FINAL

September 18, 2020

Letter of Amendment 1

Protocol

Version 1.0

HVTN 136/HPTN 092

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

DAIDS-ES ID 38634

IND #146153—HELD BY DAIDS

HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN)
Clinical Research Site (CRS) filing instructions

The following information impacts the HVTN 136/HPTN 092 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.

Upon receiving final IRB/EC and any other RE approval(s) for this LOA, CRSs must implement the LOA immediately.

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

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

The following information may affect the sample informed consent. The CRS's IRB/EC is responsible for determining the process of informing study participants of the contents of this LOA.

List of changes

The changes described herein will be incorporated in the next version of Protocol HVTN 136/HPTN 092 if it undergoes full protocol amendment at a later time. New text is shown as **bold underlined**. Deleted text is shown with ~~strikethrough~~.

Item 1 Updated with changes described in Protocol Version 1, Clarification Memo 1, dated September 3, 2020

The following changes as itemized in Clarification Memo 1 have been incorporated:

A Added IND number to the cover page

When the HVTN 136/HPTN 092 protocol was submitted to the FDA, the IND number had not yet been assigned. The IND number has been added to the cover page

Added:

IND ~~TBD~~ 146153 HELD BY DAIDS

B Clarified throughout the protocol (in accordance with COVID-19-precautions): "Clinic Visits"

In accordance with COVID-19 precautions to maintain social distancing, certain "clinic visit" procedures and data collection may be performed remotely.

Throughout the protocol, "clinic visits" for data collection and procedures (scheduled and ad hoc) may be conducted by phone, text message, or email, or other electronic means. An in-person clinic visit is required only for physical exam, point-of-care testing, collecting biological samples, or administering study agents.

Item 2 Added in Section 9.3, *Enrollment and study product administration*, Section 9.4, *Follow-up visits,* Section 15, *Acronym and abbreviations,* and Appendices J– M, *Laboratory Procedures*: ALT, AST, alkaline phosphatase and creatinine in the chemistry panel

In response to comments received from the FDA on December 27, 2019, ALT, AST, Alkaline Phosphatase, and creatinine have been added to the enrollment and follow-up Chemistry panel as shown below.

A Section 9.3, Enrollment and study product administration visits

Revised:

- Clinical laboratory tests including:
  - CBC with differential;
  - Chemistry panel ~~(see Section 9.2)~~ **(alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [Alk Phos] and creatinine**), and
  - Urine or serum pregnancy test (for participants who were assigned female sex at birth). Persons who are NOT of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;

B Section 9.4, Follow-up visits

Revised:

- Clinical laboratory tests including:
  - CBC with differential,
  - Chemistry panel ~~(see Section 9.2)~~ **(alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [Alk Phos] and creatinine)**;

- Urine dipstick (urinalysis if appropriate; see Section 9.7); and
- Urine or serum pregnancy test (for participants who were assigned female sex at birth). Persons who are NOT of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. During follow-up in persons who are confirmed pregnant, pregnancy testing is not required, unless clinically indicated

C Section 15, Acronym and abbreviations

The definitions of Alk Phos and AST have been added to the list of acronyms and abbreviations to accompany the revisions to Section 9.3 and 9.4 described above.

Added:

Alk Phos	**alkaline phosphatase**
ALT	alanine aminotransferase
AMP	Antibody Mediated Prevention
ANOVA	analysis of variance
ART	antiretroviral therapy
AST	**aspartate aminotransferase**
AUC	area-under-the-curve

D Appendix J, *Laboratory procedures for Part A, - Groups 1, 2, and 3*, Appendix K, *Laboratory procedures for Part A – Group 4*, Appendix L, *Laboratory procedures for Part B – Group 5*, and Appendix M, *Laboratory procedures for Part B – Group 6*.

Footnote #5 was updated to add AST, ALT, alkaline phosphatase, and creatinine testing at enrollment and follow-up visits to harmonize with the edits to Sections 9.3 and 9.4 described above.

Revised:

[5]~~Chemistry panels are defined in Section 9.2 (pre-enrollment)~~ **Chemistry panels are defined in Section 9.2 (pre-enrollment), and Sections 9.3 and 9.4 (enrollment and follow-up).**

Item 3 Removed from Section 1, *Overview* and Appendices J-M, *Laboratory procedures:* Fred Hutch/University of Washington (Seattle, Washington, USA)

Fred Hutch/University of Washington is removed from the list of endpoint assay laboratories as shown below.

A Section 1, Overview

Revised:

Endpoint assay laboratories

- Duke University Medical Center (Durham, North Carolina, USA)
- ~~Fred Hutch/University of Washington (Seattle, Washington, USA)~~
- Dartmouth College (Hanover, New Hampshire, USA)

B Appendix J, *Laboratory procedures for Part A, - Groups 1, 2, and 3*, Appendix K, *Laboratory procedures for Part A – Group 4*, Appendix L, *Laboratory procedures for Part B – Group 5*, and Appendix M, *Laboratory procedures for Part B – Group 6*

Fred Hutch/University of Washington (Seattle, Washington, USA) is removed from Footnote #2.

Revised:

[2] HVTN Laboratories include: ~~Fred Hutch/University of Washington (Seattle, Washington, USA);~~ Duke University Medical Center (Durham, North Carolina, USA); Dartmouth College (Hanover, New Hampshire, USA). Non-HVTN laboratories: ARUP Laboratories (Salt Lake City, Utah, USA).

Item 4 Revised in Appendices S-V, *Visit Windows*: lower and upper allowable windows from visit 9.0 onwards

To address the impact of the COVID-19 pandemic on on-site protocol visits and the need to reduce both staff and participant time in the clinic, this modification will expand the upper and lower allowable windows from visit 9.0 onwards for all the groups. The widening of the visit windows is not expected to have an impact on the assessment of the safety/tolerability objective (primary objective 1). It is also not expected to have a significant impact on the assessment of serum concentrations and neutralization (primary objectives 2 & 3), although a larger variation may be seen in the endpoints due to the widened visit windows. Such variation will be accounted for in supportive analyses of these endpoints by accounting for actual visit dates (rather than visit numbers). This is a compromise to balance the need of accomplishing the

study objectives and ensuring quality of the trial (minimizing missing data) in this special era of the COVID-19 pandemic. Revised tables with changes shown are appended.

Item 5 Updated in Section 1.1, *Protocol Team*: Membership

The Protocol Team list has been updated in Section 1.1 as shown below.

Revised:

DAIDS Medical officer HVTN	**Catherine Yen** ~~Jane Baumblatt~~ DAIDS, NIAID **240-292-4783** ~~301-761-7754~~ **catherine.yen@nih.gov** ~~jane.baumblatt@nih.gov~~
Study product developer representatives	Lucio Gama VRC Dan Barouch BIDMC ~~Nandini Sane~~ **Michael Pensiero** DAIDS, NIAID Jennifer Grossman DAIDS, NIAID
HVTN Clinical trials manager	**India Tindale** ~~Carissa Karg~~ HVTN Core, Fred Hutch
HVTN community educator/recruiter	**Harlan Smith** ~~Machel Hunt~~ Emory Hope Clinic
*HVTN Protocol development manager**s***	**Kajari Mondal** **Daciana Margineantu** ~~Ramey Fair~~ HVTN Core, Fred Hutch

Appendix S Visit Windows for Part A Groups 1-3

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day	Upper Target Day	Upper Allowable Window
01.0	Screening	-56	-		-	-
02.0	**Enrollment[1] Infusion**	-	-	0	-	-
03.0	1 day post infusion	-	-	1	-	-
04.0	2 days post infusion	-	-	2	-	-
05.0	3 days post infusion	-	-	3	-	-
06.0	6 days post infusion	-2	-	6	-	+2
07.0	2 weeks post infusion	-7	-3	14	+3	+7
08.0	4 weeks post infusion	-7	-3	28	+3	+7
09.0	8 weeks post infusion	-~~7~~**14**	-3	56	+3	+~~7~~**14**
10.0						
11.0	16 weeks post infusion	-~~7~~**14**	-3	112	+3	+~~7~~**14**
12.0						
13.0	24 weeks post infusion	-~~7~~**14**	-3	168	+3	+~~7~~**14**
14.0						
15.0	Final Visit 32 weeks post infusion	-~~14~~**21**	-7	224	+7	+~~14~~**21**

[1]Screening should be conducted within 56 days of Enrollment (Infusion.)

Appendix T Visit Windows for Part A Group 4

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day	Upper Target Day	Upper Allowable Window
01.0	Screening	-56	-		-	-
02.0	**Enrollment[1] Infusion**	-	-	0	-	-
03.0	1 day post infusion	-	-	1	-	-
04.0	2 days post infusion	-	-	2	-	-
05.0	3 days post infusion	-	-	3	-	-
06.0	6 days post infusion	-2	-	6	-	+2
07.0	2 weeks post infusion	-7	-3	14	+3	+7
08.0	4 weeks post infusion	-7	-3	28	+3	+7
09.0	8 weeks post infusion	-~~7~~**14**	-3	56	+3	+~~7~~**14**
10.0						
11.0	16 weeks post infusion	-~~7~~**14**	-3	112	+3	+~~7~~**14**
12.0						
13.0	Final Visit 24 weeks post infusion	-~~7~~**14**	-3	168	+3	+~~7~~**14**

[1]Screening should be conducted within 56 days of Enrollment (Infusion).

Appendix U Visit Windows for Part B Group 5

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day	Upper Target Day	Upper Allowable Window
01.0	Screening	-56	-		-	-
02.0	**Enrollment[1] Infusion #1**	-	-	0	-	-
03.0	1 day post infusion #1[2]	-	-	1	-	-
04.0		-	-		-	-
05.0	3 days post infusion #1[2]	-	-	3	-	-
06.0	6 days post infusion #1[2]	-2	-	6	-	+2
07.0	2 weeks post infusion #1[2]	-7	-3	14	+3	+7
08.0	4 weeks post infusion #1[2]	-7	-3	28	+3	+7
09.0	8 weeks post infusion #1[2]	-~~7~~**14**	-3	56	+3	+~~7~~**14**
10.0	12 weeks post infusion #1[2]	-~~7~~**13**	-3	84	+3	+~~7~~**13**
11.0	**Infusion #2**	-14	-7	112	+7	+14
12.0	4 weeks post infusion #2[2]	-~~7~~**13**	-3	140	+3	+~~7~~**14**
13.0	8 weeks post infusion #2[2]	-~~7~~**13**	-3	168	+3	+~~7~~**14**
14.0	12 weeks post infusion #2[2]	-~~7~~**13**	-3	196	+3	+~~7~~**13**
15.0	**Infusion #3**	-14	-7	224	+7	+14
16.0	4 weeks post infusion #3[2]	-~~7~~**13**	-3	252	+3	+~~7~~**14**
17.0	8 weeks post infusion #3[2]	-~~7~~**13**	-3	280	+3	+~~7~~**14**
18.0	16 weeks post infusion #3[2]	-~~7~~**14**	-3	336	+3	+~~7~~**14**
19.0	24 weeks post infusion #3[2]	-~~7~~**14**	-3	392	+3	+~~7~~**14**
20.0	Final Visit 32 weeks post infusion #3[2]	-~~14~~**21**	-7	448	+7	+~~14~~**21**

[1]Screening should be conducted within 56 days of Enrollment (Infusion #1).
[2]Postinfusion visits are scheduled according to date of the prior infusion visit.

Appendix V Visit Windows for Part B Group 6

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day	Upper Target Day	Upper Allowable Window
01.0	Screening	-56	-		-	-
02.0	**Enrollment[1] Infusion #1**	-	-	0	-	-
03.0		-	-		-	-
04.0		-	-		-	-
05.0	3 days post infusion #1[2]	-	-	3	-	-
06.0	6 days post infusion #1[2]	-2	-	6	-	+2
07.0	2 weeks post infusion #1[2]	-7	-3	14	+3	+7
08.0	4 weeks post infusion #1[2]	-7	-3	28	+3	+7
09.0	8 weeks post infusion #1[2]	-~~7~~**14**	-3	56	+3	+~~7~~**14**
10.0	12 weeks post infusion #1[2]	-~~7~~**13**	-3	84	+3	+~~7~~**13**
11.0	**Infusion #2**	-14	-7	112	+7	+14
12.0	4 weeks post infusion #2[2]	-~~7~~**13**	-3	140	+3	+~~7~~**14**
13.0	8 weeks post infusion #2[2]	-~~7~~**13**	-3	168	+3	+~~7~~**14**
14.0	12 weeks post infusion #2[2]	-~~7~~**13**	-3	196	+3	+~~7~~**13**
15.0	**Infusion #3**	-14	-7	224	+7	+14
16.0	4 weeks post infusion #3[2]	-~~7~~**13**	-3	252	+3	+~~7~~**14**
17.0	8 weeks post infusion #3[2]	-~~7~~**13**	-3	280	+3	+~~7~~**14**
18.0	16 weeks post infusion #3[2]	-~~7~~**14**	-3	336	+3	+~~7~~**14**
19.0	Final Visit 24 weeks post infusion #3[2]	-~~7~~**14**	-3	392	+3	+~~7~~**14**

[1]Screening should be conducted within 56 days of Enrollment (Infusion #1).
[2]Postinfusion visits are scheduled according to date of the prior infusion visit.

Protocol modification history

Protocol modifications are made via clarification memos, letters of amendment, or full protocol amendments. The version history of, and modifications to, Protocol HVTN 136/HPTN 092 are described below.

Date: September 18, 2020

Protocol version: Version 1.0
Protocol modification: Letter of Amendment 1

Item 1 Updated with changes described in Protocol Version 1, Clarification Memo 1, dated September 3, 2020

Item 2 Added in Section 9.3, *Enrollment and study product administration*, Section 9.4, *Follow-up visits,* Section 15, *Acronym and abbreviations,* and Appendices J– M, *Laboratory Procedures*: ALT, AST, alkaline phosphatase and creatinine in the chemistry panel

Item 3 Removed from Section 1, *Overview* and Appendices J-M, *Laboratory procedures:* Fred Hutch/University of Washington (Seattle, Washington, USA)

Item 4 Revised in Appendices S-V, *Visit Windows*: lower and upper allowable windows from visit 9.0 onwards

Item 5 Updated in Section 1.1, *Protocol Team*: Membership

Date: September 03, 2020

Protocol version: Version 1.0
Protocol modification: Clarification Memo 1

Item 1 Added IND number to the cover page

Item 2 Clarified throughout the protocol (in accordance with COVID-19 precautions): "Clinic Visits"

Date: October 8, 2019

Protocol version: 1.0

Original protocol

Protocol Signature Page

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies

Investigator of Record Name (print)	Investigator of Record Signature	Date

DAIDS Protocol Number: HVTN 136/HPTN 092

DAIDS Protocol Version: Version 1.0

Protocol Date: October 8, 2019