{33} Data from these phase 1 studies have demonstrated the safety and favourable PK profiles of these bnAbs when used subcutaneously.\textsuperscript{34,35}

Based on preclinical and clinical data, the bnAb combination of CAP256V2LS and VRC07-523LS was selected for further evaluation in the CAPRISA 012C phase 2 trial. In CAPRISA 012B, the median CAP256V2LS and VRC07-523LS concentrations after a 20 mg/kg subcutaneous dose were 4.07 µg/mL and above 10 µg/mL at 24 weeks, respectively.\textsuperscript{35}

The CAPRISA 012C trial is designed to evaluate a fixed dose of both bnAbs, in contrast to previous studies that used a defined mg/kg dosing. The effect of body weight on drug biodistribution was demonstrated previously for some monoclonal antibodies, but body weight-based dosing is not necessarily required for adults.\textsuperscript{36} Body weight-based dosing may overadjust for the body size effect, as body weight has a significantly less than proportional effect on PK parameters.\textsuperscript{37}

Fixed dosing simplifies administration and can be more cost-effective and convenient to manufacture and deliver programmatically, if efficacious.\textsuperscript{38} Furthermore, subcutaneous administration of bnAbs removes the need for venous access and may be more scalable for widespread use.

The breadth and potency of VRC07-523LS and CAP256V2LS, as well as their compatible PK profiles and concentrations at 24 weeks observed in the phase 1 trials makes this combination suitable for further assessment in larger clinical studies. CAPRISA 012C is evaluating the extended safety and PK of VRC07-523LS and CAP256V2LS. The data from this trial are pivotal in the planning and conduct of larger phase 2b/3 studies and will determine if this combination proceeds to further clinical development.

**METHODS AND ANALYSIS**

**Patient and public involvement statement**

Prior to study activation, the study concept was presented to the CAPRISA Community Advisory Board (CAB) members for their input. The CAB plays a fundamental role in study planning and is composed of leadership of local HIV/AIDS organisations, health service provider representatives, community leaders, faith-based and traditional leaders, previous study participants and HIV-positive community members. The CAB also plays a pivotal role in study conduct, including recruitment and retention of participants.

**Study sites**

The CAPRISA 012C trial will be conducted at three clinical research sites (CRS): the CAPRISA eThekwini CRS in Durban, the CAPRISA Vulindlela CRS in Howick, South Africa and the Centre for Infectious Disease Research in Zambia Matero CRS in Lusaka, Zambia.

**Sample size**

The study population will consist of HIV-negative women; approximately 90 in part A and 900 in part B, aged 18–30 years.

**Study design**

CAPRISA 012C is a double-blinded, randomised, placebo-controlled phase 2 trial (table 1).

All inclusion and exclusion criteria must be met for eligibility to enrol (table 2).

Enrolment will take place within 56 days of screening. In part A, participants will be randomised in a 2:1:2:1 ratio, with 2 active vs 1 placebo for each product administration schedule at either 16 or 24 weeks. Ninety participants received CAP256V2LS 20 mg/kg and VRC07-523LS 20 mg/kg administered subcutaneously every 16 weeks or placebo; or CAP256V2LS and VRC07-523LS antibodies administered subcutaneously every 24 weeks or placebo. Depending on study-arm allocation, each participant will receive two or three doses and exit the study at month 12.

In part B, 900 participants will be randomised in a 1:1 ratio to receive an initial loading dose of 1.2 g each of CAP256V2LS and VRC07-523LS or placebo followed by 600 mg of CAP256V2LS and 1.2 g of VRC07-523LS or placebo administered subcutaneously 6 monthly. The accrual period is planned for approximately 12 months and eligible participants will receive between 2 and 4 doses depending on when they are recruited into the study. Participants will be followed up for a minimum of 12 months, an approximate average of 18 months and a maximum of 24 months.

Safety assessments will be conducted at baseline, following product administration and at regular intervals as per the schedule of evaluations. Once the last dose is received, participants will be followed up for safety and PK over a 12-month period.

Analyses were conducted using the Gilbert et al method, which demonstrated that the VRC07-523LS concentrations required for 90% protective efficacy far exceeded the concentrations required for CAP256V2LS. We then simulated PK concentrations of CAP256V2LS and VRC07-523LS administered at a loading dose of 1.2 g, followed by 600 mg of CAP256V2LS and 1.2 g of
VRC07-523LS (figure 1). The values at steady state were equivalent, but not exactly the same as those observed with a fixed dose of 600 mg throughout. The minor differences were not ‘real’ and were due to the different simulation runs and the use of 1000 virtual participants. While the current simulation size had overall good precision, these minor differences would disappear with a larger simulated population size.

The study products are available in 6.25 mL vials, which each contain 600 mg of VRC07-523LS and CAP256V2LS. The 1200 mg dose of both antibodies equates to two vials to be administered to participants at baseline, followed by a 6-month dosing interval of 1200 mg of VRC07-523LS and 600 mg of CAP256V2LS. When applied across a range of weights, 1200 mg translates to a dose of 20 mg/kg for a 60 kg person, 15 mg/kg for a 90 kg person and 10 mg/kg for a 120 kg person.

## Table 1  Study schema showing dosing regimen and distribution of participants in part A and part B

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Regimen*</th>
<th>N=90</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part A*</td>
<td>HIV negative</td>
<td>CAP256V2LS+VRC07-523LS</td>
<td>30</td>
<td>20 mg/kg SC+20 mg/kg SC at 16 weeks (4 monthly) dosing intervals</td>
</tr>
<tr>
<td>1a</td>
<td>HIV negative</td>
<td>Placebo</td>
<td>15</td>
<td>Normal saline SC at 16 weeks (4 monthly) dosing intervals</td>
</tr>
<tr>
<td>1b</td>
<td>HIV negative</td>
<td>CAP256V2LS+VRC07-523LS</td>
<td>30</td>
<td>20 mg/kg SC+20 mg/kg SC at 24 weeks (6 monthly) dosing intervals</td>
</tr>
<tr>
<td>1b</td>
<td>HIV negative</td>
<td>Placebo</td>
<td>15</td>
<td>Normal saline SC at 24 weeks (6 monthly) dosing intervals</td>
</tr>
</tbody>
</table>

| Part B | HIV negative | Placebo | 450 | CAP256V2LS initial loading dose 1.2 g SC+VRC07-523LS initial loading dose 1.2 g SC, followed by CAP256V2LS 600 mg and VRC07-523LS 1.2 g at 24 weeks (6 monthly) dosing intervals |
| 1a | HIV negative | Placebo | 15 | Normal saline equivalent to initial loading doses and repeat doses |

* Ninety participants will be randomised 2:1:2:1 active to placebo in both arms as follows: 30 participants will receive active study product (group 1a) and 15 will receive placebo (group 1a) at 4-monthly dosing intervals. Thirty participants will receive active study product (group 1b) and 15 will receive placebo (group 1b) at 6-monthly dosing intervals.

SC, subcutaneous.

## Table 2  Eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ 18–30 years of age</td>
<td>▶ Any significant acute or chronic medical condition, situation or circumstance that in the opinion of the PI/designee makes the participant unsuitable for participation in the study, or jeopardises the safety or rights of the participant.</td>
</tr>
<tr>
<td>▶ Persons born female (assigned female sex at birth) and identifying as female</td>
<td>▶ If planning a pregnancy for the duration of the study, currently pregnant or breastfeeding.</td>
</tr>
<tr>
<td>▶ Able and willing to complete the informed consent process</td>
<td>▶ A history of alcohol or substance use judged by the PI to potentially interfere with participant study compliance.</td>
</tr>
<tr>
<td>▶ Able to understand the information provided including the potential impact and/or risks linked to subcutaneous administration of the study product, willing to comply with protocol procedures, having access to the clinical research site and being available for follow-up for the study duration</td>
<td>▶ Prior participation in an investigational HIV vaccine trial, except if proof of allocation to the placebo arm is available.</td>
</tr>
<tr>
<td>▶ Based on clinical assessment, participant must be in good general health as per opinion of the principal investigator (PI) or designee</td>
<td>▶ Receipt of any vaccines within 28 days prior to enrolment.</td>
</tr>
<tr>
<td>▶ Haemoglobin &gt;100 g/L</td>
<td>▶ Administration of a monoclonal antibody or polyclonal immunoglobulin within 6 months prior to enrolment.</td>
</tr>
<tr>
<td>▶ Creatinine ≤1.25×upper limit of normal (ULN)</td>
<td>▶ Investigational HIV-related products received within 6 months prior to enrolment.</td>
</tr>
<tr>
<td>▶ ALT&lt;1.25×ULN</td>
<td>▶ Any history of anaphylaxis and related symptoms such as hives, respiratory difficulty or angioedema.</td>
</tr>
<tr>
<td>▶ HIV negative</td>
<td>▶ Evidence of autoimmune disease or currently receiving immunosuppressive therapy.</td>
</tr>
<tr>
<td>▶ Negative β-HCG pregnancy test on day of enrolment</td>
<td>▶ Current participation in any other research studies that would interfere with the objectives of this study. The determination of whether participation in another study would be exclusionary for a given participant will be made by the PI/designee.</td>
</tr>
<tr>
<td>▶ If of reproductive potential, has evidence of effective contraceptive use and is willing to adhere to effective contraceptive use during the study period</td>
<td></td>
</tr>
<tr>
<td>▶ Sexually active in the last 3 months</td>
<td></td>
</tr>
</tbody>
</table>

ALT, Alanine transaminase.
Study objectives
The aim of the trial is to assess extended safety and PK in young HIV-negative women in South Africa and Zambia.

Primary objectives
- To evaluate the safety of subcutaneously administered CAP256V2LS and VRC07-523LS among young HIV-negative women.

Primary endpoints
- Proportion of participants with any grade 3 or higher solicited reactogenicity events within the first 3 days after administration of CAP256V2LS in combination with VRC07-523LS versus placebo.
- Proportion of participants with any grade 3 or higher unsolicited adverse events (AEs) related to the administration of CAP256V2LS in combination with VRC07-523LS versus placebo.

Secondary objectives
- To assess the plasma PK profile of study products administered at a fixed dose every 24 weeks.

Secondary endpoints
- To compare HIV incidence rates in participants who receive antibodies against those receiving placebo.
- To assess CAP256V2LS and VRC07-523LS systemic and mucosal concentrations in relation to breakthrough HIV infections.
- To assess participant acceptability of the subcutaneous injections.

Figure 1  CAP256V2LS dosing simulations. Concentrations of CAP256V2LS in µg/mL is shown graphically following 600 mg, 900 mg and 1200 mg doses. The table insert shows the median and 90% prediction intervals of steady-state trough percentiles (5th percentile-P05 and 95th percentile-P9) and the expected frequencies of trough concentrations above 1, 5 and 10 µg/mL.
Study procedures

Written informed consent will be obtained from every participant prior to study participation, in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. The informed consent procedure will be conducted in English and/or local preferred language. In the case of an illiterate participant, an impartial witness will be present throughout the procedure to ensure that the participant understands the study and to certify that any questions posed are answered to the participant’s satisfaction.

At screening, the participant will provide all relevant identification documents and complete the informed consent procedure. The Biometric Co-Enrolment Prevention System will be used in South Africa and the iRespond (eye(iris) Biometric system) will be used in Zambia to identify and prevent potential co-enrolments. The study team will counsel participants on contraceptive use and review family planning records. HIV pretest and post-test counselling will be performed, and sociodemographic and behavioural data will be collected.

Participants will be provided with a comprehensive HIV prevention package that will include risk reduction behavioural counselling, free condoms, STI treatment. Access to PrEP will be made available at screening, enrolment and during follow-up. As new HIV risk-reduction methods are recommended and made available, they will be added to the prevention package. Access will be facilitated to standard of care PrEP options as they become available.

The study clinician will obtain a comprehensive medical history and perform a physical examination. All pre-existing conditions and any concomitant medication information will be reviewed and documented. To determine eligibility, screening laboratory tests including haematology, blood chemistry and liver function tests will be conducted. A genital specimen using a menstrual cup device will be obtained and stored prior to enrolment. Serum and plasma specimens will be stored for further analyses, as per informed consent.

With the exception of study pharmacists, all participants and study staff will be blinded to study treatment allocation. An unblinded study statistician will generate the randomisation list containing unique sequential treatment codes that will be used to assign individual study participants to a study arm dosing schedule. The randomisation list will be obtained by computer generated random numbers, where a randomly permuted block design, stratified by research site, will be used.

Data will be managed, using DFdiscover 2021 V.5.4.0. Data will be collected on case report forms (CRFs) designed specifically to address the protocol requirements. The site will record data on paper CRFs that will be scanned into the DFdiscover database and validated. All source documents will be kept in the participants’ study files and medical charts at the research sites. All original CRFs and study related documents will be securely stored at the sites, during the study and after study completion.

At enrolment, a targeted physical examination will be conducted, and all laboratory results will be reviewed. A negative pregnancy test for women of childbearing potential must be obtained prior to product administration. The study team will ensure that the participant is eligible to receive study product. Following randomisation, two separate injections, each containing a single bnAb, will be administered subcutaneously on either side of the abdomen.

Reactogenicity events are solicited from the start of study product administration up to 3 days postinfusion. After study product administration, each participant will be observed for a minimum of 1 hour at the clinic. A virtual visit will take place on day 3, and day 7 and the study nurse will retrieve all required safety information. Participants will also keep a daily diary of symptoms and record their temperature for 3 days after each product administration. In the event of a missed virtual visit, study staff will continue to follow up to ensure that the participant is still engaged and reactogenicity information will be collected on contact with the participant. For any reactogenicity symptoms that are not resolved within 3 days, clinicians will follow and collect resolution information.

AEs will be recorded throughout the study follow-up period. The protocol safety review team will monitor the safety data and will be responsible for decisions related to participant safety. An independent data and safety monitoring board will review the study data at predetermined time points or on an ad hoc basis. Following product administration, the participant will be seen at the clinic as per the schedule of procedures for safety assessments, blood draws and HIV testing.

Statistical analysis plan

Sample size calculations are based on the preliminary data from the phase 1 CAPRISA studies. Based on these statistical observations, the administration of fixed doses of antibodies is expected to cause less grade 3 or higher reactogenicity events than the weight-based dose. We assume that 4.8% of participants in the intervention arm compared with 1% in the control arm will experience at least one local or systemic grade 3 or higher reactogenicity event within the first 3 days after administration of study product. A sample size of 900 will provide 90% power to detect a minimum 4.8-fold higher rate of an event. These calculations are based on a Fisher’s exact test with a two-sided type I error rate of 0.05. Given a longer interval between study visits, we assume a drop-out rate of 10%, which has been incorporated into the total sample size.

The goal of this study is to identify safety concerns associated with dual bnAb administration. The ability of the study to detect rare events was determined by calculating the probability of detecting no events, at least one or at least two events at a specified true event rate. These probabilities indicate the likelihood of the study to detect either rare or common grade 3 or higher reactogenicity
events or even serious AEs. In addition, the 95% CI for the true event rate was calculated as shown in table 3.

For the 450 participants who will receive CAP256V2LS and VRC07-523LS, there is a 10% chance of observing no event if the true event rate is 0.5% and there is a very low probability of detecting no event when the event rate is 2% or higher. The chance of observing at least one event is ≥90% if the true event rate is 0.5% or more.

Since this extended safety study is being undertaken in high HIV burden populations, where a potential future phase 3 trial could be conducted, it is expected that a preliminary estimate of HIV efficacy may be generated. The statistical power to demonstrate 67% efficacy is expected to be 82% if the background incidence rate in the phase 2 trial is 4 per 100 person-years and 90% if the HIV incidence rate is 5 per 100 person-years. The rationale for using the background HIV incidence rate ranging from 3 to 5 per 100 person-years, is that the HIV incidence rate in the placebo arm of the AMP, ASPIRE and RING trials were 2.98, 4.5 and 6.1 per 100 women-years, respectively.

Power calculations shown in table 4 were based on an exponential maximum likelihood test of equality of survival curves from nQuery (2021) (Statistical Solutions, Cork, Ireland).

Descriptive statistics will be used to summarise baseline characteristics. The number and percentage of participants experiencing any AE or reactogenicity will be analysed and presented along with 95% CI. Each participant’s reactogenicity events will be counted once under the maximum severity for each injection. The proportion of participants experiencing at least one grade 3 or higher reactogenicity event across all injection visits will be compared using Fisher’s exact test. AEs will be coded as per Medical Dictionary for Regulatory Activities preferred terms. Boxplots and descriptive statistics will be used to summarise bnAb concentrations over time. Depending on the distribution of bnAb concentrations, a longitudinal model using either mixed effects models or generalised estimating equations will be built and adjusted for variables that are potentially correlated with bnAb concentrations.

The date of HIV infection diagnosis will be estimated as the midpoint between dates of the last negative HIV test and the first confirmed positive HIV test. Where a participant has a positive HIV PCR and a negative or discordant rapid HIV antibody result on the same date, the date of infection is calculated as 14 days prior to this date. Alternatively, the single random-point method would be used in case of missed visits. Participants who stay negative for HIV until their last study visit will be censored on the day of their last negative HIV test. Time at risk in days will be computed as the difference between the estimated date of HIV infection or date of censoring and the randomisation date. The HR comparing CAP256V2LS plus VRC07-523LS versus placebo and a 95% CI will be estimated using the univariable Cox proportional hazards model. Product efficacy calculated as 1 minus the HR and a 95% CI will be presented. In a secondary analysis, Cox proportional hazards regression models will be used to estimate the hazard rate ratio and product efficacy along with a 95% CI, controlling for baseline prognostic variables to improve precision. In the event where the proportional hazards assumption is violated, a Poisson model with person-years of follow-up as an offset will be used.

As current HIV prevention technologies are improving, designing clinical trials to assess the efficacy of newer HIV prevention agents against active comparator groups is increasingly challenging as these trials require extremely large sample sizes and/or longer trial duration. Given that current approved PrEP agents will also be made available, a sensitivity analysis will be conducted where the counterfactual placebo HIV incidence rate will be compared with the HIV incidence rate among those receiving CAP256V2LS and VRC07-523LS. The number and percentage of participants who discontinue the study product or prematurely withdraw from the study will be reported by study arm, with reasons for discontinuation summarised. Analyses will be conducted using either SAS (V.9.4 or higher, Cary, North Carolina, USA) or R.

PK disposition of CAP256V2LS and VRC07-523LS will be evaluated and conducted retrospectively on stored samples for all HIV seroconvertors and a subset of participants at a minimum of two time points. CAP256V2LS and VRC07-523LS systemic and mucosal concentrations in relation to breakthrough infections will also be evaluated. Summary descriptive results of PK parameters will be reported. PK parameters will be calculated using standard non-compartmental methods. A population PK analysis

Table 3  Number of participants needed to reach 90% power to detect a safety event

<table>
<thead>
<tr>
<th>Scenario</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event rate in the intervention arms</td>
<td>6.0%</td>
<td>6.0%</td>
<td>5.0%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Event rate in the control arm</td>
<td>1.0%</td>
<td>1.5%</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Sample size per arm</td>
<td>300</td>
<td>400</td>
<td>423</td>
<td>450</td>
</tr>
<tr>
<td>Total sample size</td>
<td>600</td>
<td>800</td>
<td>846</td>
<td>900</td>
</tr>
</tbody>
</table>

Table 4  Statistical power and HIV endpoints for varying effectiveness and background incidence rates

<table>
<thead>
<tr>
<th>HIV incidence per 100 person-years</th>
<th>67% effectiveness</th>
<th>80% effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV events</td>
<td>Power</td>
<td>HIV events</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>53%</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>82%</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>90%</td>
</tr>
</tbody>
</table>

*The statistical power for varying effectiveness and background HIV incidence rates is tabulated when the sample size is 900. These calculations are based on an accrual period of 9–12 months with a minimum follow-up of 12 months, average follow-up of 18 months and a maximum follow-up of 24 months.
will be performed using a two-compartment model and the computer program NONMEM, V.7.3 or later.33

Ethics and data dissemination

Regulatory review and oversight will be undertaken by the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (BREC) and by the South African Health Products Regulatory Authority (SAHPRA) (Trial reference numbers: BREC/00002492/2021 and SAHPRA 20210317). Data emanating from the trial will be shared by the study team with the scientific community at international conferences and through peer-reviewed journal publications. Data will be shared throughout study conduct with the CAB and other stakeholders, with study participants and the wider community through presentations, infographics and other materials. Trial results will be uploaded onto the UKZN repository and the Pan-African Clinical Trial Registry.

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Contributors

SAK and QAK conceived the trial. SAK, QAK, SM and NG designed the trial. SM wrote the study protocol. EC conducted the PK simulations and will lead the PK analysis. FO and NVZ performed sample size calculations and the statistical analysis strategy. LG, RAK, KC, NDR, PM and LM contributed to antibody development. LG, RAK, KC, SN, LS, ITS, DP, IH, TNG, LM, DA, NM, PR, NS, CW, BP and CH contributed to the planning and conduct of the trial. All authors reviewed the manuscript and consented to publication.

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Competing interests

NDR, PM, LM and SAK are listed on patent applications involving CAP256V2LS and/or VRC07-523LS. There are no other competing interests to declare.

Patient and public involvement

Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

REFERENCES


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