Safety and pharmacokinetics of escalating doses of neutralising monoclonal antibody CAP256V2LS administered with and without VRC07-523LS in HIV-negative women in South Africa (CAPRISA 012B): a phase 1, dose-escalation, randomised controlled trial

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Summary

Background Young women in sub-Saharan Africa continue to bear a high burden of HIV infection. Combination anti-HIV monoclonal antibodies are a potential HIV prevention technology that could overcome adherence challenges of daily oral pre-exposure prophylaxis. In this phase 1 clinical trial we aimed to determine the safety and pharmacokinetic profile of the broadly neutralising monoclonal antibody CAP256V2LS.

Methods CAPRISA 012B, a first-in-human dose-escalation phase 1 trial evaluated the safety, pharmacokinetics, and neutralisation activity of CAP256V2LS alone and in combination with VRC07-523LS in young HIV-negative women in Durban, South Africa. Groups 1 and 2 were open label with CAP256V2LS administered at 5 mg/kg and 10 mg/kg intravenously and 5 mg/kg, 10 mg/kg, and 20 mg/kg subcutaneously. In group 3, participants were randomly allocated to receive a combination of CAP256V2LS and VRC07-523LS at 10 mg/kg and 20 mg/kg subcutaneously comixed with ENHANZE, a recombinant human hyaluronidase. Once safety was established in the first three participants, dose escalation took place sequentially following review of safety data. Primary endpoints were the proportion of participants with mild, moderate, and severe reactogenicity or adverse events, graded as per the Division of AIDS toxicity grading. The trial is registered on the Pan African Clinical Trial Registry, PACTR202003767867253, and is recruiting.

Findings From July 13, 2020, to Jan 13, 2021, 42 HIV-negative women, aged 18–45 years, were enrolled. All 42 participants, eight with intravenous and 34 with subcutaneous administration, completed the trial. There were no serious adverse events or dose-limiting toxicities. Most commonly reported symptoms following intravenous administration were headaches in seven (88%) and nausea in four (50%) participants. Commonly reported symptoms following subcutaneous administration were headache in 31 (91%), chills in 25 (74%), and malaise or fatigue in 19 (56%) participants. Adverse events included transient lymphocytopenia in eight (19%), proteinuria in nine (21%), elevated aspartate aminotransferase in ten (24%), and alanine aminotransferase in five (12%) participants.

Interpretation CAP256V2LS administered alone and in combination with VRC07-523LS was safe with favourable pharmacokinetics and neutralisation activity, supporting further assessment in larger clinical studies.

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Introduction

In 2020 there were an estimated 1·5 million new HIV infections worldwide;[1] three times higher than the 2020 target of 500 000. Sub-Saharan Africa accounts for 70% of global infections and young women contribute to a disproportionate burden of new infections. In KwaZulu-Natal, South Africa, the HIV prevalence has been reported as high as 50% when women reach the age of 25 years.[2] Safe and effective HIV prevention technologies are needed, particularly for young women in Africa.

Currently, daily oral tenofovir in combination with emtricitabine for oral pre-exposure prophylaxis (PrEP) is available in most African countries, but adherence poses a major barrier to uptake. New classes of long-acting antiretroviral drugs such as a bimonthly integrase inhibitor cabotegravir and the monthly dapivirine-containing vaginal ring have been approved by some regulatory authorities for HIV prevention but are not yet licensed or available in South Africa.[3] Passive immunisation using broadly neutralising

Research in context

Evidence before this study

At least 17 different broadly neutralising monoclonal antibodies (bNAbs), administered either alone or in combination have been evaluated for both HIV-1 treatment and prevention indications in clinical trials. We searched PubMed on June 23, 2022, without any language restriction, using the search string "HIV" AND "monoclonal antibody" AND "clinical trial". Only publications from clinical trials evaluating bNAbs targeting the HIV-1 envelope in adults were included. Review articles, antiretroviral or vaccine-related research, and research involving samples from HIV-1 chronically infected individuals, were excluded. We retrieved 19 clinical trial publications. Of these, three publications evaluated first generation bNAbs, including 2G12, 2F5, and 4E10. These earlier bNAbs were found to be safe, but displayed short elimination half-lives, ranging from 3 to 22 days. Furthermore, they did not have sufficient potency and neutralisation breadth, resulting in limited anti-viral activity. Remaining publications evaluated more recently developed bNAbs with increased breadth and potency including: VRC01, VRC01LS, 3BNC117,10-1074, VRC07-523LS, PGT121, and PGDM1400. Published data indicate that these bNAbs are safe and well tolerated, with a half-life ranging from 15 to 71 days. They also showed enhanced potency requiring less frequent administrations to maintain serum concentrations at acceptable target levels.

In antiretroviral therapy (ART)-naive individuals infected with HIV, bNAbs resulted in the reduction of plasma viraemia and delayed viral rebound in individuals during analytical antiretroviral treatment interruption. Results from the first report of a triple antibody combination evaluating PGDM1400, PGT121, and VRC07-523LS, showed safety and tolerability. However, in individuals infected with HIV, viral rebound occurred in the presence of PGDM1400 and PGT121 selected resistance mutations.

Only intravenous VRC01 has advanced to an efficacy trial. The antibody mediated prevention trials showed that VRC01 provided 75% prevention efficacy against antibody-susceptible HIV strains. This proof-of-concept trial highlighted that combinations of potent bNAbs that are complementary for breadth and neutralisation activity are required to overcome HIV viral diversity.

Added value of this study

CAPRISA 012B was a first-in-human phase 1 trial of a bNAb that emanated from Africa being tested in Africa, where young women are at highest risk of HIV acquisition. The trial evaluated two promising bNAbs, CAP256V2LS, which is highly potent, and VRC07-523LS, which has broad coverage, administered subcutaneously alone and in combination to young HIV-negative women in South Africa. In this trial both these bNAbs were administered at higher subcutaneous doses than previously tested, facilitated using a recombinant human hyaluronidase, ENHANZE Drug Product (EDP). EDP temporarily breaks down the subcutaneous tissue, allowing for administration of larger volumes of product. This is the first time that EDP has been used to facilitate the subcutaneous administration of therapeutics in the field of HIV. Data from this trial can be used to advance bNAbs as a promising HIV prevention option.

Implications of all available evidence

In this trial, subcutaneously administered CAP256V2LS and VRC07-523LS at doses of 10 mg/kg or higher achieved concentrations above 1 µg/mL and 10 µg/mL respectively, that were consistently maintained over 168 days. Furthermore, neutralisation data showed that both bNAbs retained their functional activity post-infusion and were not prone to degradation in vivo.

Subcutaneous administration of potent and broad bNAbs that allow administration schedules every 4–6 months could provide an alternative to ART-based prevention technologies and add to the existing HIV prevention modalities. Data from this trial together with other trials evaluating combinations of bNAbs are pivotal in the planning and undertaking of larger phase 2b and phase 3 studies.

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monoclonal antibodies (bNAbs) are also being evaluated in clinical trials.[4]

While the phase 2b Antibody Mediated Prevention trial did not show efficacy of VRC01 in HIV prevention, it provided initial evidence that bNAbs can prevent HIV infection in the subgroup of viruses that were sensitive to the administered antibody.[5,6] Intravenous VRC01 was 75% effective at preventing acquisition of HIV strains with an in-vitro sensitivity inhibitory concentration 80% (IC_{80}) of less than 1 µg/mL. These results highlighted the need for more potent bNAbs to be administered in combination to address HIV diversity and viral resistance.[7]

In 2004, the Centre for the AIDS Programme of Research (CAPRISA) established the CAPRISA 002 Acute Infection Study in KwaZulu-Natal to advance the understanding of HIV clade C pathogenesis and the clinical, virological, and immunological presentation of clade C infection.[8] This ongoing observational study initially followed HIV-negative women at high risk of acquiring HIV until HIV seroconversion and then monitored HIV-positive women until antiretroviral therapy (ART) initiation and on ART.[8] In 2013, bNAbs targeting the V2 region of the HIV-1 envelope glycoprotein were isolated from one of the participants in that cohort.[9] One particular bNAb referred to as CAP256-VRC26.25 was found to be highly potent against circulating strains of HIV-1.[10,11] Preclinical animal studies showed that CAP256-VRC26.25LS was 100% protective against a simian HIV (SHIV) challenge, even at the lowest dose of

0·08 mg/kg at serum antibody concentrations of less than 0·75 µg/mL.[12] In addition to the neutralising activity, CAP256-VRC26.25LS mediated antibody-dependent cellular cytotoxicity, phagocytosis, and trogocytosis indicating that it could act on virus infected cells.[13] Furthermore, CAP256-VRC26.25 neutralised 70% of non-clade B viruses, particularly clade C, the dominant clade circulating in sub-Saharan Africa.[10,14]

To increase the half-life of CAP256-VRC26.25, site-directed mutagenesis was performed to increase antibody binding affinity for the neonatal Fc receptor, resulting in increased recirculation of functional IgG. CAP256-VRC26.25 was subsequently modified to increase half-life and to prevent proteolytic clipping of the heavy chain via a single amino acid change made in the CDRH3 region to improve manufacturability, while preserving its neutralisation breadth and potency. This non-clipping variant of the antibody is referred to as CAP256V2LS.[15]

The neutralisation profile of CAP256-VRC26.25LS showed complementarity for coadministration with the VRC07-523 bNAb.[16] VRC07-523 targets the CD4 binding site of the HIV-1 Env protein and is a variant of VRC07, which is a clonal relative of the VRC01 bNAb, engineered to improve half-life, potency, and breadth. VRC07-523LS, modified for a longer half-life, was previously evaluated in clinical trials and showed safety with favourable pharmacokinetic profiles.[17,18]

The route of administration of bNAbs is influenced by potency and resultant volume of study product that needs to be administered. ENHANZE drug delivery technology uses a proprietary recombinant human hyaluronidase referred to as rHuPH20 (Halozyme, San Diego, CA, USA) to facilitate the subcutaneous delivery of coadministered therapies. ENHANZE drug product (EDP) works by transiently and locally degrading hyaluronan, enabling larger volumes of product to be administered in the subcutaneous space.[19]

CAPRISA 012B, a first-in-human dose-escalation phase 1 trial, evaluated CAP256V2LS alone and in combination with VRC07-523LS, and at higher doses administered subcutaneously with EDP to young HIV-negative women in South Africa.

Methods

Study design and participants

This phase 1 trial was conducted at the CAPRISA eThekwini Clinical Research Site in Durban, South Africa. The protocol was reviewed and approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee and the South African Health Products Regulatory Authority and is available online (appendix p 2).

For more on this **protocol** see https://www.caprisa.org/Pages/EDCTP-funded%20studies

See **Online** for appendix

Volunteers were recruited from Durban and surrounding areas within KwaZulu-Natal using Biomedical Research Ethics Committee-approved study materials. Consenting participants who met the trial eligibility criteria were enrolled. Participants who met the trial eligibility criteria and who gave written consent were enrolled. Inclusion criteria were: 18–45-year-old HIV uninfected women in good general health, on effective contraception and willing to adhere to safer sex practices. Exclusion criteria were pregnancy, breastfeeding, weight greater than 95 kg, history of alcohol or substance use, previous receipt of investigational HIV vaccine, monoclonal antibody, or polyclonal immunoglobulin products, or history of anaphylaxis, autoimmune disease, or current use of immunosuppressive therapy.

Following successful eligibility assessments, participants were enrolled into one of three groups (figure 1). Groups 1 and 2 were open-label, while group 3 was double-blinded and placebo-controlled. Participants in group 1a received CAP256V2LS at 5 mg/kg intravenously, followed by participants in group 1b who received CAP256V2LS at 10 mg/kg intravenously. Participants in group 2a received CAP256V2LS at 5 mg/kg subcutaneously. Participants in group 2b through to 2f received CAP256V2LS at an escalating dose of either 5 mg/kg, 10 mg/kg, or 20 mg/kg subcutaneously, with EDP. Participants in groups 2d and 2f received a repeat dose at either 16 or 24 weeks. Groups 3a and 3b each enrolled five participants at an active: placebo ratio of 4 to 1, who received both CAP256V2LS and VRC07-523LS at 10 mg/kg and 20 mg/kg subcutaneously, together with EDP.

Once safety was established in the first three participants, dose escalation and enrolment into the remaining study arms took place sequentially following review of safety data at timepoints specified by the protocol safety review team. A safety pause rule was initiated if one or more participant experienced a related serious adverse event, or two or more participants experienced the same grade 3 or higher related adverse events.

Randomisation and masking

An unblinded statistician was responsible for generating the randomisation sequences where required, using SAS software (version 9.4). Participants were allocated unique study participant identification numbers. The study team used sequentially numbered, opaque, sealed envelopes consisting of the group, envelope number, and treatment code. Once eligibility was confirmed, before enrolment the envelope was opened by the study pharmacist. The treatment code was used by the unblinded pharmacist only, who was responsible for secure storage of envelopes. A randomisation list compiled by the unblinded statistician consisting of a unique three-digit number, together with the study group and corresponding study drug or placebo and dosage was also provided to the unblinded pharmacist.

Procedures

The study pharmacist prepared all product doses for administration. For intravenous administration, the calculated volume of the weight-based dose of study product was added to 100 mL of 0·9% sodium chloride.

Participants assigned to an intravenous administration group received study product with a volumetric pump over 60 min. If assigned to a subcutaneous administration group without EDP, product was administered subcutaneously via a standard needle at a maximum volume of 2 mL per injection site. Up to four administration sites were used and injections were at least 5 cm apart. For the subcutaneous groups that used EDP, product was administered into the abdomen at a single site via an infusion pump at a rate of 1 mL per minute. For the antibody combination groups, CAP256V2LS and VRC07-523LS were individually mixed with EDP in the clinic pharmacy and each antibody was provided as a single individual dose. Each antibody was administered sequentially at different sites of the abdomen to allow distinction of local reactogenicity.

Following product administration, participants were observed for 60 min for reactogenicity; and then assessed daily at the clinic for 3 days. Further safety assessments were conducted at weeks 1, 2, and 4 and then monthly until 24 weeks after product administration. To provide additional safety monitoring, blood tests for safety were done 1 day after product administration. All adverse events were recorded until study exit and graded using the Medical Dictionary for Regulatory Activities system as per the Division of AIDS table for grading the severity of adult and paediatric adverse events. Regular safety reviews were conducted by the protocol safety review team and the data and safety monitoring board. Plasma, serum, and peripheral blood mononuclear cells samples were collected at predetermined timepoints for endpoint analysis. All safety laboratory results were reviewed by a clinician before study product administration. HIV testing was conducted using an algorithm and HIV immunoassays were also evaluated for cross-reactivity.

To evaluate the acceptability of the study product, a questionnaire was administered to participants at every injection visit and at the study exit visit.

The neutralising activity of antibodies present in participant sera was measured in the TZM-bl neutralising antibody assay using two Env-pseudotyped viruses CE2103 and Q769.d22, with known sensitivity to CAP256V2LS and VRC07-523LS, respectively. Env-pseudotyped viruses were generated by transfection of 293T/17 cells with Env-expressing plasmid and backbone vector (pSG3DEnv). A tier two virus that is sensitive to VRC07-523LS but not CAP256V2LS (Q769.d22; subtype A) and another sensitive to CAP256V2LS but not VRC07-523LS (CE2103; subtype C) were assayed for neutralisation titres of each antibody in the serum. A murine leukaemia pseudovirus was included in the assays as a negative control. Results were displayed as the serum dilution that produced 50% neutralisation (inhibitory dilution [50%], ID_{50}) of viruses tested.

A quantitative electrochemiluminescence sandwich immunoassay technique was performed on the Meso Scale Discovery platform to individually determine CAP256V2LS and VRC07-523LS concentrations in plasma samples (appendix p 2). The amount of CAP256V2LS and VRC07-523LS sandwiched by the anti-idiotypic and anti-human IgG antibodies was directly proportional to the concentration of reactive CAP256V2LS and VRC07-523LS in each sample. Sample concentrations were interpolated from standard curves using Excel and GraphPad Prism Software 9.2.0 (GraphPad Software, La Jolla, CA, USA). A population pharmacokinetic analysis was performed using a two-compartment model and the computer program NONMEM (version 7.5, ICON Clinical Research, Blue Bell, PA, USA).

A three-tiered approach was used to detect antidrug antibody. Tier one and tier two assays were based on the Meso Scale Discovery electrochemiluminescence homogeneous bridging assay used to individually detect the presence of ADA against CAP256V2LS and VRC07-523LS. A tier three confirmatory HIV neutralisation assay was performed using a pseudovirus with an ART resistant backbone to functionally characterise the ADA in any sample that was tier two positive (appendix p 3).

Outcomes

The primary outcome was the safety and tolerability of CAP256V2LS administered alone and in combination with VRC07-523LS, assessed as the proportion of participants with mild, moderate, and severe reactogenicity or adverse events, as per the Division of AIDS table for grading the severity of adult and paediatric adverse events (version 2.1, July 2017). The secondary outcomes measured the pharmacokinetics of CAP256V2LS and VRC07-523LS up to 24 weeks after the last administered dose.

Statistical analysis

Safety analyses were presented as frequencies and percentages. Continuous variables were described with medians as well as upper and lower quartiles. Each participant's reactogenicity event was counted once under the maximum severity and summarised by study group. The number and percentages of participants experiencing each specific adverse event was summarised by severity and relationship to study product. Each participant's adverse event was counted once under the maximum severity or strongest recorded causal relationship to study product. The acceptability of the subcutaneous injections was measured on a scale of 0–6 with 0–2 considered unacceptable, 3 uncertain, and 4–6 acceptable.

The trial was registered on the Pan African Clinical Trial Registry, PACTR202003767867253, and is recruiting.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

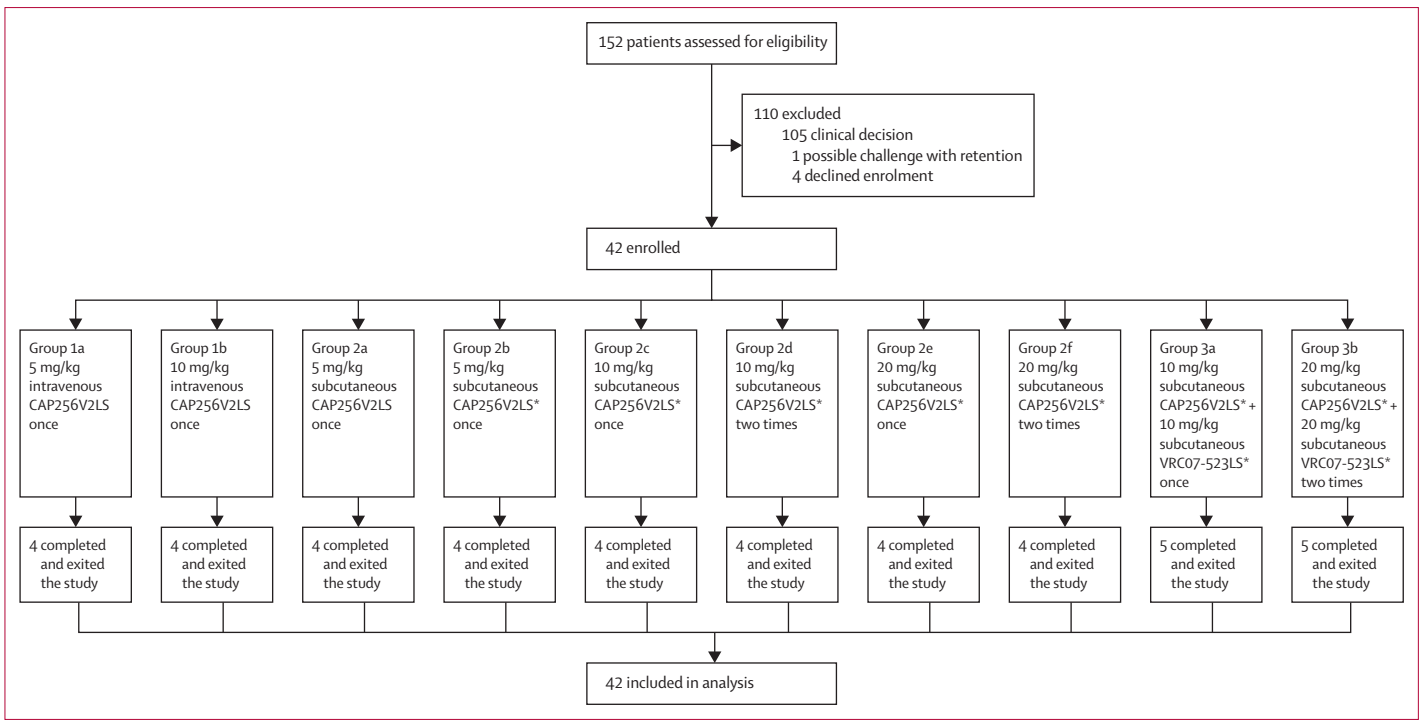

Figure 1: **CAPRISA 012B dosing table**
Groups 1 and 2 were open-label, group 3 was double-blinded and placebo-controlled. 24 participants in groups 1a–2c and 2e were enrolled to receive one dose of CAP256V2LS with or without EDP; eight participants in groups 2d and 2f were enrolled to receive two doses of CAP256V2LS (second repeat dose at either week 16 or week 24), and ten participants in group 3a and 3b were enrolled to receive CAP256V2LS plus VRC07-523LS with EDP once (n=4) or twice (second repeat dose at week 24; n=4) or placebo (control group, n=2). EDP=ENHANZE drug product. bNAb=broadly neutralising monoclonal antibody. *bNAb administered with EDP. †Four participants allocated to treatment and one participant allocated to placebo.

Results

Between July 13, 2020, and Jan 13, 2021, a total of 42 healthy women with a median age of 24 years were enrolled into the study (figure 1). 40 participants received active product and two received placebo. All 42 participants successfully completed the study. The last participant's follow-up visit occurred on Sept 29, 2021. Baseline characteristics of enrolled participants are shown in table 1.

Eight participants received study product intravenously and 34 participants received study product subcutaneously. There were no serious adverse events or dose-limiting toxicities.

Solicited reactogenicity events ranged from mild to severe and all resolved within the reactogenicity assessment period of 72 h (table 2). Commonly reported symptoms following intravenous administration were headaches in seven (88%) of eight participants and nausea in four (50%) of eight participants. Commonly reported symptoms following subcutaneous administration in the 34 participants were headache in 31 (91%), chills in 25 (74%), and malaise or fatigue in 19 (56%).

A total of 137 unsolicited adverse events were reported by 38 (90%) of 42 participants. 50 of these events were considered related to study product and reported by 21 (50%) participants. Common related events included a transient decline in lymphocyte counts (lymphocytopenia), proteinuria, and a raised aspartate aminotransferase.

Eight lymphocytopenia events occurred in eight (19%) of 42 participants on day 1 and resolved between days 3 and 7. Of these, two were mild (lymphocyte count 600–650 cells per µL), two moderate (500–599 cells per µL), two severe (350–499 cells per µL), and two were graded as potentially life threatening (<350 cells per µL). The two grade 3-related lymphocytopenia events were observed in one participant who received CAP256V2LS at 5 mg/kg subcutaneously without EDP and one participant who received CAP256V2LS at 20 mg/kg subcutaneously with EDP. The two grade 4-related lymphocytopenia events were both observed in participants who received a combination of CAP256V2LS at 10 mg/kg and VRC07-523LS at 10 mg/kg with EDP. These lymphocytopenia events occurred across all study groups and therefore were not associated with the route of administration, dosage, or EDP use.

The lymphocytopenia on day 1 was accompanied by transient non-gradable neutrophilia (as per Division of AIDS toxicity grading) and decreased eosinophils and monocytes that resolved by day 3. One participant with severe lymphocytopenia had a grade 1 transient thrombocytopenia on day 3 that resolved the same day. There were no other haematological abnormalities. The lymphocytopenia cases prompted a protocol specified safety review by the data and safety monitoring board.

A review was also conducted by six independent haematologists with consensus that these cases were transient and not clinically significant.

There were ten proteinuria events in nine (21%) of 42 participants, of which seven were mild and three were moderate. There were ten events of increased aspartate aminotransferase in ten (24%) of 42 participants, all of which were mild. There were seven events of increased alanine aminotransferase in five (12%) of 42 participants, of which six were mild and one was moderate. One participant, who had received placebo, seroconverted to HIV while on the study. No ADA was detected.

All 42 participants found intravenous and subcutaneous administration acceptable. All stated that, if effective, they were likely to recommend the injection to others and 40 (95%) of 42 participants indicated that they would be happy to disclose the receipt of the injection to their partners. 38 (90%) of 42 participants found the injection schedule of two to three injections per year acceptable.

The pharmacokinetic analysis included eight participants who received intravenous and 32 participants who received subcutaneous study product (table 2). Initial concentrations following intravenous administration were higher but declined rapidly and were slightly below subcutaneous concentrations at later timepoints suggesting high bioavailability following the subcutaneous route (figure 2A–D). CAP256V2LS concentrations were below 10 µg/mL in the 10 mg/kg and 20 mg/kg groups and remained at or above 1 µg/mL at 24 weeks. VRC07-523LS sera antibody concentrations remained above 10 µg/mL in the 10 mg/kg and 20 mg/kg combination groups at 24 weeks (figure 2A).

Median CAP256V2LS concentrations following 5 mg/kg and 10 mg/kg intravenous infusions were 1·54 µg/mL (IQR 1·19–2·51) and 3·95 µg/mL (IQR 1·68–4·61) at 16 weeks and 0·40 µg/mL (IQR 0·40–1·28) and 2·02 µg/mL (IQR 1·16–2·81) at 24 weeks. Median concentrations following 5 mg/kg subcutaneous administration without EDP were 2·30 µg/mL (IQR 1·59–2·91) at 16 weeks and 0·80 µg/mL (IQR 0·40–1·79) at 24 weeks. Concentrations following subcutaneous administration with EDP were relatively linear across doses with concentrations increasing with higher doses (figure 2B). The median observed CAP256V2LS concentrations following 5 mg/kg, 10 mg/kg, and 20 mg/kg subcutaneous doses with EDP were 2·62 µg/mL (IQR 1·88–2·73), 7·34 µg/mL (IQR 5·48–7·89), and 13·35 µg/mL (IQR 11·24–15·25) at 16 weeks and 1·80 µg/mL (IQR 1·38–2·15), 2·28 µg/mL (IQR 2·1–3·42), and 4·07 µg/mL (IQR 3·05–5·76) at 24 weeks. Concurrent administration of VRC07-523LS raised the concentration of CAP256V2LS, with a modest effect confounded by high variability and potential dose effect (figure 2C). CAP256V2LS had median concentrations of 4·07 µg/mL (IQR 3·05–5·76) when administered alone and 5·99 µg/mL (IQR 3·73–8·05) when administered in

	Group 1a (n=4)	Group 1b (n=4)	Group 2a (n=4)	Group2b (n=4)	Group 2c (n=4)	Group 2d (16 weeks; n=2)	Group 2d (24 weeks; n=2)	Group 2e (n=4)	Group 2f* (16 weeks; n=2)	Group 2f (24 weeks; n=2)	Group 3a (n=4)	Group 3b (n=4)	Control (n=2)
Age, years	26·5 (23·5–35·0)	24·0 (22·5–24·5)	26·0 (23·5–28·5)	23·0 (21·0–26·0)	21·0 (20·0–28·0)	25·0 (21·0–29·0)	24·0 (19·0–29·0)	25·5 (21·5–26·0)	23·5 (22·0–25·0)	21·0 (20·0–22·0)	23·0 (21·0–25·5)	26·0 (24·0–34·0)	24·0 (20·0–28·0)
Weight, kg	58·1 (55·1–59·7)	76·9 (72·2–80·1)	73·5 (66·0–79·5)	69·2 (57·6–76·6)	70·7 (49·4–89·6)	55·9 (49·2–62·5)	55·4 (53·4–57·3)	52·6 (47·2–66·0)	71·2 (52·9–89·5)	57·1 (52·1–62·0)	56·8 (54·4–65·9)	64·5 (54·8–81·9)	76·2 (68·9–83·5)
Highest education level													
Primary school	..	1 (25%)	..	..	1 (25%)	..	..	..	..	..	..	..	..
Secondary school	4	2 (50%)	4	3 (75%)	3 (75%)	2	2	2 (50%)	2	2	3 (75%)	2 (50%)	2
Tertiary school	..	1 (25%)	..	1 (25%)	..	..	..	2 (50%)	..	..	1 (25%)	2 (50%)	..

Data are median (IQR) or n (%). *All participants were women, Black, and unemployed.

Table 1: **Baseline characteristics of participants***

	Intravenous		Subcutaneous								Control (n=2)
	CAP 256V2LS (5 mg/kg one dose; n=4)	CAP 256V2LS (10 mg/kg one dose; n=4)	CAP 256V2LS (5 mg/kg one dose; n=4)	CAP 256V2LS* (5 mg/kg one dose; n=4)	CAP 256V2LS* (10 mg/kg)		CAP256V2LS* (20 mg/kg)		CAP256V2LS + VRC07-523LS (10 mg/kg + 10 mg/kg; n=4)	CAP256V2LS + VRC07-523LS (20 mg/kg + 20 mg/kg; n=4)	
					Dose 1 (n=8)	Dose 2 (n=4)†	Dose 1 (n=8)	Dose 2 (n=4)†			
Systemic reactions											
Arthralgia											
None	4 (100%)	3 (75%)	3 (75%)	3 (75%)	6 (75%)	3	3	1	3 (75%)	3 (75%)	1 (50%)
Mild	0	0	1 (25%)	1 (25%)	1 (13%)	1	3	1	1 (25%)	0	0
Moderate	0	1 (25%)	0	0	1 (13%)	0	2	2	0	1 (25%)	1 (50%)
Severe	0	0	0	0	0	0	0	0	0	0	0
Chills											
None	2 (50%)	3 (75%)	0	1 (25%)	3	0	3	3	1 (25%)	1 (25%)	1 (50%)
Mild	1 (25%)	0	4 (100%)	2	3	4 (100%)	1	0	3	3 (75%)	0
Moderate	0	1 (25%)	0	1 (25%)	1 (13%)	0	4	1	0	0	1 (50%)
Severe	1 (25%)	0	0	0	1 (13%)	0	0	0	0	0	0
Headache											
None	0	1 (25%)	1 (25%)	0	2	0	0	2	0	0	1 (50%)
Mild	4	3 (75%)	3 (75%)	3 (75%)	4	4	4	0	3 (75%)	4 (100%)	0
Moderate	0	0	0	1 (25%)	1 (13%)	0	4	2	1 (25%)	0	1 (50%)
Severe	0	0	0	0	1 (13%)	0	0	0	0	0	0
Increased body temperature											
None	3 (75%)	2 (50%)	2 (50%)	3 (75%)	6 (75%)	3	8 (100%)	4	3 (75%)	3 (75%)	2 (100%)
Mild	0	1 (25%)	2 (50%)	0	0	1 (25%)	0	0	0	0	0
Moderate	1 (25%)	1 (25%)	0	1 (25%)	2 (25%)	0	0	0	1 (25%)	1 (25%)	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Malaise/fatigue											
None	4 (100%)	3 (75%)	2 (50%)	3 (75%)	5 (63%)	3 (75%)	2 (25%)	1 (25%)	2	1	1 (50%)
Mild	0	1 (25%)	2 (50%)	0	1 (13%)	1 (25%)	2 (25%)	1 (25%)	1 (25%)	3 (75%)	0
Moderate	0	0	0	1 (25%)	1 (13%)	0	4 (50%)	2 (50%)	1 (25%)	0	1 (50%)
Severe	0	0	0	0	1 (13%)	0	0	0	0	0	0
Myalgia											
None	4 (100%)	4 (100%)	3 (75%)	4 (100%)	6 (75%)	3 (75%)	6 (75%)	1 (25%)	4 (100%)	1 (25%)	1 (50%)
Mild	0	0	1 (25%)	0	1 (13%)	1 (25%)	0	1 (25%)	0	3 (75%)	1 (50%)
Moderate	0	0	0	0	1 (13%)	0	2 (25%)	2 (50%)	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Nausea											
None	2 (50%)	2 (50%)	3 (75%)	4 (100%)	6 (75%)	3 (75%)	5 (63%)	3 (75%)	1 (25%)	2 (50%)	2 (100%)
Mild	1 (25%)	2 (50%)	1 (25%)	0	2 (25%)	1 (25%)	0	0	3 (75%)	2 (50%)	0
Moderate	1 (25%)	0	0	0	0	0	3 (38%)	1 (25%)	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0

(Table 2 continues on next page)

	Intravenous		Subcutaneous								Control (n=2)
	CAP 256V2LS (5 mg/kg one dose; n=4)	CAP 256V2LS (10 mg/kg one dose; n=4)	CAP 256V2LS (5 mg/kg one dose; n=4)	CAP 256V2LS* (5 mg/kg one dose; n=4)	CAP 256V2LS* (10 mg/kg)		CAP256V2LS* (20 mg/kg)		CAP256V2LS + VRC07-523LS (10 mg/kg + 10 mg/kg; n=4)	CAP256V2LS + VRC07-523LS (20 mg/kg + 20 mg/kg; n=4)	
					Dose 1 (n=8)	Dose 2 (n=4)†	Dose 1 (n=8)	Dose 2 (n=4)†			
(Continued from previous page)											
Vomiting											
None	3 (75%)	3 (75%)	4 (100%)	4 (100%)	7 (88%)	4 (100%)	6 (75%)	3 (75%)	3 (75%)	4 (100%)	2 (100%)
Mild	0	1 (25%)	0	0	1 (13%)	0	1 (13%)	1 (25%)	1 (25%)	0	0
Moderate	1 (25%)	0	0	0	0	0	1 (13%)	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Local reactions											
Erythema or redness (CAP256V2LS)											
None	4 (100%)	4 (100%)	4 (100%)	4 (100%)	8 (100%)	3 (75%)	8 (100%)	4 (100%)	3 (75%)	4 (100%)	2 (100%)
Mild	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	1 (25%)	0	0	1 (25%)	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Erythema or redness (VRC07-523LS)											
None	4 (100%)	4 (100%)	4 (100%)	4 (100%)	8 (100%)	4 (100%)	8 (100%)	4 (100%)	3 (75%)	4 (100%)	2 (100%)
Mild	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	1 (25%)	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Induration or swelling (CAP256V2LS)											
None	4 (100%)	4 (100%)	4 (100%)	4 (100%)	8 (100%)	3 (75%)	8 (100%)	3 (75%)	2 (50%)	3 (75%)	2 (100%)
Mild	0	0	0	0	0	0	0	0	1 (25%)	0	0
Moderate	0	0	0	0	0	1 (25%)	0	1 (25%)	1 (25%)	0	0
Severe	0	0	0	0	0	0	0	0	0	1	0
Induration or swelling (VRC07-523LS)											
None	4 (100%)	4 (100%)	4 (100%)	4 (100%)	8 (100%)	4 (100%)	8 (100%)	4 (100%)	3 (75%)	4 (100%)	2 (100%)
Mild	0	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	1 (25%)	0	0
Pain (CAP256V2LS)											
None	3 (75%)	4 (100%)	4 (100%)	4 (100%)	7 (88%)	4 (100%)	7 (88%)	2 (50%)	2 (50%)	4 (100%)	1 (50%)
Mild	1 (25%)	0	0	0	1 (13%)	0	1 (13%)	2 (50%)	2 (50%)	0	1 (50%)
Moderate	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Pain (VRC07-523LS)											
None	4 (100%)	4 (100%)	4 (100%)	4 (100%)	8 (100%)	4 (100%)	8 (100%)	4 (100%)	2 (50%)	3 (75%)	1 (50%)
Mild	0	0	0	0	0	0	0	0	2 (50%)	0	1 (50%)
Moderate	0	0	0	0	0	0	0	0	0	1 (25%)	0
Severe	0	0	0	0	0	0	0	0	0	0	0

(Table 2 continues on next page)

	Intravenous		Subcutaneous							Control (n=2)
	CAP 256V2LS (5 mg/kg one dose; n=4)	CAP 256V2LS (10 mg/kg one dose; n=4)	CAP 256V2LS (5 mg/kg one dose; n=4)	CAP 256V2LS* (5 mg/kg one dose; n=4)	CAP 256V2LS* (10 mg/kg)		CAP256V2LS* (20 mg/kg)		CAP256V2LS + VRC07-523LS (10 mg/kg + 10 mg/kg; n=4)	CAP256V2LS + VRC07-523LS (20 mg/kg + 20 mg/kg; n=4)	
					Dose 1 (n=8)	Dose 2 (n=4)†	Dose 1 (n=8)	Dose 2 (n=4)†			
(Continued from previous page)											
Tenderness (CAP256V2LS)											
None	3 (75%)	4 (100%)	4 (100%)	4 (100%)	7 (88%)	3 (75%)	6 (75%)	3 (75%)	2 (50%)	4 (100%)	2 (100%)
Mild	1 (25%)	0	0	0	1 (13%)	1 (25%)	2 (25%)	1 (25%)	2 (50%)	0	0
Moderate	0	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0	0
Tenderness (VRC07-523LS)											
None	4 (100%)	4 (100%)	4 (100%)	4 (100%)	8 (100%)	4 (100%)	8 (100%)	4 (100%)	2 (50%)	1 (25%)	2 (100%)
Mild	0	0	0	0	0	0	0	0	2 (50%)	2 (50%)	0
Moderate	0	0	0	0	0	0	0	0	0	1 (25%)	0
Severe	0	0	0	0	0	0	0	0	0	0	0

Percentages might not add up to 100 due to rounding. *Broadly neutralising monoclonal antibodies administered with ENHANZE drug product. †Two of eight participants at week 16 and two of eight at week 24.

Table 2: **Reactogenicity events reported in the CAPRISA 012B trial**

combination with VRC07-523LS (figure 3A, table 3; appendix p 4).

Although the pharmacokinetic analysis was limited to the first dose data only, repeat dosing of both CAP256V2LS and VRC07-523LS showed a trend towards higher concentrations with a second dose due to possible dose accumulation (appendix p 5). The maximum concentration following the second dose was more than double the first dose in all participants despite the pre-dose concentrations.

Higher concentrations of CAP256V2LS were seen at 16 weeks versus 24 weeks (figure 3A). In this study, VRC07-523LS was not administered alone; however, data from previous trials conducted in the CAPRISA 012A trial in South Africa and the USA VRC 605 trial show that concentrations of VRC07-523LS are higher when combined with CAP256V2LS (figure 3B, appendix p 6). The estimated half-life following subcutaneous administration was 43 days for CAP256V2LS and 66 days for VRC07-523LS. Participants who received repeat doses showed no evidence of diminished peak or trough concentrations.

Pharmacokinetic simulations using steady state troughs on 20 mg/kg every 24 weeks for CAP256V2LS and VRC07-523LS were also conducted. CAP256V2LS concentrations were greater than 1 μg/mL in 95% of simulations but only 46% were greater than 5 μg/mL. At the same dosage, VRC07-523LS maintained concentrations greater than 1 μg/mL in all simulations and 97% were predicted to be greater than 10 μg/mL (figure 3C).

The use of EDP with 5 mg/kg CAP256V2LS via a subcutaneous pump resulted in a modest increase in antibody concentrations, suggesting that coadministration of EDP might increase the rate of absorption (figure 2D). EDP did not appear to impact early CAP256V2LS concentrations, but concentrations at 8 weeks and beyond tended to be higher with EDP. It should be noted that CAP256V2LS without EDP was administered as multiple injections at different sites rather than via a subcutaneous pump, which is the probable cause of the earlier and higher maximum concentration for 5 mg/kg without EDP, since CAP256V2LS was dispersed over several sites resulting in improved absorption compared with the one site with EDP. When pharmacokinetic profiles were compared with data from the CAPRISA 012A and VRC 605 trials where EDP was not used, the maximum concentration was similar at earlier timepoints, but later concentrations appeared higher for CAP256V2LS and VRC07-523LS, suggesting a minor alteration in absorption although confounded by combination antibody use (figure 3B).

Serum neutralisation titres were assessed by TZM-bl neutralisation assays using two pseudoviruses that were highly sensitive to the respective antibodies. For CAP256V2LS the virus CE2103 with an inhibitory concentration ([50%] IC_{50}) of 0·0003 μg/mL was used and for VRC07-523LS the virus strain Q769.d22 with an

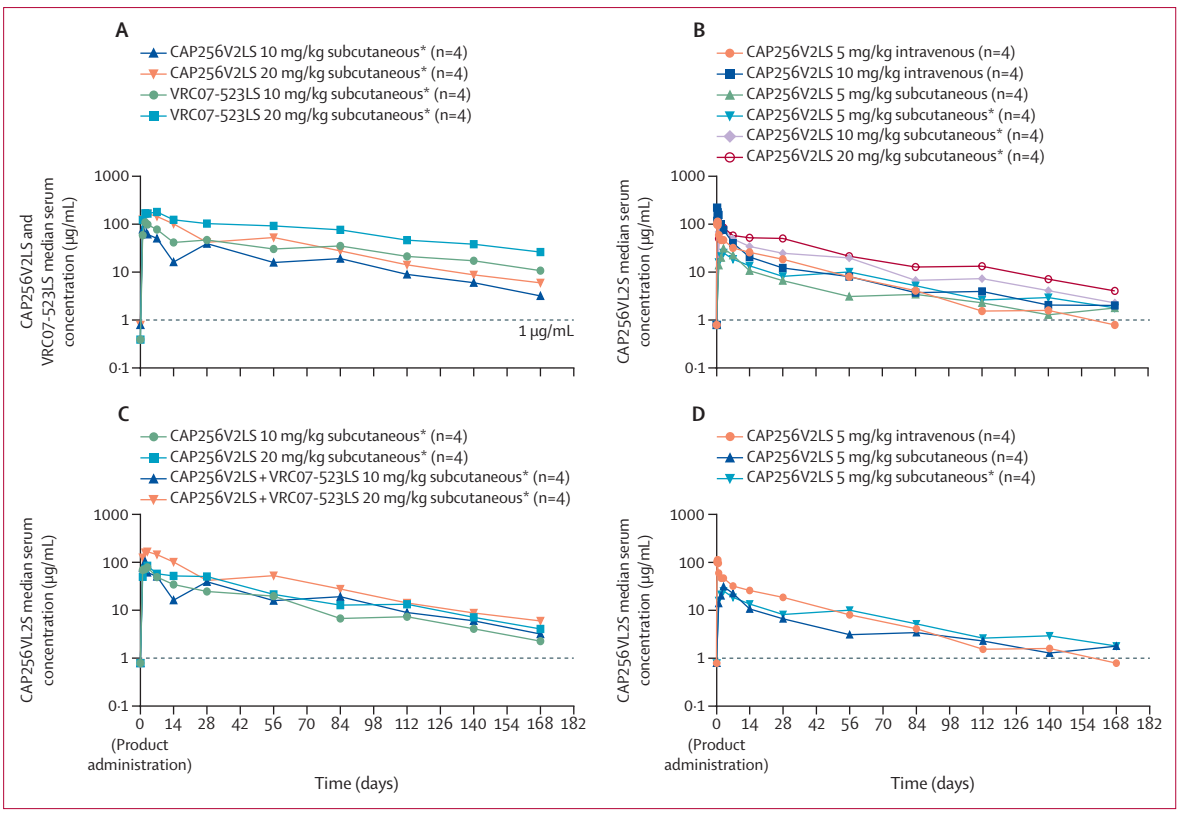

Figure 2: **Median concentrations of the study drug per study group**
(A) CAP256V2LS and VRC07-523LS. (B) CAP256V2LS. (C) CAP256V2LS administered subcutaneously alone and in combination with VRC07-523LS. (D) CAP256V2LS administered at 5 mg/kg intravenously, at 5 mg/kg without EDP, and at 5 mg/kg with EDP. EDP=ENHANZE drug product. bNAb=broadly neutralising monoclonal antibody. *bNAb administered with EDP.

IC_{50} of 0·008 µg/mL was used. As the sensitivity of the virus strain determined the titre measured in plasma, higher absolute titres were recorded for CAP256V2LS compared with VRC07-523LS. There was a wider range observed for neutralisation in the 5 mg/kg group who received CAP256V2LS via subcutaneous administration compared with those given intravenous infusions. For the 10 mg/kg group the peak titre was higher in the intravenous group compared with the subcutaneous administration group. The neutralisation titre peak was observed on average at day 1 for intravenous administrations and from day 2 for subcutaneous administrations.

The 20 mg/kg group achieved much higher titres than the lower dose groups, but the rate of decay was similar, and titres dropped to undetectable levels by week 16. There was no difference in the peak titres whether the repeat dose was given at 16 weeks or 24 weeks. However, the peaks after the second infusion in both groups appeared slightly lower than the peaks after the first dose. When both CAP256V2LS and VRC07-523LS antibodies were administered in combination a similar profile of timing of the peaks was observed, but the decay rate was quicker for CAP256V2LS (appendix p 7). The patterns seen here correspond to ELISA data, highlighting that the antibodies are functional and are still able to neutralise at late timepoints.

Discussion

The CAPRISA 012B trial was the first trial to evaluate human safety and pharmacokinetic profile of the engineered CAP256V2LS, a potent bNAb. It was also the first trial to investigate the subcutaneous administration of a bNAb alone and in combination to women as a PrEP concept in an HIV endemic setting. Finally, this trial evaluated for the first time the use of EDP with a bNAb as a concept for HIV prevention, potentially allowing for increased volumes of bNAbs to be administered subcutaneously. The trial found that CAP256V2LS and VRC07-523LS administered subcutaneously alone and in combination, with or without EDP, was safe and well tolerated, with detectable antibody concentrations 6 months after product administration. CAP256V2LS and VRC07-523LS maintained functional activity post-administration in all groups as measured by neutralising activity in serum.

Although the safety profile of bNAbs is reassuring, reactogenicity events were reported in the majority of participants and thus the safety profile should be further

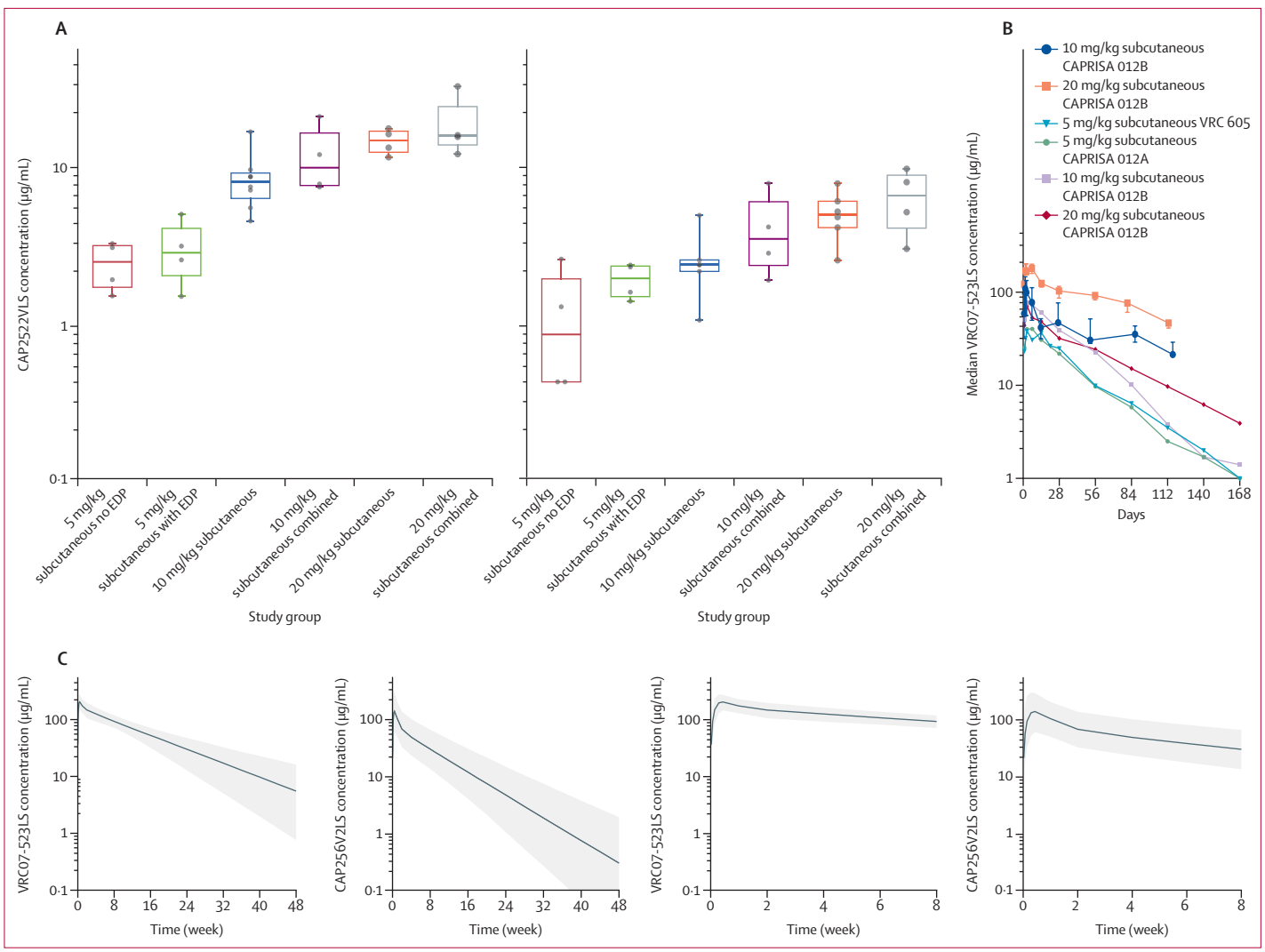

***Figure 3*: Median and predicted concentrations of the study drug per study group**

(A) CAP256V2LS concentrations at 16 weeks (left graph) and 24 weeks (right graph); in 10 mg/kg and 20 mg/kg combined group CAP256V2LS was administered in combination with VRC07-523LS. (B) VRC07-523LS concentrations in CAPRISA 012A (without EDP), CAPRISA 012B (with EDP), and VRC605 trials (without EDP). (C) Predicted bNAb concentration simulations of 20 mg/kg CAP256V2LS and VRC07-523LS using two-time scales. EDP=ENHANZE drug product. bNAb=broadly neutralising monoclonal antibodies.

evaluated in larger trials. The reactogenicity events observed in this trial could be due to the antibody being more immunogenic or due to the enhanced safety assessments specific to this trial. Factors that might influence reactogenicity include host-derived factors including age and gender, and extrinsic factors such as injection technique and dosing.[20] Although data remain scarce, it has been postulated that increased reactogenicity is a predictive sign of a robust immune response after vaccination.[21,22] In this trial reactogenicity monitoring occurred daily at the clinic for 3 days, in contrast with previous bNAb trials where participants were not assessed at the clinic daily, unless warranted.[17,23] Participants were not pre-medicated with anti-inflammatory medication before the administration.

This trial identified a transient lymphocytopenia 1 day after product administration in some participants. Pre-clinical toxicity studies of CAP256V2LS and other antibodies concur with the transient lymphocytopenia. Possible explanations are the margination, migration, and redistribution of lymphocytes. Transient lymphocytopenia has been observed in animal studies and human studies following the administration of immunotherapy with antibodies in oncology. It is not clear whether this occurs with other anti-HIV bNAbs in human trials because none of the other trials evaluated blood profiles on day 1 after product administration.

CAP256V2LS in combination with VRC07-523LS resulted in higher antibody concentrations. In the CAPRISA 012A trial, VRC07-523LS antibody

concentrations were similar when given in combination with PGT121, with repeat pharmacokinetic dosing resulted in similar profiles after the first and second dose.[18] In other trials, combinations of 3BNC117 and 10-1074 showed that single versus co-administration did not significantly influence the elimination half-life of 3BNC117.[24] The combination of PGDM1400, PGT121, and VRC07-523LS has been shown to be safe with a favourable pharmacokinetic profile,[25] and a triple combination trial assessing VRC07-523LS, PGT121.414.LS, and PGDM1400LS is ongoing. Preclinical evidence of synergistic neutralisation potency and enhanced therapeutic activity have been observed with bi-specific and tri-specific antibodies, and 10E8.4/iMab and SAR441236 are also being assessed in human trials.[4]

Target trough concentrations sufficient for protection have not been defined or selected for CAP256V2LS or VRC07-523LS. In non-human primate SHIV-325c challenge studies, PGDM1400 was fully protective at 0·4 mg/kg whereas CAP256-VRC26.25-LS was fully protective at the lowest dose of 0·08 mg/kg, even with serum antibody concentrations of less than 0·75 µg/mL.[26] In-vitro IC_{80} values were 0·104 µg/mL and 0·006 µg/mL for PGDM1400 and CAP256-VRC26.25-LS respectively. Challenge studies of VRC01, PGT121, 3BNC117, and 10-1074 have also shown protection.[27,28] In VRC01 challenge studies, infections occurred when VRC01 concentrations were less than 10 µg/mL for viruses with an IC_{50} of 2·06 µg/mL and IC_{80} of 7·14 µg/mL and in the Antibody Mediated Prevention trial, antibody concentrations above 1 µg/mL were sufficient for protection.[28]

This is the first time EDP has been used to facilitate the subcutaneous administration of therapeutics in HIV prevention.[18] Although use of a subcutaneous pump was required in this trial, administration was relatively rapid (maximum of 18 min) and uneventful. Clinical trials in oncology evaluating EDP have shown safety and improved antibody pharmacokinetic profile.[19] Several monoclonal antibodies used in the treatment of cancers have now been licenced as co-formulated products using the ENHANZE technology.[29] Unfortunately, in this trial, all higher doses of bNAbs administered were co-mixed with EDP and therefore a comparison between EDP-containing study arms and study arms without EDP could not be made. Further assessment on practicality, safety, and effect on pharmacokinetic profile are required in larger trials. The use of EDP is being evaluated with N6LS in a phase 1 trial. EDP is also being explored for the long-acting injectable cabotegravir.[30]

Limitations of the study include the small sample size, which is characteristic of phase 1 trials and the inclusion of women only due to the prioritisation of women for HIV prevention technologies in this trial. The omission of comparator non-EDP containing study arms to determine the effect of EDP on pharmacokinetic profile is a further limitation of this study.

	Dose (mg/kg)	Route	N	Mean C_{max} (µg/mL)	SD C_{max} (µg/mL)	Median C_{max} (µg/mL)	Minimum C_{max} (µg/mL)	Maximum C_{max} (µg/mL)	Mean C_{max} per mg/kg dose (µg/mL)	Mean T_{max} (day)	SD T_{max} (day)	Median T_{max} (day)	Minimum T_{max} (day)	Maximum T_{max} (day)
1a	5	IV	4	120·54	7·27	120·01	113·08	129·06	24·11	0·13	0·11	0·09	0·04	0·29
1b	10	IV	4	250·53	86·80	243·05	170·8	345·22	25·05	0·08	0·02	0·09	0·05	0·09
2a	5	SC	4	60·12	62·22	31·61	23·97	153·29	12·02	4·87	2·33	4·86	2·81	6·95
2b	5	SC	4	27·9	5·81	28·16	21·92	33·36	5·58	3·06	2·58	2·32	0·85	6·74
2c and d combined	10	SC	8	79·42	33·29	79·8	32·45	135·62	7·94	4·08	4·36	2·82	0·78	13·84
2c	10	SC	4	95·29	35·31	97·99	49·57	135·62	9·53	3·06	2·57	2·31	0·88	6·74
2d, week 16	10	SC	2	301·62	24·08	301·62	284·59	318·65	30·16	2·53	0·51	2·53	2·17	2·89
2d, week 24	10	SC	2	333·84	15·88	333·84	322·61	345·07	33·38	2·3	0·7	2·3	1·81	2·8
2e and f combined	20	SC	8	124·49	41·83	119·02	66·07	198·58	6·22	2·99	1·68	2·77	0·80	6·78
2e	20	SC	4	102·06	26·4	106·38	66·07	129·41	5·10	2·28	0·99	2·77	0·80	2·80
2f, week 16	20	SC	2	630·49	213·07	630·49	479·82	781·15	31·52	2·27	0·63	2·27	1·83	2·72
2f, week 24	20	SC	2	733·21	103·35	733·21	660·13	806·29	36·66	1·41	0·55	1·41	1·02	1·8
3a	10	SC	4	138·92	117·3	114·34	39·51	287·5	13·89	13·22	13·46	11·73	1·73	27·7
3b	20	SC	4	184·63	32·16	177·53	155·23	228·23	9·23	3·5	2·19	2·75	1·78	6·71

Data are n, mean, or median. C_{max}=maximum concentration. T_{max}=time to peak drug concentration. SC=subcutaneous. IV=intravenous.

Table 3: **Summary of CAP256V2LS pharmacokinetic data by study group**

CAP256V2LS is one of the most potent antibodies described to date and in combination with VRC07-523LS is predicted to provide significant coverage of global isolates. Neutralisation data from this trial showed that both antibodies retained their functional activity post-infusion. This suggests that the CAP256V2LS antibody is not prone to degradation in vivo. Furthermore, the neutralising capacity of both CAP256V2LS and VRC07-523LS was not affected by subcutaneous administration or the use of EDP.

CAPRISA 012C is a phase 2 trial that is currently assessing repeat dosing of CAP256V2LS and VRC07-523LS in combination. The overall strategy is to maintain effective concentrations for both bNAbs at all times and to avoid timepoints in the dose interval where a single bNAb is at an effective concentration. The maximum dosing interval will be driven by the bNAb with the shorter half-life, VRC07-523LS. The difference in half-life can be addressed by giving larger VRC07-523LS doses than CAP256V2LS. Alternatively, VRC07-523LS or both bNAbs can be administered more frequently. In the CAPRISA 012C trial, CAP256V2LS and VRC07-523LS will be initially administered at a loading dose of 1·2 g, followed by CAP256V2LS at a dose of 600 mg and VRC07-523LS at a higher dose of 1·2 g every 6 months. Results from CAPRISA 012C will provide further guidance on whether the combination of bNAbs CAP256V2LS and VRC07-523LS is safe and effective as a HIV prevention strategy for young African women at highest risk of HIV acquisition.

Contributors

SSAK is the principal investigator of CAPRISA 012B. QAK and SM are co-principal investigators. NG contributed to conception and design. EC conducted the pharmacokinetic analysis and pharmacokinetic modelling. SM and IH contributed to clinical investigations and sample collection. NYZ and FO contributed to data analysis and interpretation. NNM, PLM, LM, SN, and AM conducted neutralisation assays and analysed the data. KC, PLM, NDR, JRM, and LM contributed to antibody development. CB, TG, LEM, DA, NS, AW, NDR, and JRM contributed to the planning and conduct of the trial. SM wrote the first draft of the manuscript. NYZ, FO, SM, NG, and SSAK accessed and verified the data. All authors reviewed the final draft of the manuscript and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

NDR, JRM, PLM, LM, and SSAK are listed as co-inventors on patent US 10 519 222, issued 2019, on broadly neutralising monoclonal antibodies against the HIV-1 V1V2 env region. QAK is a co-chair on the UN *Sustainable Development Goals* 10 Member Technology Facilitation Mechanism, on the Vice-Chair Advisory Group of the WHO–Human Reproduction Programme Alliance Advisory Board, and the President of the World Academy of Science. SAK is a member of the WHO Science Council and the Vice-President of the International Science Council. SAK has received honoraria for participation in the Sanofi medical advisory committee on COVID-19 vaccines and was sponsored by Sanofi for the 2022 Options for the Control of Influenza conference in Belfast, UK. All other authors declare no competing interests.

Data sharing

Summary results of the trial will be made publicly available through the clinical trial registry as de-identified data. Any datasets used for analysis in publications can be requested by investigators via an online request to the organisation. Any additional data may be made available upon request to the corresponding author.

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