FINAL

February 24, 2022

Letter of Amendment 1

Protocol

Version 1.0

HVTN 140/HPTN 101

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, and pharmacokinetics of PGDM1400LS alone and in combination with VRC07-523LS and PGT121.414.LS in healthy, HIV-uninfected adult participants

DAIDS-ES ID 38723

IND 154188—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 140/HPTN 101 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 does not 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

Item 1 Added in Section 1, *Overview*: HPTN Leadership and Operations Center 2

Item 2 Updated in Section 1.1, *Protocol Team*: team members 3

Item 3 Added in Section 8.3.3.3, *PGT121.414.LS fixed-dose intravenous infusion* preparation: information regarding storage times and temperatures 3

Item 4 Corrected in Appendix F, *Laboratory procedures for Part A*: Ab reaction maximum blood volume in footnote 13 3

Item 5 Corrected in Appendix G, *Laboratory procedures for Part B*: formatting 3

Item 6 Corrected in Appendix F, *Laboratory procedures for Part A* and Appendix G, *Laboratory procedures for Part B*: visit number referenced in footnote 7 4

Item 7 Corrected in Appendix I, *Procedures at HVTN CRS for Part B*: remote documentation of diary in footnote 3 4

Item 8 Added in Section 8.4.1, *General considerations for subcutaneous infusion study product administration*: reference to HVTN140/HPTN101 Study-Specific Procedures (SSP) manual) for additional details on anatomic locations for infusions 4

Item 9 Revised in Section 8.3.1.1, *Thawing instructions*: PGDM1400LS vial storage time conditions 5

The changes described herein will be incorporated in the next version of Protocol HVTN 140/HPTN 101 if it undergoes full protocol amendment at a later time. New text is shown in **bold underline** and deleted text in ~~strikethrough~~.

Item 1 Added in Section 1, *Overview*: HPTN Leadership and Operations Center

This addition corrects an oversight and adds the HPTN Leadership and Operations Center. The subheading was revised accordingly as shown below.

~~HVTN~~ Leadership and Operations Centers (LOCs)

HIV Vaccine Trials Network (HVTN) Leadership Group/Core Operations Center, Fred Hutchinson Cancer Research Center (Fred Hutch) (Seattle, Washington, USA)

HIV Prevention Trials Network (HPTN) Leadership and Operations Center (LOC), FHI 360 (Durham, North Carolina, USA)

Item 2 Updated in Section 1.1, *Protocol Team*: team members

Nicholas Hastings was removed as a HPTN Prevention Research Specialist. Marianne Gildea was added as a HPTN Clinical Research Operations Manager. Lori Proulx-Burns, Nelisiwe Xaba and Tebogo Magopane were added as HVTN Clinical Trials Managers. Simba Takuva was removed as HVTN Protocol team leader and regional medical liaison. Veronique Bailey and Azwi Takalani were added as HVTN regional medical liaisons. Kevin Gillespie was added as Statistical research associate. Fei Gao's affiliation was revised.

An updated protocol team listing is appended.

Item 3 Added in Section 8.3.3.3, *PGT121.414.LS fixed-dose intravenous infusion* preparation: information regarding storage times and temperatures

The following information was added as a new number 5 in Section 8.3.3.3:

5. **After preparation for administration in IV bags or syringes, PGT121.414.LS may be stored at 2°C to 8°C up to 24 hours or at room temperature (maximum 27°C) up to 4 hours. If stored at 2°C to 8°C, the prepared product must be equilibrated at room temperature (maximum 27°C) for a minimum of 30 minutes prior to product administration.**

Item 4 Corrected in Appendix F, *Laboratory procedures for Part A*: Ab reaction maximum blood volume in footnote 13

This revision corrects the maximum blood volume that could be collected for Ab reaction evaluation from 34 mL to 51 mL to align with the companion footnote in Appendix G. The revised footnote is shown below:

[13]The 56-day total blood volume does not include up to ~~34~~ **51**mL SST blood collected for any Ab reaction; however, the 56-day limit is not exceeded at any visit by the possible collection of SST blood for an Ab reaction.

Item 5 Corrected in Appendix G, *Laboratory procedures for Part B*: formatting

This change corrects a formatting error that inadvertently deleted the top rows of the table. A revised Appendix G with associated footnotes is appended to this document.

Item 6 Corrected in Appendix F, *Laboratory procedures for Part A* and Appendix G, *Laboratory procedures for Part B*: visit number referenced in footnote 7

These revisions correct errors in the visit number referenced in the footnote as shown below.

Revised Appendix F footnote 7:

[7]At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit ~~15~~**9** above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).

Revised Appendix G footnote 7:

[7]At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit ~~20~~**11** above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).

Item 7 Corrected in Appendix I, *Procedures at HVTN CRS for Part B*: remote documentation of diary in footnote 3

This revision was made to accurately reflect the visit schedule and visit windows. Footnote 3 was revised to remove time frame of remote documentation of the participant diary as shown below.

[3] Solicited AE assessments are performed daily for at least 3 full days following study product administration. CRS staff will review and reconcile the diary with the participant and then report Solicited AEs. Participant diary reconciliation may happen as the data is available (see the HVTN 140/HPTN 101 SSP). For Part B participants' second infusion solicited AE data collection: remote documentation of the participant diary may occur after the solicited AE assessment period and the next clinic visit (Visit 9), ~~ideally within 2 weeks post-infusion (~~see the HVTN 140/HPTN 101 SSP~~)~~.

Item 8 Added in Section 8.4.1, *General considerations for subcutaneous infusion study product administration*: reference to HVTN140/HPTN101 Study-Specific Procedures (SSP) manual) for additional details on anatomic locations for infusions

Revised first paragraph in Section 8.4.1:

Due to factors such as dose and volume, participant weight and body habitus, and participant tolerability and preference, the site clinicians and participants must decide whether to subcutaneously infuse each study product at 1, 2, or 3 anatomic locations simultaneously **(see HVTN 140/HPTN 101 SSP for detail on anatomic location)**.

In Part B, three mAbs are infused sequentially; thus, in Part B there are a minimum of 3 and a maximum of 9 infusion sites. The HVTN 140/HPTN 101 SSP provides information about subcutaneous infusion sets, recommended infusion pumps and clinical considerations for study product administration.

Item 9 Revised in Section 8.3.1.1, *Thawing instructions*: PGDM1400LS vial storage time conditions

This revision aligns the storage times at 2°C to 8°C with the Investigator's Brochure and clarifies that 15°C to 27°C is the range for "controlled room temperature".

Revised text to point 2:

2. After thawing, the PGDM1400LS vials may be stored at 2°C to 8°C for up to ~~48 hours~~ **14 days** and/or at **controlled room temperature (**15°C to 27°C**)** for up to 24 hours. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, vials must be equilibrated at controlled room temperature (15°C - 27°C) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation. PGDM1400LS vials should not be refrozen after thaw.

Protocol Team

Protocol leadership

HVTN Chairs	Colleen Kelley Emory University 404-712-1435 colleen.kelley@emory.edu Sharana Mahomed Centre for the AIDS Programme of Research in South Africa (CAPRISA) +27 31 655 0610 Sharana.Mahomed@caprisa.org	*HPTN Chair*	Marc Siegel George Washington Medical Faculty Associates 202-741-2165 msiegel@mfa.gwu.edu
HVTN Protocol Team leader	Shelly Karuna HVTN LOC, Fred Hutch 206-667-4355 mkaruna@fredhutch.org	*HPTN Protocol Team leader*	Theresa Gamble HPTN LOC, FHI 360 919-544-7040 x11350 tgamble@fhi360.org
HVTN Laboratory lead	David Montefiori HVTN Laboratory Center 919-684-5278 david.montefiori@duke.edu	*HPTN Laboratory lead*	Estelle Piwowar-Manning HPTN Laboratory Center, Johns Hopkins University 410-614-6736 epiwowa@jhmi.edu
DAIDS Medical officer	Peggy Yacovone DAIDS, NIAID 240-292-0826 margaret.yacovone@nih.gov	*DAIDS Medical officer*	Wairimu Chege DAIDS, NIAID 240-292-4786 wairimu.chege@nih.gov
HVTN Statistician	Chenchen Yu HVTN SDMC, Fred Hutch 206-667-5658 cyu@scharp.org	*HPTN Statistician*	Fei Gao HPTN SDMC, Fred Hutch fgao@fredhutch.org

Other contributors to the original protocol

HVTN Medical monitor	Shelly Karuna HVTN LOC, Fred Hutch	*DAIDS protocol pharmacist*	Shawn Chiambah Lynette Purdue DAIDS, NIAID
HVTN Regional medical liaisons	Veronique Bailey Azwi Takalani HVTN LOC, Fred Hutch	*VRC Consultant*	Lucio Gama Dale and Betty Bumpers Vaccine Research Center
HVTN Clinical safety specialist	Maija Anderson HVTN LOC, Fred Hutch	*HPTN Pharmacologist*	Julie Dumond UNC Chapel Hill
HVTN Clinical trials managers	India Tindale Lori Proulx-Burns Tebogo Magopane Nelisiwe Xaba HVTN LOC, Fred Hutch	*HPTN Senior Clinical research manager*	Bonnie Dye HPTN LOC, FHI360
HVTN Laboratory Center representative	Jen Hanke HVTN Laboratory Center, Fred Hutch	*HPTN Clinical research operations manager*	Marianne Gildea HPTN LOC, FHI360
HVTN Statistician consultant	Yunda Huang HVTN SDMC, Fred Hutch	*HPTN Laboratory Program representative*	Amber Moser HPTN Laboratory Center
SDMC Associate director of lab science	April Randhawa SCHARP, Fred Hutch	*Statistical research associates*	Chenchen Yu Kevin Gillespie HVTN SDMC, Fred Hutch
HVTN Regulatory affairs associate	Laurie Rinn HVTN LOC, Fred Hutch	*Lead clinical data manager*	Nate Holm SCHARP, Fred Hutch
Community Advisory Board (CAB) members	Lenka Tswenyana PHRU Soweto/Kliptown CAB Melissa Turner George Washington University CAB	*DAIDS product lead*	Michael Pensiero DAIDS, NIAID
HVTN Community engagement unit representative	Gail Broder HVTN LOC, Fred Hutch	*Clinic coordinators*	Geoffrey Kamau The Hope Clinic Emory Vaccine Center Hannah Yellin George Washington University
HVTN Community educator/recruiter	Chelsea Greer Emory Vaccine Center CRS	*HPTN Community program manager*	Jonathan Lucas HPTN LOC, FHI 360
HVTN Protocol development manager	Meg Trahey HVTN LOC, Fred Hutch	*HPTN Community educator/recruiter*	Ntando Yola Groote Schuur HIV CRS
HVTN Project coordinator	Anders McConachie Haven Wilvich HVTN LOC, Fred Hutch	*HPTN Prevention research specialist*	Zoe Jones HPTN LOC, FHI360
		HPTN Ethics Working Group representative	Robert Klitzman Columbia University

Appendix G, Laboratory procedures for Part B

					Visit:	1	2	3	4	5	6	7	8[16]	9	10	11
					Day:	Screening visit[3]	D0	D3	D6	D28	D56	D112	D116	D168	D224	D280
					Week:		W0			W4	W8	W16		W24	W32	W40
							Study Product Administration #1					**Study Product Administration #2**				
Procedure	**Ship to[1]**	**Assay location[2]**	**Tube Type[4]**	**Tube size (vol. capacity)[4]**			**PGDM1400LS + VRC07-523LS + PGT121.414.LS**					**PGDM1400LS + VRC07-523LS + PGT121.414.LS**				
BLOOD COLLECTION																
Screening/Diagnostic																
Screening HIV test	Local lab	Local lab	EDTA	5mL		5	—	—	—	—	—	—	—	—	—	—
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—
Syphilis[9]	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—
HIV diagnostics[7]	UW-VSL / HSML-NICD	UW-VSL / HSML-NICD	EDTA	10mL		—	—	—	—	—	—	10	—	—	—	10
Safety labs[10]																
CBC/ Differential	Local lab	Local lab	EDTA	5mL		5	—	—	—	—	5	5	—	5	—	5
Chemistry Panel[5]	Local lab	Local lab	SST	5mL		5	—	—	—	—	5	5	—	5	—	5
Drug concentrations/detection																
PGDM1400LS, VRC07-523LS, PGT121.414.LS concentrations	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	—	y	y	y
Humoral assays																
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	—	y	y	y
Non-neutralizing antiviral assays	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	—	y	y	y
Anti-Drug Antibody (ADA)																
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	y	—	—	—	y
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	y	—	—	—	y
Ab Reaction[11]																
Tryptase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL		—	See footnote 12	—	—	See footnote 12			—	See footnote 12		
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	See footnote y	—	—	—	—
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	See footnote y	—	—	—	—
STORAGE																
Serum	CSR	—	SST	8.5mL		—	76.5[14]	42.5	42.5	42.5	42.5	51[14]	—	42.5	42.5	42.5
Visit total						**25**	**76.5**	**42.5**	**42.5**	**42.5**	**52.5**	**71**	**0**	**52.5**	**42.5**	**62.5**
56-Day total[13]						**25**	**102**	**144**	**187**	**229**	**282**	**71**	**71**	**124**	**95**	**105**
URINE COLLECTION[10]																
Urine dipstick[8]	Local lab	Local lab				X	—	—	—	—	X	—	—	X	—	X
Pregnancy test[6]	Local lab	Local lab				X	X[15]	—	—	—	—	X	—	—	—	X

Footnotes for Appendix G

[1]CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); HSML-NICD = HIV Sero-Molecular Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa)

[2]HVTN Laboratories include: Duke University Medical Center (Durham, North Carolina, USA); South African Immunology Laboratory-National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Dartmouth College (Hanover, New Hampshire, USA). Non-HVTN laboratories: ARUP Laboratories (Salt Lake City, Utah, USA)

[3]Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[4]Local labs may assign appropriate alternative specimen type or tube types for locally performed tests.

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

[6]For participants assigned female sex at birth, pregnancy test must be performed on urine or blood specimens on the day of study product administration with negative results received prior to administration. 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.

[7]At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 11 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).

[8]And microscopy if needed.

[9]Syphilis testing will be done by serology.

[10]For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

[11]To investigate Ab administration-related clinical reactions, assays may be performed on serum samples taken prior to the study product administration associated with the reaction and collected after the onset of reaction. Refer to the SSP for more information.

[12]SST blood will be collected at specific time points after the onset of any Ab reaction. Refer to the SSP for more information.

[13]The 56-day total blood volume does not include up to 51mL SST blood collected for any Ab reaction; however, the 56-day limit is not exceeded at any visit by the possible collection of SST blood for an Ab reaction.

[14]Of this volume, 8.5mL of SST blood will be **collected post study product administration (**see SSP for details).

[15]Pregnancy test at enrollment does not need to be performed if negative results are received from screening pregnancy test conducted within 48 hours prior to study product administration .

[16]Phone contact only. No specimen collection at this visit.

y = SST blood collected for serum storage will also cover specimen needs for drug concentrations, HIV-1 neutralizing Ab assays, non-neutralizing antiviral assays, and ADA detection and functional assays (including for any Ab reactions); no separate blood draw is needed.

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 140/HPTN 101 are described below.

Date: February 24, 2022

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

Item 1 Added in Section 1, *Overview*: HPTN Leadership and Operations Center

Item 2 Updated in Section 1.1, *Protocol Team*: team members

Item 3 Added in Section 8.3.3.3, *PGT121.414.LS fixed-dose intravenous infusion* preparation: information regarding storage times and temperatures

Item 4 Corrected in Appendix F, *Laboratory procedures for Part A*: Ab reaction maximum blood volume in footnote 13

Item 5 Corrected in Appendix G, *Laboratory procedures for Part B*: formatting

Item 6 Corrected in Appendix F, *Laboratory procedures for Part A* and Appendix G, *Laboratory procedures for Part B*: visit number referenced in footnote 7

Item 7 Corrected in Appendix I, *Procedures at HVTN CRS for Part B*: remote documentation of diary in footnote 3

Item 8 Added in Section 8.4.1, *General considerations for subcutaneous infusion study product administration*: reference to HVTN140/HPTN101 Study-Specific Procedures (SSP) manual) for additional details on anatomic locations for infusions

Item 9 Revised in Section 8.3.1.1, *Thawing instructions*: PGDM1400LS vial storage time conditions

Date: June 23, 2020

Protocol version: 1.0
Protocol modification: not applicable

Original protocol

Protocol Signature Page

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, and pharmacokinetics of PGDM1400LS alone and in combination with VRC07-523LS and PGT121.414.LS 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 140/HPTN 101

DAIDS Protocol Version: Version 1.0

Protocol Date: June 23, 2020