March 8, 2018

Full Protocol Amendment 1

A summary of changes to

Protocol

Version 2.0

HVTN 127/HPTN 087

A multicenter, randomized, partially blinded phase 1 clinical trial to evaluate the safety and serum concentrations of a human monoclonal antibody, VRC-HIVMAB075-00-AB (VRC07-523LS), administered in multiple doses, routes, and dosing schedules to healthy, HIV-uninfected adults

DAIDS-ES ID 38458

[IND #137719—HELD BY DAIDS]

Clinical Research Site (CRS) filing instructions

The following information impacts the HVTN 127/HPTN 087 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) and any other applicable Regulatory Entity (RE) as soon as possible for their information and review. Their approval is required before implementation.

The HVTN will have operational changes to put in place before the clinical research sites (CRSs) can implement this amendment. Therefore, CRSs may have IRB/EC approval of the amendment but will not be able to implement it until the HVTN completes those changes. The HVTN will

send each CRS an amendment activation notification once all the operational changes have been addressed.

By approving this amendment, the IRB/EC approves extending the use of the previous protocol procedures until the CRS receives an amendment activation notification from the HVTN.

Upon receiving final IRB/EC and any other applicable RE approval(s), sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a Registration Notification for the amendment once the DAIDS PRO verifies that all the required amendment registration documents have been received and are complete. A Registration Notification from the DAIDS PRO is not required prior to implementing the amendment. A copy of the Registration Notification should be retained in the site's regulatory files.

For additional information on the registration process and specific documents required for amendment registration, refer to the current version of the DAIDS Protocol Registration Manual.

The following information affects the sample informed consent. Your IRB/EC will be responsible for determining the process of informing study participants of the contents of this full protocol amendment.

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Item 1 Added on Title page: IND number

IND 137719 has been added to the protocol title page. Per current FDA usage for biologics, "BB" has been removed.

Item 2 Revised on Title page and in Section 3, Appendices A, C, and J: Study title

Because the added IM injection arm (Item 3) includes placebo recipients and participants in this arm are blinded to their treatment assignments, the study title has been revised to reflect the fact that the study is now partially blinded. In addition, because all groups have been assigned the same study product administration schedule (Item 4 below), "multiple…dosing schedules" has been removed from the title.

Item 3 Added: Intramuscular injection (IM) study arm

To date, clinical trials of broadly neutralizing anti-HIV monoclonal antibodies have involved study product administration via intravenous (IV) infusions and subcutaneous (SC) injections. Since intramuscular (IM) injection may be more feasible and acceptable than these other routes of administration, an IM study arm has been added in order to assess VRC07-523LS safety, tolerability, and serum levels when administered IM.

A Primary objectives revised in Sections 3 and 5.1

Primary objective 1 has been revised in Section 3, *Overview* and in Section 5.1, *Primary objectives and endpoints* to include product administration via IM injection. Similarly, IM administration has been added and the number of regimens updated in *Primary objective 2*.

B Placebo product/route of administration added in Section 3, *Overview*

The placebo for the IM injection arm has been added under *Study products and routes of administration* in Section 3. In addition, Group 6, with 20 participants receiving VRC07-523LS at a dose of 2.5 mg/kg (n = 20) or placebo (n = 4) via intramuscular injection (IM) has been added to the Schema (Table 3-1). "IM" has been defined in a note below the table.

C Sample size revised in Section 3

The total study sample size has been revised from 100 to 124 in Table 3-1, *Schema* and under "Participants" in Section 3.

D IM administration added in Section 4.5.1, *Dose and schedule*

Notation that the dose and administration schedule for IM administration are not based on VRC07-523LS preclinical and clinical data but, rather, on an expectation that the serum concentration mean and variance will fall within the range previously observed for IV and SC administration has been added in Section 4.5.1.

E Rationale for inclusion of placebo recipients in Group 6 added to Section 4.5.2, *Rationale for the exclusion of placebo recipients in IV and SC treatment groups*

The rationale for including a small number of placebo recipients in Group 6 has been added at the end of Section 4.5.2. The section title has been revised to clarify that placebo recipients are excluded only from the IV and SC treatment groups.

F Rationale for IM administration added in Section 4.6, *Plans for future product development and testing*

The fact that this study will provide the first clinical evaluation of the safety and pharmacokinetics of IM administration of an anti-HIV monoclonal antibody has been added in Section 4.6

G Summary results of nonclinical tolerance study of IM administration added in Section 4.7.2, *In vivo toxicology studies*

A GLP local tolerance study (IITRI Project N0. 2749-001) evaluated IM administration of VRC07-523LS in Sprague-Dawley rats. Summary results from this study have been added as new Section 4.7.2.2. The repeat dose IV and SC toxicity study described previously in Section 4.7.2 has been renumbered Section 4.7.2.1 and the study number (IITRI Project NO. 2517-001-002) has been added.

H IM administration experience with Synagis® added in Section 4.10, *Potential risks of study products and administration*

A brief characterization of IM administration of Synagis® has been added in Section 4.10, along with references to published safety reviews.

I Secondary objective 1 revised in Section 5.2

Secondary objective 1 has been revised to include IM study product administration.

J Sample size and study design description revised in Section 6.1, *Accrual and sample size calculations*

The total sample size, the number of treatment groups, and the description of the different regimens have been revised in Section 6.1.

K Sample size, event probabilities, and confidence intervals revised in Section 6.1.1, *Sample size calculations for safety*

The total number of study product recipients has been revised from 100 to 120 in the first and second paragraphs in Section 6.1.1 and in Tables 6-1 and 6-2. True rates for which there is a 90% change of observing safety events have been recalculated in the first paragraph and the probabilities of observing 0, 1+, or 2+ events at different true event rates for different group sizes have been revised in Table 6-1. Confidence intervals around observed event rates have been revised for the largest group size in Table 6-2. The caption to Table 6-2 has been corrected to include arms of size "40", as shown in the table.

L Explanation for not simulating serum concentrations following IM injection added in Section 6.1.2, *Sample size calculations for serum levels of VRC07-523LS*

IM administration has been added to the first sentence in Section 6.1.2 and explanation for the lack of serum concentration simulations following IM injection has been added as the final paragraph in Section 6.1.2.

M Randomization revised in Section 6.2

Description of block randomization has been revised in Section 6.2, *Randomization*, to take account of the addition of the IM arm to the randomization scheme after Groups 1 through 5 are already partially enrolled.

N Revised Section 6.3, *Blinding*

The statement that the study is unblinded has been replaced by text explaining that participants and CRS staff will be unblinded to participant group assignments and that, while Safety Monitoring Board (SMB) members are unblinded to treatment assignments for all 6 groups, Group 6 participants and CRS staff (except for CRS pharmacists) will be blinded to treatment assignments in Group 6. Instructions regarding maintaining blinding have been added along with instructions regarding messaging to participants who terminate prior to study completion and procedures for emergency unblinding.

O IM added in Section 6.4.5, *ADA and drug functionality analysis*

IM administration has been added in the first paragraph of Section 6.4.5.

P Group 6 added in Section 8.1, *Study product regimen*

Group 6 study product and placebo descriptions have been added to Section 8.1.

Q IM injection preparation added as Section 8.3.1.3, *Intramuscular injection preparation instructions (T6 and P6)*

Pharmacy instructions for preparation of study product and placebo for IM injection have been added as Section 8.3.1.3.

R IM administration instructions added as Section 8.4.3, *VRC07-523LS (Intramuscularly)*

Instructions for IM administration of VRC07-523LS have been added as Section 8.4.3.

S *Belief questionnaire* added in Section 9.4 and Appendix G

To help control for potential participant bias and to help support blinding in Group 6, participants in that group will be asked at their final study visit whether they believe they received the active study product or the placebo. This procedure has been added in Section 9.4, *Follow-up visits*, and in Appendix G, *Procedures at CRS*.

T Appendix A, *Sample informed consent form*, revised to include IM arm

The number of persons to be enrolled has been revised in the second paragraph of "About the study" in Appendix A. Item 3 has been modified (in two locations) to note that the study antibody has not been tested previously IM in humans and that a rat study did not reveal any safety issues. In addition, Item 10 has been revised; since some IM group participants will receive placebo, the topic line and first paragraph now refers to "study products" rather than "study antibody". Also, description of IM injection has been added to the third paragraph, notation that treatment assignment within Group 6 is assigned randomly has been added to the fourth paragraph, and that unblinding to Group 6 treatment assignment will take place after completion of all study visits, with exceptional unblinding allowed for medical need has been added to the final paragraph. Placebo has been added to the header line in Item 12.

U Appendix E, Schema graphic (for sample informed consent form), revised to include IM arm

Group 6 has been added to the schema graphic in Appendix E (see Item 27).

Item 4 Revised: Product administration and follow-up visit schedules

Based on interim pharmacokinetic data from the ongoing VRC605 study that suggest the VRC07-523LS half-life is somewhat shorter than that observed for VRC01LS (though still longer than VRC01-class monoclonal antibodies lacking the LS

mutation), the administration schedule for all groups has been revised to q16 weeks. In addition, follow-up following the final infusion/injection has been reduced to 48 weeks, three times the interval between study product administrations, as was the case in protocol Version 1.0. The protocol text and procedure tables have been revised accordingly.

A Primary objective 1 revised in Sections 3 and 5.1

Because all groups will now receive study product on the same schedule, the four parts of *Primary objective 1* have been collapsed into a single primary safety/tolerability objective encompassing all study product regimens.

B Product administration schedule revised in Table 3-1, *Schema*

Table 3-1 has been revised to show study product administration for all groups at Weeks 0, 16, 32, 48, and 64.

C Duration per participant and Estimated total study duration revised in Section 3

Revision of the study product administration schedule and reduction of post-product follow-up to 48 weeks reduces the study duration for each participant to 112 weeks, or approximately 26 months. The *Duration per participant* and *Estimated total study duration* in Section 3 have been revised accordingly.

D Study design revised in Section 4.5.1, *Dose and schedule*

Section 4.5.1 has been revised to indicate the data informing the revised study design, to add the IM arm, and to describe the range of comparisons between dose groups and routes of administration supported by the revised study design.

E Comparison of dosing intervals removed in Section 4.6, *Plans for future product development and testing*

Since the same administration schedule has been instituted for all study groups, comparison of dosing intervals has been removed from the first sentence in the second paragraph of Section 4.6.

F Study design description revised in Section 6.1, *Accrual and sample size calculations*

The number of groups and group descriptions have been revised in Section 6.1 per the revised product administration schedules. The follow-up duration has also been updated.

G Items 8 and 11 revised in Appendix A, *Sample informed consent form*

The number of visits and the visit schedule length have been updated in the header line of Item 8. The header line in Item 11 has been updated to indicate that the IV and injection schedule is the same for all participants. The first sentence in Item 11 and the *IV and Injection Schedule* table have been revised to show that all participants will receive IVs or injections five times, about once every 4 months.

Item 5 Updated in Section 4.9.3: *Clinical studies of VRC07-523LS; VRC 605*

Summary safety information from the VRC 605 clinical trial has been updated in Section 4.9.3, as has the interim data on serum titers shown in Figure 4-8.

Item 6 "Pharmacokinetics" removed in Section 6.1.2, *Sample size calculations for serum levels of VRC07-523LS*

Since development of population pharmacokinetic models is a secondary objective and the study is not powered to characterize pharmacokinetic parameters with a specific precision, the term "pharmacokinetics" has been removed from discussion of Primary objective 2 in Section 6.1.2.

Item 7 Updated in Section 6.4.6: *Analyses and data sharing prior to end of scheduled follow-up visits*

The title of Section 6.4.6 has been revised to include "data sharing" and text in this section has been revised to clarify constraints on access to study data (including blinded safety data) and analyses by treatment assignment prior to the completion of all scheduled clinic visits. Accordingly, "analyses" has been added to the title of Section 6.4.6.1.

Item 8 Updated in Sections 7, Appendix B, and Appendix D: Use of "sex assigned at birth"

Use of "assigned male/female sex assigned at birth" has been made consistent throughout the protocol document, including revisions to text in Sections 7.1 (Items 10 and 20), Appendix B, and Appendix D.

Item 9 Removed in Section 9.1.2, *Protocol-specific consent forms*: Instruction to follow protocol-specific memo regarding when to start using site-specific consent forms

Because instructions regarding when sites may begin using protocol-specific consent forms have been removed from the memos accompanying protocol distribution, the second to last paragraph in Section 9.1.2, which advises sites to follow these instructions in the memo, has been removed.

Item 10 Clarified in Sections 9.3 and 9.4: HIV assessment procedure includes HIV diagnostic testing

Bullets for "HIV infection assessment" in Section 9.3, *Enrollment and study product administration visits*, and Section 9.4, *Follow-up visits*, have been revised to clarify that the HIV infection assessment procedure includes HIV diagnostic testing as well as pretest counseling and acute infection symptom assessment.

Item 11 Clarified in Section 9.8 *Assessments of Solicited AEs*: CRS clinician assessment

The right-hand column in Table 9-1 has been revised to clarify that assessment of solicited adverse event (AE) at a clinical research site must be performed by a CRS clinician.

Item 12 Clarified in Section 9.8.1, *Assessment of systemic and local symptoms*: Thermometry

The second paragraph in Section 9.8.1 has been revised to clarify that all body temperature measurements in the clinic and by study participants during the solicited AE assessment period outlined in Table 9-1, must be performed using non-axillary thermometry.

Item 13 Clarified in Section 9.8.2, *Assessment of infusion/injection site*: Infusion/injection site reaction measurements

Section 9.8.2 has been revised to clarify that injection site reactions should be measured by diameter rather than by maximum horizontal and vertical measurements.

Item 14 Updated in Section 10.1, *CRS laboratory procedures*: Special instructions and research assays

Section 10.1 has been revised to clarify that special laboratory instructions will be posted if a study entails redirection of blood collection tubes to other laboratories or special study-specific processing techniques. In addition, text has been added clarifying that all laboratory assays described in this protocol section are performed as research assays that are not approved for use in medical care and that results from these assays are not made available to study participants or medical professionals to guide treatment decisions.

Item 15 Clarified in Section 11.2.1, *Submission of safety forms to SDMC*: Submittal deadlines

Language in Section 11.2.1 has been revised to clarify deadlines for submittal of safety forms to the SDMC, including circumstances involving multiple holidays.

Item 16 Revised in Section 11.2.2, *AE reporting*: Unsolicited AE reporting period

For consistency with the revised product administration and clinic visit schedules (Item 4), the Unsolicited AE reporting period has been set from enrollment to the Week 80 visit (Visit 16.0) for all study participants.

Item 17 Clarified in Section 11.2.3, *Expedited reporting of AEs to DAIDS*: Unblinding procedures

Text has been added as the second to last paragraph in Section 11.2.3 clarifying the roles of the Protocol Safety Review Team (PSRT) and the Safety Monitoring Board (SMB) in decisions to unblind participants and instructing that any unblinding should be performed in such a manner as to maintain the study blind of the PSRT and the study team.

Item 18 Added in Section 11.3, *Safety pause and prompt PSRT AE review*: Submission of unanticipated problems to IRB/EC

"Unanticipated problems involving risks to participants or others" has been added to the list of items that the HVTN and HPTN require CRSs to submit to their IRBs/ECs and to other applicable regulatory entities.

Item 19 Clarified in Section 12.2, *Emergency communication with study participants*: Circumstances under which communication is allowed prior to IRB/EC approval

The second paragraph in Section 12.2 has been revised to clarify that communication without prior IRB/EC approval is allowed if such communication is necessary to avoid imminent harm to the study participant.

Item 20 Clarified in Appendix A, Item 8: Visit intervals

A sentence has been added at the beginning of Item 8 indicating that most visits will be about 8 weeks apart.

Item 21 Clarified in Appendix A, Item 14: Sample testing

The heading and text in Item 14 have been revised to clarify that samples will be tested to measure study antibody levels and potential immune responses to the study antibody.

Item 22 Clarified in Appendix A Item 16 and Appendix C: Other research on stored samples

Language in these locations has been revised to clarify that additional studies conducted using participant samples and data may not contribute to this specific study, that any participant genomes be entered into databases will not be associated

with participant names or other personal information, and that there may be other as yet unknown risks associated with genomic testing and storage of genome data.

Item 23 Added in Appendix A and in Appendix C: Participants may change their minds regarding use of samples and data in other studies

A sentence has been added to the header line in Appendix A Item 26 and to Item 13 in Appendix C clarifying that participants can change their minds regarding use of their samples and information in other studies after signing their consent forms.

Item 24 Clarified in footnote to Appendix A and Appendix C signature blocks: Witness requirement

The footnote at the end of the signature blocks in Appendices A and C has been revised to clarify that such a witness must have been present for the entire discussion of the pertinent consent form with the study volunteer.

Item 25 Clarified in Appendix B, *Approved birth control methods (for sample informed consent form)*: Condom use for HIV and STI prevention

The reminder at the end of Appendix B has been edited to clarify that condoms (male and female) are the only birth control methods known to also provide protection against HIV and other sexually transmitted infections.

Item 26 Revised in Appendix D: Table of procedures (for sample informed consent form)

The second and third tables previously shown in Appendix D have been removed. The single remaining table shows the clinic visit schedule, procedures, and product administration schedule for all study participants.

Item 27 Revised in Appendix E: Product administration schedule graphic

The schema graphic in Appendix E has been revised to show all groups receiving study product 5 times at q16 week intervals. In addition, the graphic has been revised to include Group 6 (both VRC07-523LS and placebo recipients) and to show IM injection locations as well as those for IV infusions and subcutaneous injections. IM injection has also been added to the key and to the graphic that illustrates SC injection. For consistency with the IV dose designations, the Group 5 SC dose has been revised from “High Dose” to “Medium dose.”

Item 28 Revised in Appendix F: *Laboratory procedures* table

The laboratory procedures table in Appendix F has been revised to show follow-up visits to Week 112. In addition, “Groups 1 and 4” has been removed from the title, since this procedures table now applies to participants in all groups. Accordingly, the laboratory procedure tables previously shown in Appendices G and H have been

removed and the remaining appendices have been renumbered. In footnote 2 beneath the table, the VRC laboratory has been removed, as it does not appear in the table.

Item 29 Revised in Appendix G: *Procedures at CRS* table

The clinic procedures table in Appendix G has been revised to show follow-up visits to Week 112 and "Groups 1 and 4" has been removed from the title, since this procedures table now applies to participants in all groups. Accordingly, the CRS procedure tables previously shown in Appendices J and K have been removed and the remaining appendices have been renumbered. A column labelled "Post" and a row labeled "Post-study unblinding" have been added along with a footnote indicating that unblinding of participants following completion of the study applies only to Group 6. In addition, the table has been reformatted per the HVTN template; it now shows local lab assessments as well as clinic procedures. The footnotes to the table have been updated accordingly.

Item 30 Clarified in Appendix H, *Adverse events of special interest (AESI)*: Update provisions

Introductory text in Appendix H has been revised to clarify that while updates to the AESI list will be provided in the Study Specific Procedures, they will not necessarily be shown in an appendix to that document.

Item 31 Added as Appendix I: *Low risk guidelines for the US and Switzerland*

In response to a request from the Division of AIDS, guidelines for assessing whether volunteers are at "low risk" for HIV infection have been added as new Appendix I. Cross references to this appendix have been added in Section 7.1 (Item 9) and Section 9.2, *Pre-enrollment procedures*.

Item 32 Updated and corrected in Section 3.1: Protocol team

The Clinical Safety Specialist has been updated in the list of *Contributes to the original protocol* and spelling has been corrected for the Clinical Data Manager's last name.

Item 33 Updated: Section and appendix numbers and cross-references

Protocol sections and appendices have been renumbered as appropriate and cross-references have been updated throughout the protocol document.

Item 34 Corrected: Acronyms, spelling and grammatical errors, page layout, and stylistic inconsistencies

A Acronyms corrected in text and in Section 15, *Acronyms and abbreviations*

The full name of ICH has been corrected in Sections 1, 14, and 15. In addition, failures to define acronyms at first use have been corrected in several locations.

B Minor errors and stylistic inconsistencies corrected

Corrections include:

- removing periods at the end of primary objective statements in Sections 3 and 5.1
- spelling correction in Section 6.1
- spacing between characters in the first paragraph in Section 6.1.1
- word order correction in the third paragraph in Section 6.4.4.1
- making “forms” plural in the fourth paragraph in Section 9.1.2
- removing an extraneous hyphen in Section 9.3
- removing extraneous phrasing in Section 11.4.2, and
- making punctuation consistent in Section 14.

Protocol modification history

Protocol modifications are made to HVTN and HPTN protocols via clarification memos, letters of amendment, or full protocol amendments. Protocols are modified and distributed according to standard procedures described in the Networks' Manuals of Operations (MOP).

The version history of, and modifications to, Protocol HVTN 127/HPTN 087 are described below.

Date: March 8, 2018

Protocol version: Version 2.0
Protocol modification: Full Protocol Amendment 1

Item 1 Added on Title page: IND number

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Date: November 28, 2017

Protocol version: 1.0
Protocol modification: Original protocol