PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing the safety and pharmacokinetics of the monoclonal antibodies, VRC07-523LS and PGT121 in HIV negative women in South Africa: Study protocol for the CAPRISA 012A randomised controlled Phase I trial
AUTHORS	Mahomed, Sharana; Garrett, Nigel; capparelli, edmund; Baxter, Cheryl; Zuma, Nonhlanhla; Gengiah, Tanuja; Archary, Derseree; Moore, Penny; samsunder, Natasha; Barouch, Dan; Mascola, John; Ledgerwood, Julie; Morris, Lynn; Abdool Karim, Salim

VERSION 1 - REVIEW

REVIEWER	Yotam Bar-On The Rockefeller University, NY USA
REVIEW RETURNED	13-Apr-2019

GENERAL COMMENTS	This is a very important protocol that will facilitate the evaluation of potential antibody therapy/prevention against HIV. This has great value in protecting from HIV infection. The author did a good job describing the importance of this protocol and provide the appropriate details to repaet this protocol. I have only minor comments: - Please add a more clear description of the time interval between the antibodies injections and a more detailed plan on the time points in which PK data will be analyses - The abstract nicely explains the aims of this study. However please verify if neutralizing should be written like as you wrote 'neutralising' (British spelling) or as neutralizing. -Please be consistent when writing the name of the antibodies. VRC07-523.LS or VRC07-523LS - Please add the number of antibodies administration and the amount of the antibodies in each injection to the 'methods and analysis' section - Please explain in the introduction that the LS mutation is in the Fc region - Please add up-to-date papers about mono therapy and combination antibody therapy in humans to the references. - Please add few sentences about the limitation of this study protocol

REVIEWER	Sue Li Fred Hutch, Seattle, US
REVIEW RETURNED	16-Apr-2019

GENERAL COMMENTS	The manuscript is well written. This trial was well designed to provide the initial safety, pharmacokinetic (PK) and function activity data of VRC07-523LS and PGT121 individually or jointly when administered subcutaneously to HIV negative women in South Africa. I have some minor comments. 1. On page 10 and line 40, “Primary Sample” might be changed to “Primary Outcomes”. 2. In Figure 1, what are the vertical lines (bars)? 3. Figure 3 shows two curves of the concentrations following a repeated dose instead of the concentrations following single dose administration as indicated in title.

REVIEWER	Henning Gruell Laboratory of Experimental Immunology Institute of Virology Faculty of Medicine and University Hospital Cologne University of Cologne Cologne Germany
REVIEW RETURNED	29-Apr-2019

GENERAL COMMENTS	This manuscript and the accompanying study protocol by Mahomed and colleagues describe the clinical trial entitled “A Phase I Study to determine the Safety and Pharmacokinetics of the Human monoclonal Antibodies, VRC07-523LS and PGT121 administered subcutaneously to HIV negative adults in South Africa” (CAPRISA 012A). VRC07-523LS and PGT121 are potent broadly neutralizing anti-HIV-1 antibodies (bNAbs) that target the CD4 binding site and V3 loop of the HIV-1 envelope protein, respectively. Both antibodies have potential use in the prevention and treatment of HIV-1 infection. The current study aims to identify a suitable candidate for a planned follow-up trial, in which a combination with the V1/V2-loop-targeting bNAb CAP256.VRC26LS is to be administered to HIV-negative women (CAPRISA 012B). To this end, CAPRISA 012A will investigate the safety, PK and acceptability of VRC07-523LS and PGT121 when given alone or in combination to HIV-negative women in South Africa. CAPRISA 012A is a randomized, double-blind, placebo-controlled phase I study that will enroll 35 women in 7 groups at a 4:1 antibody:placebo ratio, and antibodies will be dosed at up to 10 mg/kg (VRC07-523LS) or 5 mg/kg (PGT121) for one or two doses. The rationale, objectives, endpoints, outline and study procedures are generally straightforward and presented mostly clearly throughout the protocol. While both antibodies are being administered subcutaneously (sc) to HIV-negative individuals in other trials at some of the doses investigated here, this study will provide important information on PK, safety and applicability in women in South Africa, an important target group for HIV prevention efforts. In addition, in contrast to earlier/parallel studies, a higher dose of VRC07-523LS will be tested (10 mg/kg sc), PGT121 will be given for up to two doses, and a combination of both bNABs will be given sc. Some questions came up while reading manuscript and protocol:

	a) Enrollment into group 1 (VRC07-523LS, 5 mg/kg) will be staggered. Will enrollment into groups 2 and/or 4 (10 mg/kg, which to my knowledge has not been given sc before) also be staggered? b) Based on the comments (section on randomization/blinding, 7.7) that are still attached to the protocol text, it appears as if this paragraph has not yet been finalized? Will unblinding occur and how do emergency unblinding procedures look like? Will participants be made aware of their group assignment while blinded? In this regard, enrollment into group 7 (combination of VRC07-523LS and PGT121) will only occur once 8 participants have received active product - how will this call be made while the study is still blinded? c) Section on DSMB (9.4.2; page 66, lines 15 and 23): Does the unblinded review of primary endpoint data only refer to being unblinded in terms of study arms? In the list just below, it says that the DSMB "will be asked to review the following blinded data: reactogenicity, AEs, etc.". In addition, there are some inconsistencies or inaccuracies that perhaps can be addressed in an updated version of the protocol. 1) In the introduction that accompanies the study protocol, the authors state (p7, line 13) that PGT121 has potency and breadth that is higher than that of VRC01. Actually, the breadth of VRC01 is generally considered higher than that of PGT121 (see, for example, CATNAP). 2) In the introducing manuscript (p8, line 42), AST above the upper limit of the normal range is listed as an exclusion criterion; however, this is not mentioned in the actual protocol (only ALT listed, page 55, line 18). 3) Introduction, page 18: Legend for fig. 3 should also include "repeat dose administration", and perhaps add doses to fig. 2 and fig. 3. 4) The title of the protocol states that this is a study in "HIV negative adults". Because it is limited to women, this should be reflected in the study title ("HIV negative women", similar to the manuscript title). 5) Introduction (p34, line 14): VRC is short for Vaccine Research Center (not Vaccine Research Council). 6) 1.2 (p43, line 40): "Regulatory authorities have recently approved TDF/FTC..": Could add that this more recent approval is referring to the use of TDF/FTC as PrEP. 7) 1.3 (p44, line 44): PGT121 was actually isolated at Scripps (Burton Lab) (ref. 34 is for PGDM1400, not PGT121), and the neutralizing activity of PGT121 against a wide panel of viruses was shown in vitro, not in animal models (only a few viral strains tested in vivo).

	8) 1.3 (p44, line 47): Second to last sentence of 1.3 (“VRC26.25LS + PGT121 have now been administered in human subjects”): VRC26.25LS has to my knowledge not been administered to humans yet; this is probably meant to say “VRC07-523LS and PGT121”. 9) 1.4 (p45, line 38): The authors state that their antibodies may be potent enough to be provide a s.c. alternative to VRC01, which “has to be given intravenously”. The higher potency (and half-life) of VRC07-523LS is a very relevant aspect, but VRC01 does not necessarily “need” to be given i.v. (could for example be given more frequently). 10) 3.2 (p51, line 33): One of the secondary objectives is to characterize the profile of VRC07-523LS, when given as two doses 12, 16 and 24 weeks apart. However, there is no group where the doses are given 16 weeks apart (only 12 and 24). 11) 4.1 (p52, line 12): One of the primary endpoints listed here is missing in the study scheme (proportion of participants with SAEs related to sc administration). 12) 6.3 (p57, line 11): Is there a reason why reactogenicity events are not recorded with an attribution assessment? Or will they be separately recorded as AEs? 13) References in the protocol should be revised (quite a few are numbered incorrectly or referencing unrelated work).

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1 COMMENTS	RESPONSE
This is a very important protocol that will facilitate the evaluation of potential antibody therapy/prevention against HIV. This has great value in protecting from HIV infection. The author did a good job describing the importance of this protocol and provide the appropriate details to repeat this protocol.	We thanks Reviewer for this positive comment.
Please add a more clear description of the time interval between the antibody injections and a more detailed plan on the time points in which PK data will be analyses	
The abstract nicely explains the aims of this study. However please verify if neutralizing should be written like as you wrote 'neutralising' (British spelling) or as neutralizing.	Spelling is standardized as neutralizing.
Please be consistent when writing the name of the antibodies. VRC07-523.LS or VRC07-523LS	Antibodies incorrectly written have been amended throughout the document.
Please add the number of antibodies administration and the amount of the antibodies in each injection to the 'methods and analysis' section	The number and dose of antibody has now been dded to the manuscript.

Please explain in the introduction that the LS mutation is in the Fc region	This has been specified in the manuscript.
Please add up-to-date papers about monotherapy and combination antibody therapy in humans to the references.	Up-to-date papers added as per comment.
Please add few sentences about the limitation of this study protocol	Limitations of the study added in.
REVIEWER 2 COMMENTS	RESPONSE
The manuscript is well written. This trial was well designed to provide the initial safety, pharmacokinetic (PK) and function activity data of VRC07-523LS and PGT121 individually or jointly when administered subcutaneously to HIV negative women in South Africa.	Thank you for these positive comments on our manuscript.
On page 10 and line 40, “Primary Sample” might be changed to “Primary Outcomes”.	This change has been made, as suggested.
In Figure 1, what are the vertical lines (bars)?	This refers to the point of sample collection for PK analyses.
Figure 3 shows two curves of the concentrations following a repeated dose instead of the concentrations following single dose administration as indicated in title	Edited..
REVIEWER 3 COMMENTS	RESPONSE
The rationale, objectives, endpoints, outline and study procedures are generally straightforward and presented mostly clearly throughout the protocol. While both antibodies are being administered subcutaneously (sc) to HIV-negative individuals in other trials at some of the doses investigated here, this study will provide important information on PK, safety and applicability in women in South Africa, an important target group for HIV prevention efforts. In addition, in contrast to earlier/parallel studies, a higher dose of VRC07-523LS will be tested (10 mg/kg sc), PGT121 will be given for up to two doses, and a combination of both bNABs will be given sc.	Thanks you for this positive comments on our manuscript.
Enrollment into group 1 (VRC07-523LS, 5 mg/kg) will be staggered. Will enrollment into groups 2 and/or 4 (10 mg/kg, which to my knowledge has not been given sc before) also be staggered?	As mentioned by Reviewer 3, enrolment into Group 1 will be staggered. After ensuring safety for all participants in Group 1, we will randomise Groups 2-6 together. Although Groups 2 and 4 will not be staggered as such, in actual practice there is a waiting period between enrolments for all the participants in Groups 2-6. In addition, all participants will be monitored closely for a minimum of 60 minutes

	post administration of study product in the clinic, the will receive a phone call in the evening of the vaccination and will be reviewed on Day 1 to 3 post vaccination.
Based on the comments (section on randomization/blinding, 7.7) that are still attached to the protocol text, it appears as if this paragraph has not yet been finalized? Will unblinding occur and how do emergency unblinding procedures look like? Will participants be made aware of their group assignment while blinded? In this regard, enrollment into group 7 (combination of VRC07-523LS and PGT121) will only occur once 8 participants have received active product - how will this call be made while the study is still blinded?	Yes, participants are aware of the group allocation (receiving the injection once or twice allows them to determine the group they are in, however they are not aware if the product is active or placebo). This is a double-blinded study with both the study team and participants blinded to the study product assignment. The unblinded pharmacist will work with the unblinded statistician to formulate treatment codes correlating with study product prescription. The unblinded statistician will inform the PSRT chair and PIs when 12-week safety data is available for the first 8 participants who received active study products . To maintain blinding, the following will be done: (i) the unblinded statistician will only communicate with the PSRT chair when more than 8 participants have been enrolled and have completed the week 12/later visit. (ii) this data will be reviewed (without any distinctions) in the weekly PSRT meetings together with the safety data for all the other participants.
Section on DSMB (9.4.2; page 66, lines 15 and 23): Does the unblinded review of primary endpoint data only refer to being unblinded in terms of study arms? In the list just below, it says that the DSMB “will be asked to review the following blinded data: reactogenicity, AEs, etc.”. Will unblinding occur and how do emergency unblinding procedures look like?	Yes, the unblinding refers to the study arm because the group allocation is not concealed. During the DSMB meetings, the DSMB members will review the blinded reports which will be presented by the study PI. Thereafter, the study team (including PIs) will excuse themselves from the meeting so that the DSMB members can review the unblinded reports or data.
In addition, there are some inconsistencies or inaccuracies that perhaps can be addressed in an updated version of the protocol.	Thank you for these comments. We have submitted clarification memos that address some of these issues and will address all comments/suggestions further in the updated version of the protocol.
In the introduction that accompanies the study protocol, the authors state (p7, line 13) that PGT121 has potency and breadth that is higher than that of VRC01. Actually, the breadth of VRC01 is generally considered higher than that of PGT121	Corrected in the manuscript.

the introducing manuscript (p8, line 42), AST above the upper limit of the normal range is listed as an exclusion criterion; however, this is not mentioned in the actual protocol (only ALT listed, page 55, line 18).	This is an error and has been corrected.
Introduction, page 18: Legend for fig. 3 should also include “repeat dose administration”, and perhaps add doses to fig. 2 and fig. 3.	This has been amended as suggested.
The title of the protocol states that this is a study in “HIV negative adults”. Because it is limited to women, this should be reflected in the study title (“HIV negative women”, similar to the manuscript title).	Considering that this study title has already been approved, this change will have to be amended in an updated version of the protocol.
Introduction (p34, line 14): VRC is short for Vaccine Research Center (not Vaccine Research Council).	Will be amended in an updated version of the protocol
1.2 (p43, line 40): “Regulatory authorities have recently approved TDF/FTC..”: Could add that this more recent approval is referring to the use of TDF/FTC as PrEP.	Will be amended in an updated version of the protocol
1.3 (p44, line 44): PGT121 was actually isolated at Scripps (Burton Lab) (ref. 34 is for PGDM1400, not PGT121), and the neutralizing activity of PGT121 against a wide panel of viruses was shown in vitro, not in animal models (only a few viral strains tested in vivo).	Will be corrected in an updated version of the protocol
1.3 (p44, line 47): Second to last sentence of 1.3 (“VRC26.25LS + PGT121 have now been administered in human subjects”): VRC26.25LS has to my knowledge not been administered to humans yet; this is probably meant to say “VRC07-523LS and PGT121”.	Will be corrected in an updated version of the protocol
1.4 (p45, line 38): The authors state that their antibodies may be potent enough to be provide a s.c. alternative to VRC01, which “has to be given intravenously”. The higher potency (and half-life) of VRC07-523LS is a very relevant aspect, but VRC01 does not necessarily “need” to be given i.v. (could for example be given more frequently).	Will be amended in an updated version of protocol
3.2 (p51, line 33): One of the secondary objectives is to characterize the profile of VRC07-523LS, when given as two doses 12, 16 and 24 weeks apart. However, there is no group where the doses are given 16 weeks apart (only 12 and 24).	Will be corrected in an updated version of protocol

4.1 (p52, line 12): One of the primary endpoints listed here is missing in the study scheme (proportion of participants with SAEs related to sc administration).	Omitted in error. Added to the manuscript. All changes tracked.
6.3 (p57, line 11): Is there a reason why reactogenicity events are not recorded with an attribution assessment? Or will they be separately recorded as AEs?	Yes, reactogenicity are a subset of adverse events (AEs) and have specific reporting requirements.
References in the protocol should be revised (quite a few are numbered incorrectly or referencing unrelated work).	Will be revised in an updated version of the protocol