

PROTOCOL

CAPRISA 012C

A double-blinded, randomized, placebo-controlled phase II trial to assess extended safety and tolerability of subcutaneous CAP256V2LS and VRC07-523LS in HIV-negative women

CLINICAL TRIAL SPONSORED BY

Centre of the AIDS Programme of Research in South Africa
(CAPRISA)

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Protocol Signature Page

A double-blinded, randomized, placebo-controlled phase II trial to assess extended safety and tolerability of subcutaneous CAP256V2LS and VRC07-523LS in HIV-negative women

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information as needed.



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TABLE OF CONTENTS

PROTOCOL TEAM	2
COLLABORATING ORGANIZATIONS	3
TABLE OF CONTENTS.....	5
1.0 STUDY SCHEMA	7
2.0 INTRODUCTION	8
2.1 Background /Rationale for trial concept	8
2.2 Study products selected for this trial	8
2.3 Trial design rationale.....	9
2.4 Plans for future product development and testing	9
2.5 Preclinical studies	9
2.5.1 CAP256V2LS.....	9
2.5.2 VRC07-523LS.....	10
2.6 Clinical studies.....	12
2.6.1 CAP256V2LS.....	12
2.6.2 VRC07-523LS.....	14
3.0 TRIAL OVERVIEW	15
3.1 Clinical trial objectives.....	15
3.2 Primary objective	15
3.3 Secondary objectives.....	15
3.4 Primary endpoints.....	15
3.5 Secondary endpoints	15
4.0 STUDY DESIGN	15
4.1 Study population	15
4.2 Enrollment plan.....	16
4.3 Eligibility criteria	17
5.0 CLINICAL PROCEDURES	17
5.1 Recruitment	17
5.2 Screening visits.....	18
5.3 Enrolment Visits.....	18
5.4 Administration of study product/s	18
5.5 HIV counselling and testing	18
5.6 HIV risk reduction counselling.....	18
5.7 Care for participants identified as HIV-infected during the study	18
5.8 Family planning counselling	19
5.9 Pregnancy.....	19
5.10 Follow-up visits	19
6.0 LABORATORY PROCEDURES	19
6.1 Laboratory specimens and tests.....	20
6.2 On site testing.....	20
6.3 Collection of specimens	20
6.4 Specimen storage for quality assurance and potential future research	20
6.5 Laboratory quality control and quality assurance procedures.....	20
7.0 PHARMACY PROCEDURES	20
7.1 Study Products	20
7.2 Storage.....	21
7.3 Preparation of study product	21
7.4 Study product accountability	21
7.5 Study product dispensing.....	21
7.6 Study product returns.....	21
7.7 Study product destruction	21

8.0	SAFETY AND ADVERSE EVENTS REPORTING	21
8.1	Adverse events	21
8.2	Serious Adverse Events	22
8.3	Reporting adverse events of special interest (AESIs)	22
8.4	Discontinuation of study product/s administration	23
8.5	Clinical management and Reporting of Adverse Events	24
8.6	Safety monitoring	24
9.0	STATISTICAL CONSIDERATIONS	24
9.1	Accrual, sample size and follow-up	24
9.2	Randomisation and allocation concealment	26
9.3	Statistical analyses	27
9.3.1	Study populations	27
9.3.2	Data analyses	27
10.0	PHARMACOKINETIC ANALYSES	28
11.0	DATA MANAGEMENT	28
11.1	Data Sharing	30
12.0	HUMAN SUBJECT PROTECTION AND ETHICAL OBLIGATIONS	30
12.1	Regulatory and Ethical Approval	30
12.2	Informed consent	30
12.3	Risks and Benefits	31
	References	33

1.0 STUDY SCHEMA

Purpose	To assess extended safety and tolerability of subcutaneous CAP256V2LS and VRC07-523LS monoclonal antibodies in HIV-negative women
Study design	A double blinded, randomized, placebo-controlled phase II trial
Rationale	<p>Current pharmacokinetic data on CAP256V2LS and VRC07.523LS suggest that plasma antibody concentrations projected out to 120 days and 180 days are above 1 µg/ml. In the macaque model, all animals were protected from challenge at CAP256-VRC26.25-LS plasma concentrations as low as <0.75 µg/ml. CAP256-VRC26.25-LS was fully protective even at the 0.08 mg/kg dose.</p> <p>In the absence of a plasma antibody concentration that correlates with protection in humans, this dose-ranging phase II trial will assess safety of CAP256V2LS and VRC07.523LS administered at 4-monthly and 6-monthly dosing intervals, using antibody concentrations and breakthrough HIV infections, if any to guide dose and dosing interval selections for the future phase III trial.</p>
Study participants	HIV negative (N=990) 18 to 30 years.
Study sites	<ul style="list-style-type: none"> • CAPRISA eThekweni Clinical Research Site, Durban, KwaZulu-Natal, South Africa • CAPRISA Vulindlela Clinical Research Site, Howick, KwaZulu-Natal, South Africa • The Centre for Infectious Disease Research in Zambia (CIDRZ): Matero Clinical Research Site, Lusaka, Zambia
Study duration	<ul style="list-style-type: none"> • Enrolment will take place within 56 days of screening. • In Part A (N=90): Participants will receive two weight-based doses of study product if in the 24-week (6-monthly) schedule or three doses of study product if in the 16-week (4- monthly) schedule and exit at month 12. • In Part B (N=900): Participants will receive an initial fixed dose of 1.2g of CAP256V2LS and 1.2g VRC07-523LS or placebo, followed by 600mg of CAP256V2LS and 1.2g of VRC07-523LS or placebo every 24- weeks (6-monthly) • Depending on the dosing interval and study product availability, participants will continue in follow up until approximately 16,18 or 20 months, until study end.
Study products	CAP256V2LS and VRC07-523LS administered as separate injections
Primary objective	<ul style="list-style-type: none"> • To evaluate the safety of CAP256V2LS and VRC07-523LS in HIV-negative women
Secondary objectives	<ul style="list-style-type: none"> • To evaluate the tolerability of CAP256V2LS and VRC07-523LS • To assess the PK profile of study products administered 16 weekly (4 monthly) in comparison to 24 weekly (6 monthly) administration • To assess the PK profile of study products administered as a fixed dose 24 weekly (6 monthly) • To compare HIV incidence rates in antibody and placebo recipients • To assess CAP256V2LS and VRC07-523LS systemic and mucosal concentrations in relation to breakthrough infections • To determine the prevalence of autoantibody induction • To assess participant acceptability of the subcutaneous injections

2.0 INTRODUCTION

2.1 Background /Rationale for trial concept

The ongoing high incidence of HIV infections remains a major global public health concern. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported more than 38 million people living with HIV in 2019, with 1.7 million new infections (1). Although global incidences of new infections have declined due to extensive prevention and treatment efforts such as increased availability of antiretroviral therapy (ART) and prevention of mother-to-child transmission (PMTCT) programs, some groups remain heavily burdened by the HIV pandemic (1). In South Africa, young women between the ages of 18 to 25, carry the greatest burden of the disease with persistent high HIV incidence and prevalence (2, 3). Similarly, in Zambia, young women and adolescent girls are worse affected than men. Studies have demonstrated that the use of ART decreases HIV transmission (4) and the use of pre-exposure prophylaxis (PrEP) decreases HIV acquisition (5). However, poor adherence, side effects, implementation costs and access to treatment remain a challenge (6).

A variety of prevention technologies will result in improved uptake and coverage and thus are urgently required, particularly in vulnerable populations. Existing strategies such as long-acting injectable ART and ART-containing intravaginal rings (IVRs) offer specific advantages over daily oral PrEP (7-11). However, the dapivirine IVR needs to be replaced monthly and the user can remove the product at any time, thereby reducing its effectiveness. Recently, results from the HIV Prevention Trials Network (HPTN) 083 clinical trial showed that an 8-weekly long-acting cabotegravir containing PrEP regimen was superior to daily FTC/TDF for HIV prevention among cisgender men and transgender women who have sex with men (12). Although this may overcome the adherence challenges with other HIV prevention options, long-acting injectables have distinct challenges, including: the route of administration, the dosing intervals and the pharmacokinetic (PK) tail that may allow for the development of resistant viral variants (13).

Passive immunisation using broadly neutralizing monoclonal antibodies (bnAbs) is a promising alternate HIV prevention strategy that may address some of the challenges faced with other PrEP options. bnAbs have a longer half-life, especially with LS mutations, allowing for a longer dosing interval and less frequent administration. Furthermore, bnAbs can be administered subcutaneously (SC) and this relative ease of administration provides advantages over IVR and ART-containing intramuscular injectables. These characteristics are distinct advantages, making long-acting bnAbs a substantially improved PrEP technology with potential for wide-scale implementation. Pre-clinical animal studies have demonstrated that passively administered bnAbs protects rhesus macaques from simian-human immunodeficiency virus (SHIV) infection (14-17). Additionally, *in vitro* studies have demonstrated that bnAb combinations result in an improved neutralization breadth and potency (18).

To date, an array of antibodies have been investigated, both alone and in combination and have demonstrated safety and favourable PK profiles (19, 20). Results from the first efficacy trial, HPTN 081/HVTN703 evaluating VRC01 are expected soon and will define the concentration of antibody required to prevent HIV acquisition and inform future trials (21). The CAPRISA 012C trial will evaluate the combination of CAP256V2LS and VRC07-523LS in young HIV-negative South African and Zambian women. The overall goal of the CAPRISA 012 trials is to develop a new, safe and effective long-acting HIV prevention technology principally for women, to alter the course of the HIV epidemic in Africa. Data from this trial will be crucial for designing future antibody prevention trials and will determine if this antibody combination can proceed to advanced clinical development.

2.2 Study products selected for this trial

CAP256-VRC26.25, a potent bNAb, targets the V2 region of the HIV-1 envelope glycoprotein. CAP256V2LS is a member of the CAP256-VRC26 antibody lineage, which was originally isolated from a South African woman participating in the CAPRISA 002 Acute Infection study conducted by the Centre for the AIDS Programme of Research in South Africa, in KwaZulu-Natal (22-25). The native antibody, CAP256VRC26.25, was subsequently modified to a LS version and thereafter engineered to prevent proteolytic clipping of the heavy chain through mutation of the Lysine at position 100 to an

Alanine (26). This single amino acid change was made in the CDRH3 region to improve manufacturability without altering neutralization breadth or potency. This non-clipping variant of the antibody is referred to as CAP256V2LS. Interim data from first in human studies conducted in South Africa (27), have demonstrated safety with favourable PK profiles.

VRC07-523LS targets the CD4 binding site of the HIV-1 Env protein. VRC07-523LS is a variant of VRC07, which is a clonal relative of the bnAb VRC01, and has been engineered to improve half-life, potency and breadth. VRC07-523LS has been evaluated in several clinical trials, including South African clinical trials (27, 28) and has demonstrated safety with favourable PK profiles.

CAP256V2LS and VRC07-523LS in combination has been evaluated in a South African population and interim data has demonstrated safety with favourable PK profiles. The CAPRISA 012 clinical trials programme consists of three trials. The CAPRISA 012A trial, which is complete, was a phase I study that assessed the safety and PK of VRC07-523LS and PGT121 individually and in combination (28). CAPRISA 012B is a phase I trial that evaluates the safety and PK of CAP256V2LS administered intravenously (IV) to HIV-negative and HIV-positive women or SC alone and in combination with VRC07-523LS and/or PGT121 to HIV-negative women in South Africa (27). Based on available data, the bnAb combination of CAP256V2LS and VRC07-523LS has been selected for evaluation in the CAPRISA 012C phase II trial.

2.3 Trial design rationale

The doses of each antibody and dosing interval selected is based on prior clinical experience with CAP256V2LS and VRC07-523LS, as well as on antibody PK modelling using both nonclinical and clinical data. Current pharmacokinetic data on CAP256V2LS and VRC07.523LS suggest that plasma antibody concentrations projected out to 120 days and 180 days are above 1 µg/ml. In the macaque model, all animals were protected from challenge at CAP256-VRC26.25-LS plasma concentrations as low as <0.75 µg/ml. CAP256-VRC26.25-LS was fully protective even at the 0.08 mg/kg dose, which correlated with its greater in vitro neutralization potency against the challenge virus. In the absence of a plasma antibody concentration that correlates with protection in humans, this dose- ranging phase II trial will assess safety of CAP256V2LS and VRC07.523LS administered at a significantly increased dose of 20mg/kg at 4-monthly and 6-monthly dosing intervals, using antibody concentrations and breakthrough HIV infections, if any, to guide dose and dosing interval selection for the future phase III trial.

2.4 Plans for future product development and testing

Passively administered bnAbs can be used as an HIV prevention strategy for both men and women. This trial focuses on women only due to the urgent need for woman-controlled HIV prevention technologies. A positive signal from the CAPRISA 012C trial will create parallel research and development paths for both men and women. Furthermore, data from this trial will help guide the design of future HIV prevention trials and vaccine development.

2.5 Preclinical studies

2.5.1 CAP256V2LS

***In vitro* Pharmacology**

In vitro Neutralization Activity

The neutralization potency and breadth of CAP256V2LS was assessed on a panel of 208 viral envelope pseudoviruses. CAP256V2LS neutralized 63% of pseudoviruses with a median IC₅₀ of 0.001 µg/mL. Furthermore, CAP256V2LS neutralized 72% of the 58 clade C pseudoviruses, with a median IC₅₀ of 0.001 µg/mL.

***In vivo* Pharmacology**

Pharmacokinetic Study in Human FcRn Transgenic Mice

CAP256V2LS administered at 5 mg/kg IV in transgenic mice (n=5) produced sera antibody levels

above 1 µg/mL, that were maintained up to day 21 post infusion. Sera levels gradually decreased and reached levels below detection limit from day 42 post infusion. The average half-life was 7.7 days.

Pharmacokinetic Study in Rhesus Macaques

CAP256V2LS administered in rhesus macaques (n=3) at 10 mg/kg either SC or IV route (n=3) produced sera antibody levels above 10 µg/mL that were maintained for up to 14 days post infusion in all animals irrespective of route. Initial sera antibody levels were higher in the IV groups compared to SC, but by day 2, were similar in all animals irrespective of administration route. The average half-life for CAP256V2LS was 14.3 days for the IV route and 9.9 days for the SC route.

SHIV Challenge Study in Rhesus Macaques

CAP256.VRC26.25LS, the parent antibody, demonstrated potent dose dependent protection to rhesus macaques against mucosal challenge with a chimeric simian/human immunodeficiency virus (SHIV-325c) (16). Since both CAP256V2LS and CAP256.VRC26.25LS show similar neutralization titres against SHIV-325c, it is postulated that CAP256V2LS would have similar protective efficacy against SHIV-325c challenge.

Toxicology and Immunogenicity

In vitro Tissue Cross Reactivity

Plasma membrane staining was not observed in human and rat tissues. There was unexpected tissue cross-reactivity in the cytoplasm or extracellular material; with the cytoplasm of a few specific tissue elements stained in either the human or rat tissues. Due to the limited ability of antibody drugs to access the cytoplasmic compartment in vivo, this finding is not significant (29, 30). The significance of the extracellular binding is unknown.

Repeat Dose Toxicity Study

Repeat dosing of CAP256V2LS at 20 or 200 mg/kg/day IV on Days 1 and 11 or, 10 or 100 mg/kg/day SC on Days 1, 11 and 21, was administered to Sprague Dawley rats. There were minor test article-related non-adverse effects on body temperature, haematology, coagulation, and macroscopic/microscopic examinations at the SC injection site. The maximum tolerated dose (MTD) for CAP256V2LS was >200 mg/kg/day IV and >100 mg/kg/day SC. The no observed adverse effect level (NOAEL) was 200 mg/kg/day IV and 100 mg/kg/day SC.

Other Safety Studies

CAP256V2LS has lower polyspecific autoreactivity than other anti-HIV-1 antibodies. CAP256V2LS demonstrated higher binding to cardiolipin than VRC01LS, but lower binding than 4E10. 4E10 binds strongly to cardiolipin with no serious adverse reactions seen in multi-dose phase I and II trials (31, 32). CAP256V2LS displays low binding to the phospholipid cardiolipin and no binding to HEP-2 cells. No lengthening of activated partial thromboplastin time (aPTT) intervals were seen, demonstrating no anti-phospholipid characteristics.

Conclusion from Nonclinical Studies

Minimal safety concerns have been demonstrated from toxicology and immunogenicity studies. This supports clinical trial evaluations of CAP256V2LS.

2.5.2 VRC07-523LS

***In vitro* Pharmacology**

In vitro Neutralization Activity

VRC07-523LS neutralised 96% of primary HIV-1 isolates at an IC₅₀ <50 µg/mL. and neutralised 92% of HIV-1 isolates at an IC₅₀ <1 µg/mL. VRC07-523LS demonstrated an increased breadth and potency when compared to VRC01.

***In vivo* Pharmacology**

Pharmacokinetic Study in Macaques

VRC07-523LS administered at 10 mg/kg IV in rhesus macaques (n=4), produced plasma concentrations exceeding 10 µg/mL at day 14 and levels greater than 2 µg/mL at day 28 [4]. Detectable concentrations of >10 µg/mL/mL were measured in rectal secretions for at least 14 days in 2 animals. The half-life was about 10 days. VRC07-523LS administered at 10 mg/kg in cynomolgus macaques IV, produced plasma concentrations exceeding 10 µg/mL at day 14 and levels greater than 3 µg/mL at day 28. Detectable concentrations were found in rectal and vaginal secretions and tissues for at least 28 days. The half-life was about 12 days. VRC07-523LS administered at 20 mg/kg IV to rhesus macaques (n=6) produced average plasma concentrations of VRC07-523LS of 114.2 µg/mL on Day 1. VRC07-523LS administered at 10 mg/kg SC in rhesus macaques (n=6), produced detectable concentrations of VRC07-523LS in rectal, vaginal and nasal secretions in all animals, for at least 49 days. The half-life was about 14 days. The half-life for VRC07-523LS administered SC was 14.17 days in rhesus macaques.

SHIV Challenge Study in Rhesus Macaques

VRC07-523LS showed a >5-fold increase in potency compared to the VRC01LS antibody, consistent with its ability to better neutralize virus in vitro (11). VRC07-523LS at 20 mg/kg IV was administered in rhesus macaques (n=6). At day 5 post infusion, all animals were challenged intrarectally with SHIV-SF162P3. In parallel, rhesus macaques (n=12) were challenged with the same virus to confirm infectivity of the challenge stock. The average plasma concentration on the day of the first challenge (Day 5) was 114.2 µg/mL. All 6 animals that received 20 mg/kg were protected from infection after the mucosal SHIV challenge, whereas all 12 control animals became infected. Therefore, complete protection from a mucosal SHIV SF162P3 challenge (at day 5) was demonstrated at 20 mg/kg dose IV.

Toxicology and Immunogenicity

Repeat Dose Toxicity Study

Doses up to 400 mg/kg/dose administered IV or SC were well tolerated and produced acceptable VRC07-523LS concentration levels post-dose; with IV groups resulting in sustained levels through Day 56. No treatment-related or toxicologically significant physical or clinical signs of toxicity were observed. There were no post-dose signs of dermal reactogenicity at the SC injection site. No toxicologically significant effects on body temperature were seen during the study. Alterations in various clinical pathology parameters were seen but most of these findings were reversible and thus the toxicological significance was considered minimal. None of these clinical pathology findings resulted in any limiting toxicity. Hematologic findings observed were mild, with no corresponding microscopic findings and not considered adverse. All changes were reversible following cessation of dosing, except for red cell distribution width (RDW) which remained slightly increased in the high dose IV group at Day 56. The NOAELs for this study were 400 mg/kg IV and 40 mg/kg SC.

Local Tolerance of VRC07-523LS administered IM to Sprague-Dawley Rats

There were no treatment-related findings noted at the injection site. No evidence of systemic toxicity and no adverse clinical findings were seen. Statistically significant changes in plasma fibrinogen levels were of minimal toxicological significance.

In vitro Tissue Cross Reactivity

There was staining of cytoplasmic and extracellular elements seen in human tissues that was more intense and frequent compared to rat tissues. Staining was observed in cytoplasm, cytoplasmic granules, and/or perinuclear cytoplasm of various neonatal human tissues. No membrane specific binding was observed suggesting that there is no cross-reactivity of toxicologic concern.

Other Safety Studies

Minimal reactivity to phospholipids is seen when compared to 4E10 that reacts strongly with phospholipids. VRC07-523LS does react with a small subset of nuclear antigens showing some reactivity with nuclear antigens and has minimal reactivity with HEP-2 cells. VRC07-523LS does not

impact a PTT by binding phospholipids. The constant region LS mutation does not affect autoreactivity results.

Conclusion from Nonclinical Studies

Minimal safety concerns have been demonstrated from toxicology and immunogenicity studies. This supports clinical trial evaluations of VRC07-523LS.

2.6 Clinical studies

2.6.1 CAP256V2LS

CAPRISA 012B Phase 1 study

The CAPRISA 012B trial is a phase 1 dose-escalation study of the safety, tolerability and PK of CAP256V2LS administered IV to HIV-negative and HIV-positive women or SC alone and in combination with VRC07-523LS and /or PGT121 to HIV-negative women and is currently underway in South Africa. Groups 1a, 1b, 2, 3 and 4 consist of HIV-negative women (N=52), while Group 1c and 1d will enrol HIV-positive women (N=14) who have not yet started antiretroviral therapy (**Table 1**).

Table 1: CAPRISA 012B dosing table

Group	Participants	Regimen	N=76	Dose (mg/kg)
Group 1: Dose escalation of IV administration of CAP256V2LS				
1a	HIV negative	CAP256V2LS	4	5 mg/kg IV one dose
1b	HIV negative	CAP256V2LS	4	10 mg/kg IV one dose
1c	HIV positive	CAP256V2LS	4/2	20 mg/kg IV one dose
1d	HIV positive	CAP256V2LS	4/4	20 mg/kg IV one dose
Group 2: Dose escalation of SC administration of CAP256V2LS				
2a	HIV negative	CAP256V2LS	4	5 mg/kg SC one dose
2b	HIV negative	CAP256V2LS*	4	5 mg/kg SC one dose
2c	HIV negative	CAP256V2LS*	4	10 mg/kg SC one dose
2d	HIV negative	CAP256V2LS*	4	10 mg/kg SC with one repeat dose at 16/24 weeks [#]
2e	HIV negative	CAP256V2LS*	4	20 mg/kg SC one dose
2f	HIV negative	CAP256V2LS*	4	20 mg/kg SC with one repeat dose at 16/24 weeks [#]
Group 3: Dose escalation of the two antibody combinations				
3a	HIV negative	CAP256V2LS* + VRC07-523.LS*	4/1	10 mg/kg SC / 10 mg/kg SC one dose
3b	HIV negative	CAP256V2LS* + VRC07-523.LS*	4/1	20 mg/kg SC / 20 mg/kg SC one dose
3c	HIV negative	CAP256V2LS + VRC07523.S	4/1	20 mg/kg SC / 20 mg/kg SC one dose
Group 4: Fixed Dosing				
4a	HIV negative	CAP256V2LS	4/1	1.2g
4b	HIV negative	VRC07-523.LS	4/1	1.2 g
4c	HIV negative	CAP256V2LS + VRC07523.LS	4/1	1.2 g

*Antibody/placebo will be injected with hyaluronidase, ENHANZE™ drug product (EDP), so that the antibody/placebo dose can be administered as a single SC injection; [#] First two participants will receive two doses 24 weeks apart and the next two participants will receive two doses 16 weeks apart

All CAPRISA 012B safety data presented remains blinded to date. As of 25 January 2021, 39 HIV-negative participants were enrolled into Groups 1a and 1b, 2a-f, 3a and 3b (Table 1).

Overall, reported reactogenicity events ranged from mild to severe and all reactogenicity events resolved within the three-day reactogenicity assessment period. There have been no infusion reactions during study product administration. Common related events that were observed included lymphocytopenia, proteinuria, increased aspartate aminotransferase and increased alanine aminotransferase.

There were two related grade 3 adverse events of transient declines in lymphocyte counts observed in one participant who received CAP256V2LS at 5mg/kg SC without hyaluronidase and one participant who received CAP256V2LS at 20mg/kg SC with hyaluronidase. There were also two related grade 4 adverse events of transient declines in lymphocyte counts observed. Both participants received either a combination of CAP256V2LS 10mg/kg and VRC07-523LS 10mg/kg, or a placebo, with hyaluronidase. These events occurred at day 1 post study product administration and resolved by day 3 to day 7.

The transient decline in lymphocyte counts observed during conduct of the trial prompted a protocol specified study pause by the principal investigators and a DSMB meeting was convened. The DSMB concluded that this was not a safety concern, as the laboratory abnormalities observed had no clinical significance. All participants were clinically stable and remain well to date. Furthermore, occurrences of transient declines in lymphocyte count have been observed in animal studies and human studies following the administration of many monoclonal antibodies (mAbs) (33-38). After review of the data and consultation with expert haematologists, the DSMB advised that the trial resume given the absence of a clinical safety concern.

There were no serious adverse events (SAE) and adverse events (AE) did not result in study product discontinuation in any participant. There have been no suspected unexpected serious adverse reactions (SUSAR) reported to the South African Health Products Regulatory Authority (SAHPRA).

Interim pharmacokinetic analysis demonstrates detectable antibody serum concentrations following both IV and SC administration (**Figure 1**). PK results are limited to shortly after the dose following SC administration, especially at higher doses. An increase in SC dose appears to be associated with a proportional increase in concentration. Although data is limited, current PK analysis suggest that plasma antibody concentrations projected out to 120 days and 180 days are above 1 mcg/ml. Additional analyses are ongoing.

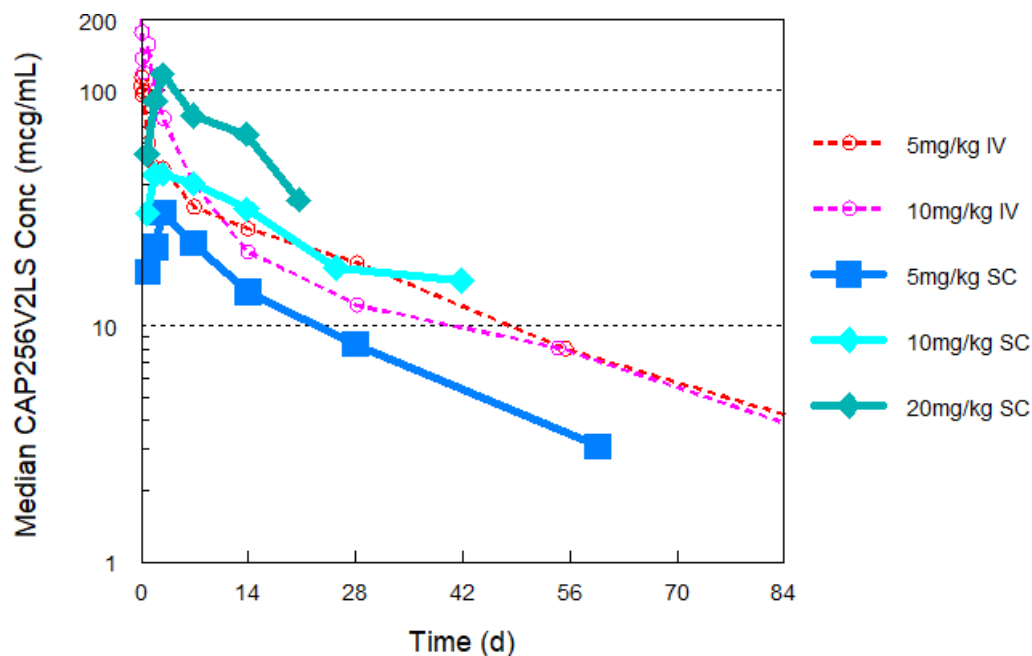


Figure 1: Comparison of median Concentrations by dose and route

VRC 611 Phase 1 study

VRC 611 is another planned phase 1 study that aims to evaluate CAP256V2LS administered via subcutaneous and intravenous injection in 10 healthy adults. This study will be conducted at the VRC Vaccine Evaluation Clinic in the NIH Clinical Centre.

2.6.2 VRC07-523LS

VRC07-523LS is being evaluated in 10 clinical trials in the USA and South Africa. Nine trials are ongoing, and one trial has been completed with published data. VRC07-523LS has been administered by IV, SC, or intramuscular infusion/injection, either individually or in combination with other HIV bNAbs. Overall, single-dose regimens of VRC07-523LS ranging from 1 to 40 mg/kg IV or 5 to 10 mg/kg SC; or repeat-dose regimens ranging from 2.5 to 30 mg/kg IV, 2.5 to 10 mg/kg SC, or 2.5 mg/kg IM; have generally been well-tolerated in all adult populations examined. SC injection in 8 HIV-1 exposed infants administered VRC07-523LS at a maximum 100 mg per dose was also well tolerated.

CAPRISA 012A, described above, has been completed and closed to further data collection. All safety data presented remains blinded to date. As of February 17, 2020, 30 participants received VRC07-523LS/placebo by the SC route. The dosing ranges were 5mg/kg, 10mg/kg and 20mg/kg for SC administrations. Doses were given as a single injection or as two injections, 12 or 24 weeks apart (28). There were no safety concerns reported with favourable PK. Overall product administrations were generally well tolerated with all reported reactogenicity events either mild or moderate in severity. There was one grade 3 (severe) adverse event observed in a participant from Group 1 who was diagnosed with a urinary tract infection, which was assessed as not related to study product. There was one reported SAE of polytrauma due to a motor vehicle accident, that was determined to be unrelated to study product. None of the adverse events experienced in the study resulted in study product discontinuation in any participant. There have been no SUSARs reported to SAHPRA and no study pauses due to safety concerns. PK analysis is currently underway.

A phase 1, open-label, dose-escalation clinical trial conducted at the NIH has been completed with published data (39). Four groups received a single intravenous dose of 1, 5, 20, or 40 mg/kg of VRC07-523LS, and one group received a single 5 mg/kg subcutaneous dose. Two groups received

three doses of either 20 mg/kg intravenous VRC07-523LS, or 5 mg/kg subcutaneous VRC07-523LS at 12-week intervals. There were no safety concerns with favourable PK reported. VRC07-523LS had an elimination half-life of 38 days for the IV groups and 33 days for SC groups. Sera containing VRC07-523LS displayed equivalent or greater neutralisation activity than those containing VRC01 or VRC01LS from previous trials.

Rationale for trial design amendment

Assessment of Preliminary CAPRISA 012B phase 1 PK data indicates that concentrations above the 1mcg/ml 'target' concentration is achievable for doses above 10mg/kg for both CAP256V2LS and VRC07-523LS, consistently maintained over 168 days after a single subcutaneous administration (Figure 2). The study products CAP256V2LS and VRC07-523LS are available in 6ml vials and contain 600mg of antibody per vial. We propose an initial fixed dose of 1200mg of both VRC07-523LS and CAP256V2LS which equates to 2 vials of each bnAb used per participant, followed by a 6-month dosing interval of 1200mg (2 vials) of VRC07-523LS and 600mg (1 vial) of CAP256V2LS. This dosing strategy is based on a recent analysis (*Gilbert P et al, Neutralization titer biomarker for antibody-mediated prevention of HIV-1 acquisition. Nature Medicine. 2022 Sep;28(9):1924-32*) that estimates concentrations of bnAbs required for protection. When applied across a range of weights this dose is adequate to reach well beyond the target concentration, example: 1200mg translates to a dose of 20mg/kg for a 60kg person, 15mg/kg for a 90kg person and 10mg/kg for a 120kg person.

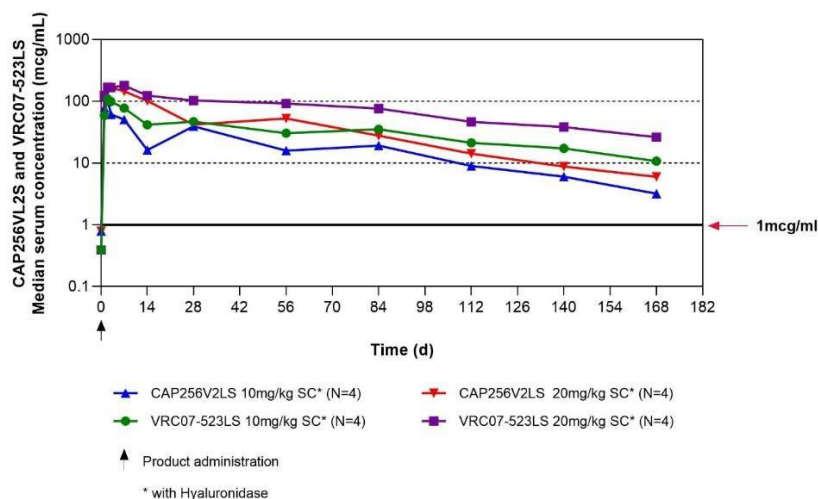


Figure 2: Median CAP256V2LS and VRC07-523LS over 168 days from the CAPRISA 012B phase 1 trial.

3.0 TRIAL OVERVIEW

3.1 Clinical trial objectives

The aim of the CAPRISA 012C trial is to assess extended safety and obtain an estimate of efficacy in preventing HIV infection in young women.

3.2 Primary objective

- To evaluate the safety of CAP256V2LS and VRC07-523LS in HIV-negative women

3.3 Secondary objectives

- To evaluate the tolerability of CAP256V2LS and VRC07-523LS
- To assess the PK profile of study products administered 16 weekly (4 monthly) in comparison to 24 weekly (6 monthly) administration
- To assess the PK profile of study products administered as a fixed dose 24 weekly (6 monthly)
- To compare HIV incidence rates in antibody and placebo recipients
- To assess CAP256V2LS and VRC07-523LS systemic and mucosal concentrations in

relation to breakthrough infections

- To determine the prevalence of autoantibody induction
- To assess participant acceptability of the subcutaneous injections

3.4 Primary endpoints

- Proportion of participants with any grade 3 or higher reactogenicity events within the first 3 days after administration of CAP256V2LS in combination with VRC07-523LS
- Proportion of participants with any grade 3 or higher adverse events related to the administration of CAP256V2LS in combination with VRC07-523LS

3.5 Secondary endpoints

- Documented HIV-1 infection during follow up
- Differences in the PK profile of study products administered 16 weekly (4 monthly) in comparison to 24 weekly (6 monthly) administration
- Differences in the PK profile of study products administered as weight-based dosing in comparison to fixed dosing.
- Changes in the concentration of systemic and mucosal concentrations of CAP256V2LS and VRC07-523LS titres in breakthrough infections
- Proportion of participants reporting CAP256V2LS injections to be acceptable as per study questionnaire

4.0 STUDY DESIGN

This is a double blinded, randomized, placebo-controlled phase II trial.

4.1 Study population

Approximately 990 HIV negative women, aged 18 to 30 years, will enrol into the study at the CAPRISA eThekweni Clinical Research Site in Durban and the Vulindlela Clinical Research Site, Howick, KwaZulu-Natal, South Africa, as well as at the Matero Clinical Research Site, Lusaka, Zambia. Approximately 75% of participants will be enrolled in South Africa and up to 25% of participants will be enrolled in Zambia (CIDRZ), however this may be adjusted depending on rates of accrual per site.

If there is insufficient data to allow endpoint analysis (e.g. product administration is not completed or there are discontinuations from the study), then the PSRT and /or DSMB can recommend additional participants to be enrolled. In these cases, the regulatory authorities will be provided with documentation of the safety review process and the rationale for the request.

4.2 Enrollment plan

The study is divided into two parts: **Part A** and **Part B**.

In **Part A (N=90)**, participants will be randomised in a 2:1:2:1 ratio to receive the following: CAP256V2LS 20mg/kg and VRC07- 523LS 20mg/kg administered SC every 16 weeks (4 monthly) or placebo; CAP256V2LS and VRC07-523LS antibodies administered SC every 24 weeks (6 monthly) or placebo (**Table 2**) They will then be followed up and exit the study at Month 12.

In **Part B (N=900)**, participants will be randomised in a 1:1 ratio. Participants will receive an initial fixed dose of 1.2g of CAP256V2LS and 1.2g VRC07-523LS or placebo followed by 600mg of CAP256V2Ls and 1.2g of VRC07-523LS or placebo administered SC every 24 weeks (6 monthly) or placebo. Participants will be followed-up for approximately an average of 18 months with a maximum follow-up of 24 months. Once the last dose is received, participants will be followed up to the next 6 month point to exit the product part of the study and start the 6-month safety and PK follow-up off-product.

All inclusion and exclusion criteria must be met for eligibility to enrol. Enrolment will take place within 56 days of screening. The study accrual period is planned for approximately 10-12 months and eligible participants will receive between approximately 2 to 4 doses in Part B depending the length of time taken to accrue the full cohort.

Safety assessments will be conducted at baseline, following product administration, and at regular intervals as per the Schedule of Evaluations (SOE). PK assessments will be conducted retrospectively on stored samples for all HIV seroconvertors and a sub-set of participants at a minimum of two timepoints. HIV testing will be conducted as per the SOE.

Table 2: CAPRISA 012C dosing table

Part A

Group	Participants	Regimen*	N= 90	Dose (mg/kg)
1a	HIV negative	CAP256V2LS + VRC07-523LS	30	20 mg/kg SC + 20 mg/kg SC at 16-week (4 monthly) dosing intervals
1b	HIV negative	CAP256V2LS + VRC07-523LS	30	20 mg/kg SC + 20 mg/kg SC at 24-week (6 monthly) dosing intervals
1c	HIV negative	Placebo	30 (15 each)	Normal saline SC at 16 or 24-week (4 or 6 monthly) dosing intervals

*Study products will be administered as two separate injections with or without hyaluronidase.

Part B

Group	Participants	Regimen*	N=900	Dose (mg/kg)
1a	HIV negative	CAP256V2LS + VRC07-523LS	450	CAP256V2LS initial loading dose 1.2g SC + VRC07-523LS initial loading dose 1.2g SC, followed by CAP256V2LS 600mg and VRC07523LS 1.2gat 24-week (6 monthly) dosing intervals
1b	HIV negative	Placebo	450	Normal saline equivalent to initial loading doses and repeat doses

A placebo-controlled trial was carefully considered and assessed to be ethically justifiable because all participants will be provided with a comprehensive HIV prevention package consistent with all HIV prevention clinical trials. This will include risk reduction behavioural counselling, free condoms, STI treatment. Access to PrEP (daily TDF/FTC) will be made available at screening, enrolment and during follow-up. In addition, counselling and postexposure prophylaxis (PEP) will be provided when clinically indicated. 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 in SA including LA injectables or arv vaginal rings.

As the current technologies to prevent HIV are improving, designing clinical trials to evaluate the efficacy of new HIV prevention agents against active comparator groups are increasingly more challenging as they require huge sample sizes and/or longer trial duration. In light of this, and given that a secondary objective of the study is to measure efficacy, this study will also estimate the counterfactual background HIV incidence rate (i.e. HIV incidence rate for women of a similar background and risk) to infer a secondary estimate of efficacy. In this exploratory approach, a counterfactual background HIV incidence rate will be calculated and compared to the HIV incidence rate among those receiving CAP256V2LS and VRC07-523LS antibodies. Understanding the validity of the counterfactual placebo group in this trial will lay a foundation for this approach to be well understood and improved upon in preparation for Phase 3 studies. Methods such as recency assays, local

surveillance data, risk prediction methods, etc can be used to estimate the background or counterfactual HIV incidence (40). In this trial, a less biased and cost-effective method will be used. The methodology adopted will be one that minimises bias and costs and details will be provided in the statistical analyses plan.

4.3 Eligibility criteria

Inclusion criteria

- 18 to 30 years of age
- Persons born Female (assigned female sex at birth) and identifying as female.
- Able and willing to complete the informed consent process
- Able to understand the information provided including the potential impact and/or risks linked to SC administration of the study product, willing to comply with protocol procedures, has access to the clinical research site and is available for follow-up for the study duration
- Based on clinical assessment, participant must be in good general health as per opinion of the Principal Investigator (PI) or designee
- Haemoglobin > 10g/dl
- Creatinine $\leq 1.25 \times$ ULN
- ALT < 1.25 x ULN
- HIV negative
- Negative β -HCG (human chorionic gonadotropin) pregnancy test on day of enrolment
- If of reproductive potential, has evidence of effective contraceptive use and is willing to adhere to effective contraceptive use during the study period
- Sexually active in the last 3 months

Exclusion criteria

- 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
- If planning a pregnancy for the duration of the study, currently pregnant or breastfeeding
- A history of alcohol or substance use judged by the PI 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.
- Receipt of any vaccines within 28 days prior to enrolment
- Administration of a monoclonal antibody or polyclonal immunoglobulin within 6 months prior to enrolment
- Investigational HIV-related products received within 6 months prior to enrolment
- Any history of anaphylaxis and related symptoms such as hives, respiratory difficulty, or angioedema
- Evidence of autoimmune disease or currently receiving immunosuppressive therapy
- 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

5.0 CLINICAL PROCEDURES

Study staff will be trained to conduct study procedures in a standardised manner as specified in the study specific procedures (SSP) manual and standard operating procedures (SOPs) documents. Assessment of safety will include evaluation of medical history, physical assessments and laboratory results. The study schedules is provided in Appendix 1 and 2. The total blood volume drawn from each participant will comply with regulatory guidelines.

5.1 Recruitment

Recruitment will take place via a consultative process with the communities at each clinical research site. This will involve the community and local community-based organisations. The study teams will inform, educate and mobilise the community to enhance community input into the research process. The study teams will 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 aware of any concerns within the community about the research being conducted.

5.2 Screening visits

All screening evaluations and sample collections will take place as per the SOE. At screening, a comprehensive medical history will be collected. This will include but is not limited to previous medical history of note, history of anaphylaxis and pregnancy prevention practices. At subsequent visits, an interim medical history will be performed. At screening, a comprehensive physical examination will take place and include, but will not be limited to, an examination of head/ears/eyes/nose and throat, skin, respiratory, cardiovascular, abdominal, neurological, musculoskeletal and urogenital systems. At subsequent visits, a symptom-directed physical examination, which is a targeted examination based on the history given by the participant, previously reported AEs or concomitant medication as applicable, or current clinical observation, will take place. All screening laboratory tests will be reviewed by the trial clinician. If there are any isolated abnormalities, screening laboratory test(s) may be repeated at the discretion of the PI or designee. Additional assessments of health and/or laboratory tests may be conducted at visits based on clinical judgement.

5.3 Enrolment Visits

In this study, enrolment is defined as the receipt of the SC dose of study product. The participant will be assigned to a participant identification number (PID) at the screening visit and this PID will be used throughout the study. All study visit days will be assigned with a study visit number. All clinical procedures and sample collections will take place as per the SOE. Eligibility to enrol will be assessed at screening and enrolment and eligibility to qualify for study product administration will be assessed at subsequent injection visits. Day 0 will be defined as the day of study product administration.

5.4 Administration of study product/s

All study product/s administrations will be completed according to the assigned group. Study product/s administration will not proceed unless a negative pregnancy test has been obtained on the day of study product receipt. The study product will be administered SC as per SSP. The preferred SC administration site is the abdomen, but the arm or thigh may also be used. More than one injection site may be used if deemed necessary by the clinician.

5.5 HIV counselling and testing

HIV-test counselling will take place as per SOP. Study staff will perform counselling before collecting the blood for the HIV test, and after the HIV test results are available.

5.6 HIV risk reduction counselling

HIV risk reduction counselling will be conducted as per SOE. Participants will be counselled routinely during the trial on the avoidance of HIV infection. In addition, all study participants will be offered a comprehensive HIV prevention package, previously described, at screening, enrolment and during follow-up. As new data emerge and HIV prevention standards of care advance, the information provided during risk reduction counselling will be updated to conform to current best practices.

5.7 Care for participants identified as HIV-infected during the study

Potential study participants who volunteer to undergo HIV testing as part of the study screening process may discover that they are HIV-positive. Study staff will provide all HIV test results with post-test counselling. Potential study participants who have been identified as HIV-positive (and not enrolled) will be referred to local HIV treatment services, for provision of medical and psychosocial HIV care and support.

During the study follow up period, if a participant tests positive for HIV infection, then the participant will be contacted immediately, counselled, and will continue in the study for safety assessments as per the SSP, but will receive no further study products. HIV-positive South African participants will be offered enrollment into the CAPRISA 002 Acute Infection cohort study, which provides care, ART and

support for those infected with HIV. Participants who do not wish to join/continue in any of these studies post-seroconversion, will be referred to their preferred governmental HIV care provider for ongoing clinical management and care.

Based on the SOE HIV testing timepoints, there is a possibility that a participant who is newly infected, may receive repeat dose study products, prior to staff becoming aware of their HIV status. Pre-existing data suggests that this will not pose a safety risk. Pre-clinical studies of CAP256V2LS administered to SHIV-infected animals demonstrated protection against HIV acquisition (16). In addition, VRC07-523LS administered to HIV-infected participants resulted in reductions in HIV viral load with no clinical harm (41).

5.8 Family planning counselling

Study staff will counsel participants about the importance of preventing pregnancies and using an effective family planning method throughout study participation. All chosen pregnancy prevention methods and compliance will be documented. Participants may be referred for family planning services as necessary according to site specific SOPs.

5.9 Pregnancy

Although not considered an AE, if a female participant becomes pregnant during the study, it is the responsibility of the PI or designee to report the pregnancy to all relevant regulatory authorities as required. Study product will be discontinued as per SSP, and the participant will be followed for safety as per SSP until the end of pregnancy or study completion, whichever occurs last. Infants will be referred to a paediatrician for assessment and the results will be reported to all relevant parties. Complications of pregnancy that meet the SAE criteria will be reported as a SAE. All pregnancy outcomes will be captured on a Pregnancy Outcome case report form (CRF).

5.10 Follow-up visits

All follow up visits will take place as per the SOE. For all participants, reactogenicity assessments are performed before (baseline) and after each study product administration as per the SSP. A reactogenicity assessment will be conducted at the clinical site on Day 0, approximately 60 minutes post study product administration. In addition, all participants will be asked to keep a daily diary of local and systemic symptoms for 3 days after each product administration. All participants will be counselled on the expected reactogenicity events and on how to record these events. Participants will also be asked to record their temperature daily from Day 0 to Day 3.

A virtual visit will be conducted by study staff on Day 3 and Day 7 post study product administration or sooner if indicated. In this protocol, a virtual visit refers to any remote or web-based consult with a participant and includes but is not limited to telephonic communication, email communication, messaging, video calls or web applications. At these virtual visits, study staff will discuss reactogenicity events and/or adverse events with the participant and record the relevant information on either the appropriate CRF(s) or participant chart note as per SSP. Clinic staff will follow new or unresolved reactogenicity symptoms present at day 3 to resolution. In general, a participant who self-reports any event greater than moderate and/or requires medical intervention is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved.

All laboratory tests will take place as per the SOE. The total blood volume drawn from each participant will comply with regulatory guidelines. Additional assessments of health and/or laboratory tests may be conducted at follow up visits based on clinical judgement. Laboratory test(s) may be repeated at the discretion of the PI or designee.

5.11. Injection Site Photography

During the course of the study, based on the opinion of the clinical team, any local reactogenicity (injection site reactions included) events of interest may be photographed. Only participants who provide consent for photography will have photographs taken. If obtained, these photographs may be shared with the study's Protocol Safety Review Team (PSRT).

6.0 LABORATORY PROCEDURES

The study laboratory plan will include the procedures for specimen management (e.g. chain of custody, handling, labelling and transport), assay procedures, proficiency testing, quality assurance procedures and specimen storage procedures. Blood samples will be collected for safety and research purposes. For genital sample collection, specimens will be obtained using swabs, cytobrushes and the SoftCup device.

6.1 Laboratory specimens and tests

Clinical laboratory tests will be conducted as per SOE. Urine, blood and genital mucosal sampling specimens will be collected according to Good Clinical Practice standards and processed as per Good Laboratory Practice standards, as described in the SOPs for collection of specimens.

Note: Participants have the option of refusing the genital swab but still participating in the study.

6.2 On site testing

The study laboratory plan will detail the procedures to be followed for on-site testing as well as proficiency testing for all on-site testing.

6.3 Collection of specimens

All specimens (bloods, urine and genital) will be collected as per SOE, according to methods described in the SOPs for proper collection, processing, labelling, and transport to the laboratories conducting the assays.

6.4 Specimen storage for quality assurance and potential future research

Serum, plasma, PBMC and genital specimens will be stored for potential post-trial assessments as per SOE timepoints. For those participants who subsequently withdraw consent for long-term storage of their specimens, any residual specimens will be destroyed at the end of the study after all protocol-required and quality assurance testing has been completed.

6.5 Laboratory quality control and quality assurance procedures

The laboratories involved in the study will follow the quality assurance and quality control procedures outlined in the study laboratory plan.

7.0 PHARMACY PROCEDURES

7.1 Study Products

CAP256V2LS

The study product, CAP256V2LS (VRC-HIVMAB0102-00-AB) is a sterile aqueous buffered solution filled into 10 mL single-dose vials. Each vial contains 6.25 ± 0.1 mL at a concentration of 100 ± 10 mg/mL in formulation buffer. The formulation buffer is composed of 20 mM Sodium Phosphate, 100 mM Sodium Chloride, 75 mM L-Arginine HCl, 3% (w/w) Sucrose, and 0.01% (w/v) Polysorbate 80 at pH 7.0.

VRC07-523LS

VRC07-523LS is an aqueous buffered solution filled into 10 ml single-dose glass vials. Each vial contains a volume of 6.25 ± 0.1 ml or 2.25 ± 0.1 ml at a concentration of 100 ± 10 mg/ml in a formulation buffer. The buffer is composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose and 2.5% sorbitol, at a pH of 6.8. Vials contain a sterile solution which is a clear, colourless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. Vials are intended for single use only and thus do not contain a preservative.

Sodium Chloride

The placebo used in the study contains 0.9% Sodium Chloride (Normal Saline). In order to ensure

blinding of the study product and placebo prior to administration, an overlay will be used for both the placebo and study product syringes at the pharmacy.

7.2 Storage

Storage of each study product will be as per guidance from the latest version of the study products' Investigators brochure.

7.3 Preparation of study product

Preparation of the study product will take place aseptically and is detailed in the CAPRISA 012C Pharmacy SOPs and the latest version of the study products' Investigators brochure.

7.4 Study product accountability

Study pharmacist/s will be unblinded to product assignment in the trial. The study pharmacist/s are required to maintain complete accountability and storage condition records of all study products received from the manufacturer and subsequently dispensed to study participants. All study products will be stored at the site study pharmacy. The detailed procedures to be followed are provided in the CAPRISA 012C Pharmacy SOPs and the CAPRISA 012C SSP Manual.

7.5 Study product dispensing

The study pharmacist/s will be required to maintain the blind when study product is dispensed for administration. The detailed study product dispensing procedures to be followed are provided in the CAPRISA 012C Pharmacy SOPs and the CAPRISA 012C SSP Manual.

7.6 Study product returns

All study product dispensed for a study participant and returned as not administered, must be returned to the study pharmacists for quarantine and safe disposal. Reference will be made to the CAPRISA 012C SSP Manual for further details.

7.7 Study product destruction

Study product may be destroyed only after written authorisation is received from the product manufacturer and/or the PI. Destruction will occur in accordance with the institutional procedures and legislative requirements for safe destruction of pharmaceuticals. All study product destruction records will be housed in the study pharmacy and will be subject to study monitoring and auditing.

8.0 SAFETY AND ADVERSE EVENTS REPORTING

8.1 Adverse events

Definition

An AE is defined as any untoward medical occurrence in a clinical research participant which may or may not have a causal relationship with the study product or placebo. All new or worsening symptoms or conditions that occur following the start of study product administration will be considered AEs and will be recorded on the AE CRF.

Severity of AEs will be assessed using the DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.1, July 2017 as per SSP.

An AE does not include:

- Pre-existing diseases or conditions present or detected prior to start of study drug administration that do not worsen in grade.
- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions).

The PI or designee must determine the relationship of the AE to the product under investigation and document on the appropriate CRF (AE Form). For each AE, an assessment of the relatedness to the study drug will be made. If applicable, medically indicated and available diagnostic methods (e.g. laboratory, radiology, etc.) may be used to assess the nature and cause of the AE. Best clinical and scientific judgment should be used to assess relationship of AE to the study product and/or other cause. The following should be considered:

- presence/absence of a clear temporal sequence between administration of the study product and the onset of AE
- presence/absence of another cause, that could more likely explain the AE/SAE (concurrent disease, concomitant medication, environmental or toxic factors)
- whether or not the AE follows a known response pattern associated with the study product
- If the event resolves with withdrawal of study product

Attribution categories used (i.e. terms used for assessment of relationship of AE to study agent) for this study will be consistent with those described in the DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.1, July 2017 as follows:

- **Related** – There is a reasonable possibility that the AE may be related to the study product.
- **Not Related** – There is not a reasonable possibility that the AE is related to the study product.

All AEs will be captured regardless of the association or otherwise to the study product and reported on the AE CRF in accordance with study specific procedures.

8.2 Serious Adverse Events

Definition

An adverse event is reported as a 'Serious Adverse Event' if it meets any of the following criteria [as per International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines]:

- results in death
- is life threatening
- results in persistent or significant disability/incapacity
- requires in-participant hospitalization or prolongs existing hospitalization
- is a congenital anomaly/ birth defect
- any other important medical condition that requires medical or surgical intervention to prevent permanent impairment of a body function or structure. An elective surgery for a pre-existing condition that did not increase in severity or frequency is not considered an SAE.

8.3 Reporting adverse events of special interest (AESIs)

Potential immune-mediated diseases

Potential immune-mediated diseases are a subset of AEs that include both clearly autoimmune diseases and other inflammatory and/or neurologic disorders that may or may not have an autoimmune aetiology. These events are of special interest since they could potentially be caused by immune responses to the study product. The investigator/designee should report such AEs within the

same time limits and using the same CRF pages, as utilized for SAEs. The investigator or his/her designee will evaluate the occurrence of AESIs at every visit/contact during the study. AEs to be reported and documented as AESIs include:

- Neuroinflammatory disorders: optic neuritis, cranial nerve disorders (including Bell's palsy), multiple sclerosis, demyelinating disease, transverse myelitis, Guillain-Barré Syndrome, myasthenia gravis, encephalitis, neuritis.
- Musculoskeletal disorders: systemic lupus erythematosus, cutaneous lupus, Sjögren's syndrome, scleroderma, dermatomyositis, polymyositis, myopathy, rheumatoid arthritis and juvenile rheumatoid arthritis, polymyalgia rheumatica or temporal arteritis, reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, undifferentiated spondyloarthropathy.
- Gastrointestinal disorders: Crohn's disease, ulcerative colitis or proctitis, celiac disease.
- Metabolic diseases: autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, insulin-dependent diabetes mellitus, Addison's disease.
- Skin disorders: psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases.
- Others: autoimmune haemolytic anaemia, thrombocytopenia, antiphospholipid syndrome, *vasculitis, pernicious anaemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune myocarditis/cardiomyopathy, sarcoidosis, Stevens-Johnson syndrome, Behçet's syndrome.
- Injection/infusion site reactions: Grade 3 or 4 injection/infusion site reactions lasting more than 2 days.
- Vasculitis: Vasculitis, Diffuse vasculitis, leucocytoclastic vasculitis, polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, anti-neutrophil cytoplasmic antibody positive vasculitis, Henoch-schönlein purpura, allergic granulomatous angiitis (Churg- Strauss disease), Kawasaki disease, Takayasu's arteritis, temporal arteritis (giant cell arteritis), renal vasculitis.

Medical judgement should be exercised in deciding whether other disorders/diseases have an autoimmune origin and should also be reported as described above, and this judgement is the investigator's prerogative. Whenever sufficient data exist to substantiate any of the diagnoses in the above list, the event must be reported as an AESIs. While the intent of AESIs reporting is to be inclusive, isolated nonspecific symptoms, which might (or might not) represent the above diagnoses, should be captured as AEs but not reported as AESIs until the diagnosis can be defended.

8.4 Discontinuation of study product/s administration

Participants will be withdrawn from study product use for any of the reasons listed below. These participants will not receive any additional dose of study product but will continue safety follow-up as per SSP.

- Pregnancy
- Immediate hypersensitivity reaction associated with the study product
- Any grade 4 reactogenicity event that is assessed as related to the study product
- Any grade 3 or higher adverse event that is assessed as related to the study product
- An SAE that is subsequently considered to be related to study product
- Intercurrent illness that is not expected to resolve prior to the next scheduled study product administration, which is assessed by the PI (or designee) to require withdrawal from the product administration
- Repeated failure to comply with protocol requirements
- Co-enrolment into another study that in the opinion of the PI may interfere with the study objectives and participant safety
- The study PI decides to stop or cancel the study.
- The regulatory authorities halt the study.

8.5 Clinical management and Reporting of Adverse Events

Adverse events will be managed by the clinical study team, who will assess, provide first line of care as appropriate and refer to health care and treatment facilities as warranted. Participants will be followed until the AE resolves or stabilizes. If at study exit, an AE (including clinically significant laboratory abnormality) that is considered related to the study product is unresolved, follow-up will continue until resolution, if possible, and/or the participant will be referred for further management. All AEs will be reviewed regularly by the Protocol Safety Review Team (PSRT).

8.6 Safety monitoring

Safety monitoring includes internal monitoring by the study team, the protocol safety review team, data safety monitoring board and/or audits.

Internal monitoring

Safety reporting of SAEs, AEs and other important reportable events will be the responsibility of the entire study team. In addition, the study statistician will prepare routine study safety progress reports which include reports of AEs experienced by study participants (blinded to treatment assignment) for review by the PSRT. The PSRT will be responsible for decisions related to participant safety.

Protocol safety review team (PSRT)

A PSRT will be formed to monitor the clinical safety data. The membership, scope of responsibility, role and modus operandi of the PSRT will be defined in the SOP. The PSRT will review the clinical safety data on a regular basis via electronic distribution of reports and will have face-to face meetings as required. Events identified as questionable, inconsistent, or unexplained will be queried for verification. Any deaths of study participants or other SAEs will be reviewed, and a decision taken by the PSRT on whether pause rules have been met and whether a Data Safety Monitoring Board (DSMB) review is warranted. An *ad hoc* PSRT review meeting will occur if any of the members of the PSRT requests a special review to discuss a specific safety issue or as specified in the SOP.

Data safety monitoring board (DSMB)

In addition to monitoring performed by the PSRT, an independent DSMB will review the study data. Details for the operation and responsibilities of the DSMB will be defined in the DSMB Charter and SOP, which will delineate the composition, duties, responsibilities and procedures of the DSMB, data required at each meeting, as well as the analyses that will be conducted.

The DSMB will meet in-person and/or via teleconference at least twice a year. More frequent or *ad hoc* reviews of safety reports may be conducted by the DSMB as needed. The DSMB could recommend that the study should proceed as designed, should proceed with design modifications, or should be discontinued.

Monitoring

The PI will permit authorized representatives to inspect the site facilities and records relevant to the study. A detailed monitoring plan will be developed prior to the start of the study. The monitor will ensure that any compliance issues are addressed with the PI/designee and study team and will report to the relevant authorities as required.

9.0 STATISTICAL CONSIDERATIONS PART A

9.1 Accrual, sample size and follow-up

Based on the preliminary data from the phase 1 CAPRISA studies that evaluated CAP256V2LS and VRC07-523LS, we assume that 6% of participants in the intervention arm will experience at least one local or systemic grade 3 or higher reactogenicity events within the first 3 days after administration of CAP256V2LS and VRC07-523LS. There were no grade 3 or higher reactogenicity events reported in the participants who received placebo injections; however, these projects were not large enough to

be able to detect rare events. As this is preliminary data, we therefore assume that 1% to approximately 1.5% of participants receiving placebo will experience local or systemic grade 3 or higher reactogenicity events within the first 3 days after administration. A sample size of 984 will provide 90% power to detect a minimum 4-fold higher rate of an event on an assumption of 1.5% rate in the placebo receiving participants. These calculations were based on a Fisher's exact with a 2- sides type I error rate of 0.05. We assume a dropout rate of 5%. **Table 3** provides the sample size for different estimates.

Table 3: Number of participants to have 90% power to detect a safety event

Scenario	1	2	3	4	5	6	7
Event rate in the intervention arms	7.0%	7.0%	7.0%	6.0%	6.0%	6%	6.0%
Event rate in the control arm	0.5%	1.0%	2.0%	0.5%	1.0%	1.5%	2.0%
Sample size: combined intervention arms (1:1)	296	360	464	336	464	656	844
Sample size: control arm	148	180	232	168	232	328	422

However, based on the rationale provided in section 2.6.2, the trial design was amended and sample size of 984 was reduced to 90. The sample size justification for part B can be found in section 9.2.

PART B

9.2 Accrual, sample size and follow-up

Based on the preliminary data from the phase 1 CAPRISA studies that evaluated CAP256V2LS and VRC07-523LS, and the fact that a fixed dose of study product will be used in part B. The fixed dose is expected to be associated with fewer grade 3 or higher reactogenicity events than the weight-based dose. We assume that 4.8% of participants in the intervention arm compared to 1% in the control arm, will experience at least one local or systemic grade 3 or higher reactogenicity events within the first 3 days after administration of CAP256V2LS and VRC07-523LS.

A sample size of 900 will provide 90% power to detect a minimum 4.8-fold higher rate of an event. These calculations were based on a Fisher's exact with a 2- sides type I error rate of 0.05. Given a longer interval between study visits, we assume a dropout rate of 10% which has been incorporated into the total sample size. **Table 4** provides the sample size for different estimates.

Table 4: Number of participants to have 90% power to detect a safety event

Scenario	1	2	3	4
Event rate in the intervention arms	6.0%	6.0%	5.0%	4.8%
Event rate in the control arm	1.0%	1.5%	1.0%	1.0%
Sample size per arm	300	400	423	450
Total sample size	600	800	846	900

The goal of this study is to identify safety concerns associated with the product. The ability of the study to detect rare events is shown in **Table 5**. This was done by calculating the probability of detecting no events, at least one or at least two events at a specified true event rate. These probabilities highlight the likelihood of the study to detect either rare or common grade 3 or higher reactogenicity events or even serious adverse events. Also, the 95% confidence interval for the true event rate was calculated in **Table 6** using the score test method (42). For the 450 participants who will receive CAP256V2LS + VRC07-523LS, there is a 10% chance of observing no events if the true event rate is 0.5%, but there is a very low probability of detecting no events when the event rate is 2% or higher. The chance of observing at least one event is $\geq 90\%$ if the true event rate is 0.5% or more.

Table 5: Probability of observing no events, at least 1 event, or at least 2 events, for a range of hypothetical true event rates (N=450).

True event rate (%)	0 events	1+ events	2+ events
0.5	0.1	0.90	0.48
1	0.01	0.99	0.94
2	<0.001	>0.99	>0.99
4.8	<0.001	>0.99	>0.99
6	<0.001	>0.99	>0.99
10	<0.001	>0.99	>0.99

Table 5 shows the two-sided exact 95% confidence interval for the observed true event rate. If one or two of the 450 participants receiving CAP256V2LS and VRC07-523LS experiences a safety event, the upper bound of the two-sided 95% confidence interval will be 1.25% or 1.61%, respectively. If 20 or 40 participants experienced an event, these estimates of 4.4% and 8.9% will be compatible with plausible event rates from 2.90% to 6.76% and 6.60% to 11.88%, respectively.

Table 6: Two-sided 95% confidence intervals based on observing a particular rate of safety endpoints

Number of events/ sample size	95% confidence interval
0/450	0 – 0.85
1/450	0.04 – 1.25
2/450	0.12 - 1.61
10/450	1.21 – 4.04
20/450	2.90 – 6.76
40/450	6.60 – 11.88

Since this extended safety study is being undertaken in the populations where a phase III trial would be conducted, it is expected to generate a preliminary estimate of efficacy. The statistical power to demonstrate 67% efficacy is 82% if the background incidence rate in the phase II 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 study were 2.98, 4.5 and 6.1 per 100 women-years, respectively. The calculations in **Table 7** allows for a lower HIV incidence in Zambia. Power calculations were based on an exponential maximum likelihood test of equality of survival curves from nQuery (2021) (Statistical Solutions Ltd), Cork, Ireland.

Table 7: Power and HIV endpoints for varying effectiveness and background incidence rate

Statistical power for background HIV incidence rates when the sample size is 900; accrual of 9-12 months and maximum follow-up of 24 months				
Incidence	67% effectiveness		80% effectiveness	
	HIV events	Power	HIV events	Power
2	13	53%	9	67%
3	20	70%	13	84%
4	27	82%	18	93%

9.3 Randomisation and arm allocation

In part A, participants will be randomised in a 2:1:2:1 ratio to receive the following: CAP256V2LS and VRC07- 523LS antibodies administered SC every 16 weeks or placebo; CAP256V2LS and VRC07- 523LS antibodies administered SC every 24 weeks or placebo. Whereas in part B, participants will be randomised in a 1:1 ratio to receive a fixed dose of CAP256V2LS and VRC07- 523LS antibodies administered SC every 24 weeks (6 monthly) or placebo.

Participants and study staff (except for study pharmacists) will be blinded as to participant treatment and initially will also be blinded to treatment schedule (where applicable). The randomization list containing, unique sequential treatment codes, will be generated by an unblinded study statistician and will be used to assign individual study participants to one of the two study arms within a 4- and 6-monthly dosing schedule. The randomization list will be obtained by computer generated random numbers, where a randomly permuted block design, stratified by research site, will be used. The site study pharmacist at each research site is responsible for secure storage of this list. A separate blinded list consisting only of the blinded treatment code, in sequential order, will be provided to the study clinic. Alternatively, this blinded list will be provided through DFdiscover system.

All the unblinding decisions will be made by the principal investigator, where possible, after consultation with the DSMB or the PSRT.

9.4 Statistical analyses

9.4.1 Study populations

Modified intention to treat population (MITT)

This population includes all randomized participants. Those who will be identified as ineligible for enrolment based on pre-randomization criteria and also those who will be randomized but not enrolled (i.e., do not receive the first dose of the injection) and therefore do not contribute data post randomisation will be excluded.

Safety population

The safety population should in essence be the same as the MITT population because participants who do not receive the study product after randomisation are excluded.

9.4.2 Data analyses

Analyses for primary endpoint(s) and some of the secondary endpoints will be performed using SAS version 9.4 or above (Statistical Analysis Software, North Carolina, USA) and or R statistical software. MITT analyses will be used for the analyses of safety endpoints. Inferential statistical analyses will be performed with all participants receiving CAP256V2LS and VRC07-523LS antibodies irrespective of the dosing frequency (in Part A) grouped and compared to all the participants receiving placebo. Sensitivity analyses may be performed where the intervention arm will be compared to the placebo arm within each dosing frequency (in Part A).

All deviations to be made to the statistical considerations in this protocol will be documented in the detailed statistical analyses plan (SAP) together with a detailed analysis plan for secondary objectives.

Participant demographics

Demographic data of all participants enrolled in the study will be summarized using descriptive statistics. No inferential statistics will be performed to compare demographics and any other baseline variables by study arm.

Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and study arm. Each participant's reactogenicity sign or symptom will be counted once under the maximum severity for each injection. In the combined intervention and controls arms, the number and proportion of participants experiencing at least one grade 3 or higher local or systemic reactogenicity signs and symptoms across all injection visits will be compared using Fisher's exact test.

Adverse events and serious adverse events

Medical Dictionary for Regulatory Activities (MedDRA) will be used to summarise all AEs and SAEs events by system organ class (SOC) and preferred terms for each of the study arms. Moreover, the number and percentages of participants experiencing each specific AE within each of the SOC and preferred term will be tabulated by severity and relationship to study product. The timing of the adverse events with respect to the injection will be reported. For the calculations in these tables, each participant's adverse experience will be counted once under the maximum severity or strongest recorded causal relationship to study product. However, all grade 3 or higher adverse events deemed related to the study product will be summarised separately. A separate listing of all SAEs will be reported.

Local laboratory values

For each local laboratory measure, summary statistics will be presented by the treatment arm at each time point where is measured. In addition, the number and percentage of participants with local gradable laboratory values recorded will be tabulated by study arm for each post-vaccination time point. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above. For ease of reference, selected laboratory tests will be presented graphically and where appropriate, horizontal lines representing the laboratory reference for the upper and lower bound values will be plotted.

bnAbs concentrations in the genital tract

Boxplots and descriptive statistics will be used to summarize bnAbs concentrations over time. Depending on the distribution of bnAbs concentrations, we will build a longitudinal model (either use mixed effects models or generalised estimating equations) and adjust for variables that are potentially correlated with bnAbs concentrations.

HIV infections

This sub-section is mostly applicable to part B because the sample size of 90 in part A will not be adequate to produce an informative HIV efficacy analyses.

The MITT population will be used for this analysis. However, sensitivity analyses may be performed, limited to participants who received a certain number of doses or an analysis comparing each of the intervention arms to all placebo receiving participants, may be performed. The date of HIV infection diagnosis will be estimated as the midpoint between the last negative HIV test and the first confirmed positive HIV test date. Where a participant has a positive PCR and a negative or discordant rapid results on the same date, the date of infection is calculated as 14 days prior to this date. Alternatively, the single random-point method will be used in instances where we have missed visits(43). Participants who do not become HIV positive before 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 randomization date. The hazard ratio comparing CAP256V2LS + VRC07-523.LS vs placebo and a 95% confidence interval will be estimated using the univariable Cox proportional hazards model. Product efficacy calculated as 1 minus the hazard ratio and a 95% confidence interval will be presented. Secondly, Cox proportional hazards regression models will be used to estimate the hazard rate ratio and product efficacy along with a 95% confidence interval, 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 utilised. Furthermore, a sensitivity analyses 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 antibodies.

Acceptability of the SC injections among participants

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.

10.0 PHARMACOKINETIC ANALYSES

Blood samples for PK evaluations will be collected as per SOE. PK disposition of CAP256V2LS and VRC07-523LS will be evaluated in this study and described in the SAP. PK assessments will be conducted retrospectively on stored samples for all HIV seroconvertors and a sub-set of participants at a minimum of two timepoints. PK profiles between the different groups will be analysed as per SAP. 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; C_{max} and T_{max} taken directly from the data, area under the curve (AUC) the trapezoidal method up to the last concentration and terminal half-life from regression of the log-linear, terminal portion of the concentration versus time profile. A population PK analysis will be performed using a two-compartment model and the computer program NONMEM, version 7.3 or later.

11.0 DATA MANAGEMENT

All data management activities will be undertaken under the applicable regulatory frameworks. This includes the U.S Food and Drug Administration (FDA) regulations, European Medicines Agency (EMA) regulations and the regulatory agencies in South Africa and Zambia. All studies will also abide by the local Ethics Committee (EC) regulations. The Data management systems in CAPRISA and CIDRZ meet FDA requirements as they are CFR Part 11 compliant. The Data Management standard processes are aligned with the Good Clinical Data Management Processes (GCDMP). Data collection for this study at each site will involve one of two methods or a hybrid method where both systems can be used simultaneously based on each site's capabilities or preferences:

Paper based method

Data will be collected on case report forms (CRFs) which will be developed by the study team. All site study staff will be trained on the correct completion of CRFs. If data entered on the CRFs are taken from an external source (e.g., laboratory reports, participant records), the source documents will be maintained in the participant's medical chart or study file at the site and will be available for review. The CRFs will be scanned into the database management system which is DFdiscover 2018 Version 5.1. DFdiscover has optical character recognition (OCR) which reads the check boxes and numerical fields on the CRFs and stores them in the study database. Any fields not recognized by the OCR system will be entered manually by the data encoders. Data encoders will verify all data by cross-checking the scanned version to what is entered into the database.

Queries arising during validation of the data will be recorded in quality control (QC) reports and sent to the sites on a regular basis. Any queries resulting in a change to the database will be documented on the original CRF and re-scanned. The data management centre staff will perform periodic quality control and validation checks on the data. Database files will be password-protected and access to the files will be limited to authorised study staff members only.

Electronic Data Capture (EDC)

DFdiscover (5.1.4, DF/Net, Seattle, USA) will be used for electronic data capturing.

DFdiscover is a validated clinical database management system which is FDA CFR Part 11 compliant. Electronic Case Report Form (eCRF) data will reside on the DFdiscover server housed at CAPRISA Doris Duke Medical Research Institute and is backed up at regular intervals by CAPRISA and securely stored at CAPRISA Doris Duke Medical Research Institute and the other at the eThekwini research clinic.

The electronic-CRF design will be guided by the study protocol with final approval by the study team and the PI. All study staff will be allocated user roles, specific to their function required for data entry. Database access will be restricted by passwords and permission levels. The study staff and statistician can access the database in “read-only” mode once data has been entered. The CAPRISA data management team will have write-access. In the event of internet downtime, power outages, or any situation that makes the DFdiscover system inaccessible, one-ply paper CRFs will be used to collect the data, which will be scanned through to the CAPRISA data centre once the internet is active again.

General data management

All study CRFs and related documents will be stored securely both during and after study completion. During the study, the original completed forms for each participant will be kept on-site at the respective sites. The forms will be stored in a secured, double-locked, fire-resistant and waterproof bulk storage filer. Upon completion of the study, and finalization of the database for analysis, the original forms will be bound and kept off-site (separate site) for long-term storage. CRF data on the DFdiscover server, housed by CAPRISA at Doris Duke Medical Research Institute and backed up at CAPRISA’s eThekwini research site, will be accessible to the study staff and the statistician in a view-only mode. The data management team will have write-access, with access being restricted by passwords and permission levels. Study staff that has access to the data on the computer will be trained on how to access the system and the importance of system security.

All queries and/or reasons for data changes will be generated electronically and will form part of the weekly QC Report that will be distributed to the appropriate study team members. Study staff also have the option of addressing any query at any time. Queries arising during validation of the data will be recorded in quality control (QC) reports sent to the sites on a regular basis. QC rates will be communicated to the site monthly. Monthly data downloads will be sent to the study statistician. These data downloads will also be made available on request. Study staff who have access to the data on their computer systems will be trained on how to use the system and the importance of system security. Support will always be available from the data manager and IT department at CAPRISA, if any issues arise.

For staff who need to access DFdiscover remotely (external organisations that are part of the study), the client software will be installed remotely by the data management team. The same security settings as CAPRISA site will apply to all external sites accessing DFdiscover. All CRFs and source documents are to be securely stored in the participant study file in a secure double-locked, fire resistant unit with restricted access in accordance with GCP requirements. Upon completion of the study, the close-out site monitoring visit and finalization of the database for analysis, any original forms will be bound and kept for long term storage. Study documentation and CRFs will not be destroyed without written permission from the sponsor.

11.1 Data Sharing

All study team scientists will disseminate the trial results as broadly as possible. The study data will be published consistent with normal scientific practices. Research data that document, support, and validate research findings will be made available after the main findings from the final research dataset have been accepted for publication. Such research data will be modified to prevent the disclosure of personal identifiers to remain in compliance with the Protection of Human Subjects. The research team will attend conferences periodically and present trial results to a multidisciplinary 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 UKZN publication repository. After sharing the results with study participants, they will be presented to communities from which participants are recruited, following Good Participatory Practice 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. A detailed communication plan will be developed specifically for this study. This communication plan will be in place to address the six major types of stakeholders for HIV prevention trials. These include the clinical research enterprise, individual users, community members, advocates and policy makers, and program implementers.

12.0 HUMAN SUBJECT PROTECTION AND ETHICAL OBLIGATIONS

12.1 Regulatory and Ethical Approval

The study will be conducted in accordance with all conditions of approval by the relevant regulatory authorities and ethics committee. In South Africa, this study will be conducted under the oversight of SAHPRA in accordance with ICH GCP guidelines. CAPRISA will be responsible for reporting study-related information to SAHPRA. The study will also be conducted under the oversight of the UKZN's BREC. In Zambia, the study will be conducted under the oversight of Zambia Medicines Regulatory Authority (ZAMRA) in accordance with ICH GCP guidelines. CIDRZ will be responsible for reporting study-related information to ZAMRA. The study will also be conducted under the oversight of the Zambia Biomedical Ethics Review Committee (UNZABREC)

12.2 Informed consent

Written informed consent will be obtained from each study participant in the language of their choice prior to screening and enrolment, in accordance with ICH GCP guidelines. Participants will be provided with copies of the informed consent forms if they are willing to receive them. A comprehension assessment will also be completed as per the SOE.

12.3 Risks and Benefits

Risks associated with the use of monoclonal antibodies

Administration of mAbs may have a risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies. However, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of murine mAbs that would have a risk of human anti-mouse antibodies (33). In this regard, because the mAbs are targeted to a viral antigen and are human mAbs, they are expected to have a low risk of such side effects.

Typically, the side effects of mAbs are mild but may include fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhoea, tachycardia or chest pain. These side effects typically occur within the first 24 hours and are generally due to the body's natural response to the receipt of the antibody. The receipt of antibodies may also cause redistribution of immune and blood cells. This may not have any clinical effect but will be observed as a transient blood laboratory abnormality (33, 34). Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infection however this is not expected to be a risk for a mAb targeted to a viral antigen (44).

Human mAbs directed against the cell surface targets on lymphocytes may be associated with cytokine release, causing a reaction known as “cytokine release syndrome” (CRS). Most infusion-related events occur within the first 24 hours after beginning administration (45). Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension and hypoxia, are infrequent and more often associated with mAbs targeted to human proteins or with non-human mAb, such as a murine mAb (46). CRS reactions most commonly occur within the first few hours after beginning the infusion and with the first mAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb treatment. With licensed therapeutic mAbs used intravenously, CRS is managed by temporarily stopping the infusion, administering histamine blockers and restarting the infusion at a slower rate. Delayed allergic reactions to a mAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. Symptoms may not appear until several days after the exposure to the mAb. This type of reaction is noted to be more common with chimeric types of mAb.

Risks of blood drawing

Blood drawing may cause pain and bruising and, infrequently, may cause a feeling of light-headedness or fainting. Rarely, it may cause infection at the site where blood is taken. Problems from blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the injection site and rarely, infection, vein irritation (called phlebitis), or blood clot.

Risks associated with genital sample collection

Collection of samples by swabs, cytobrushes and/or SoftCup could entail slight discomfort.

Benefits

There are no direct benefits to participants from study participation. Others may benefit from knowledge gained in this study that may aid in the development of HIV prevention or therapeutic methods. Participants will receive HIV/STI risk reduction counselling, HIV and STI testing, physical examination, and routine laboratory testing. Participants will be provided STI treatment in accordance with WHO guidelines free of charge. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community.

Compensation

Pending regulatory approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms. The study site will determine appropriate compensation with their overseeing regulatory boards.

Subject confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent permitted by law. Study-related information will be stored securely at the study research clinic. All participant information will be stored in lockable file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only, to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study data, as identified by PID number only, will not be released without their written permission, except as necessary for review and monitoring by authorized regulatory and study representatives.

Study discontinuation

This study may be discontinued at any time if approval for the study is withdrawn by regulatory authorities and ethics committees. In addition, the DSMB may recommend that the Protocol Team discontinue the study for safety reasons at any time.

References

1. UNAIDS. WHO, HIV/AIDS Fact sheet: 2020 statistics. 2020; [https://www.who.int/news-room/fact-sheets/detail/hiv-aids].
2. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. *Journal of the International AIDS Society*. 2015;18:19408.
3. De Oliveira T, Kharsany AB, Gräf T, Cawood C, Khanyile D, Grobler A, et al. Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study. *The Lancet HIV*. 2017;4(1):e41-e50.
4. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *New England Journal of Medicine*. 2016;375(9):830-9.
5. Elion R, Coleman M. The PrEP revolution: from clinical trials to routine practice: Implementation “view from the US. *Current Opinion in HIV and AIDS*. 2016;11(1):67.
6. Fauci AS, Marston HD. Ending the HIV–AIDS pandemic—follow the science. *New England Journal of Medicine*. 2015;373(23):2197-9.
7. Landovitz RJ, Kofron R, McCauley M. The promise and pitfalls of long acting injectable agents for HIV prevention. *Current Opinion in HIV and AIDS*. 2016;11(1):122.
8. Fernandez C, van Halsema CL. Evaluating cabotegravir/rilpivirine long-acting, injectable in the treatment of HIV infection: emerging data and therapeutic potential. *HIV/AIDS (Auckland, NZ)*. 2019;11:179.
9. Clement ME, Kofron R, Landovitz RJ. Long-acting injectable cabotegravir for the prevention of HIV infection. *Current Opinion in HIV and AIDS*. 2020;15(1):19-26.
10. Nel A, van Niekerk N, Kapiga S, Bekker L-G, Gama C, Gill K, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *New England Journal of Medicine*. 2016;375(22):2133-43.
11. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *New England Journal of Medicine*. 2016;375(22):2121-32.
12. Network HPT. HPTN 084: A phase 3 double blind safety and efficacy study of long-acting injectable cabotegravir compared to daily oral TDF/FTC for pre-exposure prophylaxis in HIV-uninfected women [Internet]. 2017 March 2 (cited 2017 May 5).
13. Landovitz RJ, Li S, Eron Jr JJ, Grinsztejn B, Dawood H, Liu AY, et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. *The Lancet HIV*. 2020.
14. Barouch DH, Whitney JB, Moldt B, Klein F, Oliveira TY, Liu J, et al. Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. *Nature*. 2013;503(7475):224-8.
15. Hessel AJ, Poignard P, Hunter M, Hangartner L, Tehrani DM, Bleeker WK, et al. Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. *Nature medicine*. 2009;15(8):951.
16. Julg B, Tartaglia LJ, Keele BF, Wagh K, Pegu A, Sok D, et al. Broadly neutralizing antibodies targeting the HIV-1 envelope V2 apex confer protection against a clade C SHIV challenge. *Science translational medicine*. 2017;9(406):eaal1321.
17. Rudicell RS, Do Kwon Y, Ko S-Y, Pegu A, Louder MK, Georgiev IS, et al. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. *Journal of virology*. 2014;88(21):12669-82.
18. Wagh K, Bhattacharya T, Williamson C, Robles A, Bayne M, Garrity J, et al. Optimal combinations of broadly neutralizing antibodies for prevention and treatment of HIV-1 clade C infection. *PLoS pathogens*. 2016;12(3):e1005520.
19. Mahomed S, Garrett N, Baxter C, Abdool Karim Q, Abdool Karim SS. Clinical trials of broadly neutralizing monoclonal antibodies for HIV Prevention: A Review. *The Journal of Infectious Diseases*. 2020.
20. Pegu A, Hessel AJ, Mascola JR, Haigwood NL. Use of broadly neutralizing antibodies for HIV-1 prevention. *Immunological reviews*. 2017;275(1):296-312.
21. Reeves DB, Huang Y, Duke ER, Mayer BT, Cardozo-Ojeda EF, Boshier FA, et al. Mathematical

- modeling to reveal breakthrough mechanisms in the HIV Antibody Mediated Prevention (AMP) trials. *PLoS computational biology*. 2020;16(2):e1007626.
22. van Loggerenberg F, Mlisana K, Williamson C, Auld SC, Morris L, Gray CM, et al. Establishing a cohort at high risk of HIV infection in South Africa: challenges and experiences of the CAPRISA 002 acute infection study. *PloS one*. 2008;3(4):e1954.
 23. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, et al. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. *Nature*. 2014;509(7498):55.
 24. Doria-Rose NA, Bhiman JN, Roark RS, Schramm CA, Gorman J, Chuang G-Y, et al. New member of the V1V2-directed CAP256-VRC26 lineage that shows increased breadth and exceptional potency. *Journal of virology*. 2016;90(1):76-91.
 25. Bhiman JN, Anthony C, Doria-Rose NA, Karimanzira O, Schramm CA, Khoza T, et al. Viral variants that initiate and drive maturation of V1V2-directed HIV-1 broadly neutralizing antibodies. *Nature medicine*. 2015;21(11):1332.
 26. Ivleva VB, Schneck NA, Gollapudi D, Arnold F, Cooper JW, Lei QP. Investigation of sequence clipping and structural heterogeneity of an HIV broadly neutralizing antibody by a comprehensive LC-MS analysis. *Journal of The American Society for Mass Spectrometry*. 2018;29(7):1512-23.
 27. Mahomed S, Garrett N, Karim QA, Zuma NY, Capparelli E, Baxter C, et al. Assessing the safety and pharmacokinetics of the anti-HIV monoclonal antibody CAP256V2LS alone and in combination with VRC07-523LS and PGT121 in South African women: study protocol for the first-in-human CAPRISA 012B phase I clinical trial. *BMJ open*. 2020;10(11):e042247.
 28. Mahomed S, Garrett N, Capparelli E, Baxter C, Zuma NY, Gengiah T, et al. 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. *BMJ open*. 2019;9(7):e030283.
 29. Hall WC, Price-Schiavi SA, Wicks J, Rojko JL. Tissue Cross-Reactivity Studies for Monoclonal Antibodies: Predictive Value and Use for Selection of Relevant Animal Species for Toxicity Testing. *Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing*. 2010:1-34.
 30. Leach MW, Halpern WG, Johnson CW, Rojko JL, MacLachlan TK, Chan CM, et al. Use of tissue cross-reactivity studies in the development of antibody-based biopharmaceuticals: history, experience, methodology, and future directions. *Toxicologic pathology*. 2010;38(7):1138-66.
 31. Armbruster C, Stiegler GM, Vcelar BA, Jäger W, Köller U, Jilch R, et al. Passive immunization with the anti-HIV-1 human monoclonal antibody (hMAb) 4E10 and the hMAb combination 4E10/2F5/2G12. *Journal of Antimicrobial Chemotherapy*. 2004;54(5):915-20.
 32. Joos B, Trkola A, Kuster H, Aceto L, Fischer M, Stiegler G, et al. Long-term multiple-dose pharmacokinetics of human monoclonal antibodies (MAbs) against human immunodeficiency virus type 1 envelope gp120 (MAb 2G12) and gp41 (MAbs 4E10 and 2F5). *Antimicrobial Agents and Chemotherapy*. 2006;50(5):1773-9.
 33. Dettmar K, Seitz-Merwald I, Lindemann C, Schroeder P, Seimetz D, Atz J. Transient lymphocyte decrease due to adhesion and migration following catumaxomab (anti-EpCAM x anti-CD3) treatment in vivo. *Clinical and Translational Oncology*. 2012;14(5):376-81.
 34. Buysmann S, Bemelman FJ, Schellekens P, van Kooyk Y, Figdor CG, Ten Berge I. Activation and increased expression of adhesion molecules on peripheral blood lymphocytes is a mechanism for the immediate lymphocytopenia after administration of OKT3. 1996.
 35. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nature reviews Drug discovery*. 2010;9(4):325.
 36. Brinkman IH, Laar MAvd, Jansen TL, van Roon EN. The potential risk of infections during (prolonged) rituximab therapy in rheumatoid arthritis. *Expert opinion on drug safety*. 2011;10(5):715-26.
 37. Schulz H, Bohlius JF, Trelle S, Skoetz N, Reiser M, Kober T, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. *Journal of the National Cancer Institute*. 2007;99(9):706-14.
 38. Soler D, Chapman T, Yang L-L, Wyant T, Egan R, Fedyk ER. The binding specificity and selective antagonism of vedolizumab, an anti- $\alpha 4\beta 7$ integrin therapeutic antibody in development for

inflammatory bowel diseases. *Journal of Pharmacology and Experimental Therapeutics*. 2009;330(3):864-75.

39. Gaudinski MR, Houser KV, Doria-Rose NA, Chen GL, Rothwell RSS, Berkowitz N, et al. Safety and pharmacokinetics of broadly neutralising human monoclonal antibody VRC07-523LS in healthy adults: a phase 1 dose-escalation clinical trial. *The Lancet HIV*. 2019;6(10):e667-e79.
40. Glidden DV. Statistical approaches to accelerate the development of long-acting antiretrovirals for HIV pre-exposure prophylaxis. *Current Opinion in HIV and AIDS*. 2020;15(1):56.
41. Chen G, Coates E, Fichtenbaum C, Koletar S, Landovitz R, Presti R, et al., editors. Safety and virologic effect of the HIV-1 broadly neutralizing antibodies, VRC01LS or VRC07-523LS, administered to HIV-infected adults in a phase 1 clinical trial. *Journal of the International Aids Society*; 2019: JOHN WILEY & SONS LTD THE ATRIUM, SOUTHERN GATE, CHICHESTER PO19 8SQ, W
42. Agresti A, Coull BA. Approximate is better than “exact” for interval estimation of binomial proportions. *The American Statistician*. 1998;52(2):119-26.
43. Vandormael A, Dobra A, Bärnighausen T, de Oliveira T, Tanser F. Incidence rate estimation, periodic testing and the limitations of the mid-point imputation approach. *International Journal of Epidemiology*. 2018;47(1):236-45.
44. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nature reviews Drug discovery*. 2010;9(4):325-38.
45. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. *Expert review of clinical immunology*. 2009;5(5):499-521.
46. Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clinical journal of oncology nursing*. 2010;14(2):E10.

Appendix 1. Part A: Group 1a/1c Schedule of Evaluations (4 monthly)

Product Administration Phase												Study Exit	
Study Month	SCR	M0			M2	M4			M6	M8		M10	M12
Study Week		W0				W16				W32			
Virtual Visit (1)			VV1	VV2			VV3	VV4			VV5	VV6	
Study Day (post study product/placebo)		D0	D3	D7		D0	D3	D7		D0	D3	D7	
Study Product/ Placebo administration		X				X				X			
Administrative, Behavioural and Regulatory Procedures													
Informed consent for study participation	X												
Comprehension assessment	X	X											
PID assignment	X												
Eligibility assessment (2)	X	X				X				X			
Locator information	X	X			X	X			X	X		X	X
Demographic information	X												
Randomisation		X											
Behavioural Assessment	X	X			X	X			X	X		X	X
Risk Reduction counselling	X	X			X	X			X	X		X	X
HIV-test Counselling (3)	X	X			X	X			X	X		X	X
Contraceptive counselling and provision (4)	X	X			X	X			X	X		X	X
Product acceptability assessment		X				X				X			
Clinical Procedures													
Comprehensive Medical History	X												
Interim Medical History		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Physical Exam	X												
Targeted Physical Exam		X			X	X			X	X		X	X
Weight	X	X			X	X			X	X		X	X
Height	X												
Vital Signs	X	X			X	X			X	X		X	X
Reactogenicity Assessment (5)		X	X	X		X	X	X		X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests (6)													
Full Blood Count, differential	X	X				X				X			
ALT, creatinine	X	X				X				X			
Pregnancy test (7)	X	X			X	X			X	X		X	X
HIV testing (8)	X	X			X	X			X	X		X	X
Storage (6)													
Plasma Storage	X	X				X				X			X
Serum Storage	X	X				X				X			X
Pharmacokinetics sampling (9)	X	X			X	X			X	X		X	X
Genital mucosal sampling (10)		X				X							
PBMCs		X											X

1. Refers to any remote consult with a participant as described in the protocol and SSP.

2. Eligibility to enrol into the study will be assessed before the first study product administration and eligibility to receive study product will be assessed thereafter

3. Includes pre-test counseling and post-test counseling as indicated. A subsequent follow-up contact may be conducted to provide post-test counseling and to report results to participant.

4. Conducted when clinically indicated

5. Reactogenicity assessments performed at approximately 60 minutes post study product administration and via virtual visit three days post study product administration as per protocol. If required, this information will be updated on Day 7 virtual visit.

6. Total blood volume collection will not exceed 500 ml within 6 weeks

7. May include urine or serum pregnancy test as clinically indicated

8. HIV testing will be conducted as per an HIV testing algorithm described in the SSP

9. PK assessments will be conducted retrospectively on stored samples for all HIV seroconvertors and a sub-set of participants at a minimum of two timepoints

10. Genital mucosal sampling will include cytobrushes, genital swab/s and/or Softcup.

Appendix 2. Part A: Group 1b/1c Schedule of Evaluations (6 monthly)

Product Administration Phase										
Study Month	SCR	M0			M3	M6			M9	Study Exit
Study Week		W0				W24				M12
Virtual Visit (1)			VV1	VV2			VV3	VV4		
Study Day (post study product/placebo)		D0	D3	D7		D0	D3	D7		
Study Product/ Placebo administration		X				X				
Administrative, Behavioural and Regulatory Procedures										
Informed consent for study participation	X									
Comprehension assessment	X	X								
PID assignment	X									
Eligibility assessment (2)	X	X				X				
Locator information	X	X			X	X			X	X
Demographic information	X									
Randomisation		X								
Behavioural Assessment	X	X			X	X			X	X
Risk Reduction counselling	X	X			X	X			X	X
HIV-test Counselling (3)	X	X			X	X			X	X
Contraceptive counselling and provision (4)	X	X			X	X			X	X
Product acceptability assessment		X				X				
Clinical Procedures										
Comprehensive Medical History	X									
Interim Medical History		X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Comprehensive Physical Exam	X									
Targeted Physical Exam		X			X	X			X	X
Weight	X	X			X	X			X	X
Height	X									
Vital Signs	X	X			X	X			X	X
Reactogenicity Assessment (5)		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests (6)										
Full Blood Count, differential	X	X				X				
ALT, creatinine	X	X				X				
Pregnancy test (7)	X	X			X	X			X	X
HIV testing (8)	X	X			X	X			X	X
Storage (6)										
Plasma Storage	X	X				X				X
Serum Storage	X	X				X				X
Pharmacokinetics sampling (9)	X	X			X	X			X	X
Genital mucosal sampling (10)		X				X				X
PBMCs		X								X

1. Refers to any remote consult with a participant as described in the protocol and SSP.
2. Eligibility to enrol into the study will be assessed before the first study product administration and eligibility to receive study product will be assessed thereafter
3. Includes pre-test counseling and post-test counseling as indicated. A subsequent follow-up contact may be conducted to provide post-test counseling and to report results to participant.
4. Conducted when clinically indicated
5. Reactogenicity assessments performed at approximately 60 minutes post study product administration and via virtual visit three days post study product administration as per protocol. If required this information will be updated on the DAY 7 virtual visit.
6. Total blood volume collection will not exceed 500 mls within 6 weeks
7. May include urine or serum pregnancy test as clinically indicated
8. HIV testing will be conducted as per an HIV testing algorithm described in the SSP
9. PK assessments will be conducted retrospectively on stored samples for all HIV seroconvertors and a sub-set of participants at a minimum of two timepoints
10. Genital mucosal sampling will include cytobrushes, genital swab/s and/or Softcup.

Appendix 3. Part B: Schedule of Evaluations (6 monthly)

Product Administration Phase																			Study Exit #
Study Month	SCR	M0		M3	M6		M9	M12		M15	M18		M21	M24	M27	M30			
Study Week		W0			W24			W48			W72								
Virtual Visit (1)			VV1	VV2		VV3	VV4		VV5	VV6		VV7	VV8						
Study Day (post study product/placebo)		D0	D3	D7		D0	D3	D7		D0	D3	D7							
Study Product/ Placebo administration		X			X			X		X									
Initiative, Behavioural and Regulatory Procedures																			
Informed consent for study participation	X																		
Comprehension assessment	X	X																	
PID assignment	X																		
Eligibility assessment (2)	X	X			X			X		X									
Locator information	X	X			X	X		X	X		X	X		X	X	X			
Demographic information	X																		
Randomisation		X																	
Behavioural Assessment	X	X			X	X		X	X		X	X		X	X	X			
Risk Reduction counselling	X	X			X	X		X	X		X	X		X	X	X			
HIV-test Counselling (3)	X	X			X	X		X	X		X	X		X	X	X			
Contraceptive counselling and provision (4)	X	X			X	X		X	X		X	X		X	X	X			
Product acceptability assessment		X			X			X			X								
Clinical Procedures																			
Comprehensive Medical History	X																		
Interim Medical History		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Comprehensive Physical Exam	X																		
Targeted Physical Exam		X			X	X		X	X		X	X		X	X	X			
Weight	X	X			X	X		X	X		X	X		X	X	X			
Height	X																		
Vital Signs	X	X			X	X		X	X		X	X		X	X	X			
Reactogenicity Assessment (5)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Clinical Laboratory Tests (6)																			
Full Blood Count, differential	X	X			X			X			X								
ALT, creatinine	X	X			X			X			X								
Pregnancy test (7)	X	X			X	X		X	X		X	X		X	X	X			
HIV testing (8)	X	X			X	X		X	X		X	X		X	X	X			
Storage (6)																			
Plasma Storage	X	X			X			X			X								
Serum Storage	X	X			X			X			X								
Pharmacokinetics sampling (9)	X	X			X	X		X	X		X	X		X	X	X			
Genital mucosal sampling (10)		X			X			X			X								
PBMCs		X														X			

- 1.Refers to any remote consult with a participant as described in the protocol and SSP.
- 2.Eligibility to enrol into the study will be assessed before the first study product administration and eligibility to receive study product will be assessed thereafter
- 3.Includes pre-test counseling and post-test counseling as indicated. A subsequent follow-up contact may be conducted to provide post-test counseling and to report results to participant.
4. Conducted when clinically indicated
- 5.Reactogenicity assessments performed at approximately 60 minutes post study product administration and via virtual visit three days post study product administration as per protocol. If required this information will be updated on the DAY 7 virtual visit.
- 6.Total blood volume collection will not exceed 500 mls within 6 weeks
- 7.May include urine or serum pregnancy test as clinically indicated
- 8.HIV testing will be conducted as per an HIV testing algorithm described in the SSP
- 9.PK assessments will be conducted retrospectively on stored samples for all HIV seroconvertors and a sub-set of participants at a minimum of two timepoints
- 10.Genital mucosal sampling will include ~~eyebushes~~, genital swab/s and/or Softcup.

#Once the last dose is received, participants will be followed up to the next 6 month point to exit the product part of the study and start the 6-month safety and PK follow-up off-product