Letter of Amendment #1 for:

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

Version 2.0, dated 29 May 2017

DAIDS ES # 20735
IND # 133,017 Held By DAIDS

Letter of Amendment Date: 14 June 2018

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2008 study, including the study informed consent forms, and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA, using site-specific informed consent forms corresponding to this LoA. For participants enrolled in the study before this LoA is approved, re-consent should be obtained using site-specific informed consent forms corresponding to this LoA.

Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, corresponding site-specific informed consent forms, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2008. If the IMPAACT 2008 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

DAIDS Study ID #20735

Version 2.0, Letter of Amendment #1
Letter of Amendment Signature Page

I will conduct this 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 US 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.

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

Summary of Modifications and Rationale

The purpose of this LoA is to:

- Update the protocol team and study site rosters
- Provide operational flexibility for conducting the Week 14 and Week 16 study visits, at which specimens are collected for primary antiviral activity analyses and secondary pharmacokinetics analyses, respectively
- Update the protocol and sample informed consent forms consistent with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) standards and current DAIDS requirements pertaining to review of study records
- Correct internal inconsistencies and procedural inaccuracies in the protocol

Implementation

Modifications of protocol text are shown below, generally in order of appearance in the protocol. Where applicable, modified protocol text is shown using strikethrough for deletions and bold type for additions.

1. The protocol team roster is updated to replace a Protocol Statistician and remove two Protocol Data Managers:

   Protocol Statisticians
   ~~Konstantia (Nadia) Angelidou, MS~~
   Jane Lindsey, ScD
   Center for Biostatistics in AIDS Research
   Harvard TH Chan School of Public Health
   651 Huntington Avenue
   Boston, MA 02115
   ~~Phone: (617) 432-2524~~
   ~~Email: kangelid@sdac.harvard.edu~~
   Phone: (617) 432-2812
   Email: lindsey@sdac.harvard.edu

   Protocol Data Managers
   ~~Amanda Golner, BS~~
   ~~Frontier Science & Technology Research Foundation (FSTRF)~~
   ~~4033 Maple Road~~
   ~~Amherst, NY 14226-1056~~
   ~~Phone: (716) 834-0900 x7382~~
   ~~Email: golner@fstrf.org~~

   ~~Jenna Kearly, MPH~~
   ~~Frontier Science & Technology Research Foundation (FSTRF)~~
   ~~4033 Maple Road~~
   ~~Amherst, NY 14226-1056~~
   ~~Phone: (716) 834-0900 x7249~~
   ~~Email: kearly.jenna@fstrf.org~~

2. The study site roster is updated to remove two sites and update contact details for three sites:

~~Site 5011, Boston Medical Center~~
~~Ellen Cooper, MD~~
~~Boston Medical Center~~
~~Division of Pediatric Infectious Diseases~~
~~670 Albany St., Rm. 623~~
~~Boston, MA 02118~~
~~Phone: (671) 414-5588~~
~~Email: ercooper@bu.edu~~

~~Site 5030, Emory University School of Medicine~~
~~Ann Chahroudi, MD, PhD~~
~~Division of Pediatrics Infectious Diseases~~
~~Emory University School of Medicine~~
~~E472 HSRB~~
~~1760 Haygood Dr.~~
~~Atlanta, GA 30322-1119~~
~~Phone: (404) 727-9209~~
~~Email: achahro@emory.edu~~

Site 5055, South Florida CDTC Ft. Lauderdale
~~Ana M. Puga, MD, FAAP~~ **Lisa-Gaye Robinson, MD, MPH**
Children's Diagnostic & Treatment Center, Inc.
1401 South Federal Highway
Fort Lauderdale, Florida 33316
Phone: ~~(954) 728-1017~~ **(954) 728-1136**
Email: ~~apuga@browardhealth.org~~ **lerobinson@browardhealth.org**

Site 30301, Johns Hopkins University Blantyre Clinical Research Site
~~Luis Gadama, MBBS FCOG~~ **Macpherson Mallewa, MRCPCH, PhD, DTM&H**
College of Medicine-Johns Hopkins Research Project
PO Box 1131
Blantyre, Malawi
Phone: +265 1 875 129
Email: ~~Lgadama@jhu.medcol.mw~~ **mmallewa@mlw.medcol.mw**

Site 31890, Harare Family Care
Tapiwa Grace Mbengeranwa MBChB
~~UZ-UCSF~~ **University of Zimbabwe College of Health Sciences – Clinical Trials Unit (UZCHS-CTU)**
15 Phillips Avenue
Belgravia
Harare, Zimbabwe
Email: tgmbenge@uzcrc.co.zw

3. Protocol Sections 6.2, 6.6, 6.9, 6.11, and 6.13 are updated to specify correct specimen types for HIV-1-specific antibody-dependent cellular cytotoxicity (ADCC) and virus neutralization assays. ADCC assays will be performed with serum; neutralization assays will be performed with plasma; as such, bullet points in the infant Laboratory/Blood row of the procedural tables in these sections are corrected as follows:

   - Stored serum for **ADCC** ~~neutralization assay~~

   The correct specimen types are also incorporated into the Schedule of Evaluations, as shown on the last five pages of this LoA, and into Section 6.17.1, as follows:

   In the event that blood collection must be limited, available specimens should be prioritized for use in the following order: (1) hematology, (2) chemistry, (3) HIV RNA, (4) CD4 and CD8 cell count and percentage, (5) stored PBMCs and plasma for primary evaluations, (6) stored serum for **ADCC** ~~neutralizing assays~~, (7) stored plasma and PBMCs for exploratory evaluations.

4. Protocol Sections 6.6 and 6.7 are updated to modify the allowable visit windows for the Week 14 and Week 16 Visits, as follows:

   Section 6.6
   The Week 14 Visit is targeted to take place on Day 98, counted from the date of randomization as Day 0, with ~~an allowable~~ **a preferred** window of ± 7 days **and an allowable window of -7 to +14 days.** In addition to other routine study procedures, blood is collected and stored at this visit for primary antiviral activity evaluations. **Therefore, every effort should be made to conduct this visit as close as possible to the target date and within the preferred window. If the visit cannot be conducted within the preferred window, the visit may be conducted within the allowable window with approval in advance from the CMC. Please contact the CMC as soon as possible upon awareness of any visit that may not be conducted within the preferred window.**

   Note: **The Week 14 and Week 16 allowable visit windows overlap by a period of seven days. The Week 14 Visit should preferably be conducted before this period of overlap. However, if this is not possible, the Week 14 Visit may be conducted during the period of overlap and, in this case, the Week 14 and Week 16 Visits may be combined (i.e., all Week 14 and Week 16 visit procedures may be performed on one day).**

   There is no required sequencing of procedures at this visit.

   Week 14 Visit Procedures ~~(Day 98 ± 7 days)~~
   (Day 98 ± 7 days preferred; Day 98 -7 to +14 days allowed)

   Section 6.7
   The Week 16 Visit is targeted to take place on Day 112, counted from the date of randomization as Day 0, with an allowable window of ~~± 7~~ **-7 to +14** days. There is no required sequencing of procedures at this visit.

   Week 16 Visit Procedures (Day 112 ~~± 7~~ -7 to +14 days)

   These updates are also incorporated into the Schedule of Evaluations as shown on the last five pages of this LoA (Week 14 and Week 16 visit windows updated; footnote 9 added).

5. Protocol Section 6.14 is updated to correct an internal inconsistency. For consistency with other sub-sections within Section 6 and the Schedule of Evaluations, Section 6.14 is corrected as follows:

   ARV History
   Infant ARV history is collected at the Screening Visit and updated as needed at ~~each scheduled visit~~ **the Entry Visit and at scheduled follow-up visits as indicated in Section 6 and the Schedule of Evaluations**. *[paragraph continues]*

6. In the protocol Table of Contents and Section 8.2, the section title is updated; also in Section 8.2, the fifth paragraph is corrected, as follows:

   8.2 Deferral of Study Product Administration **for Adverse Event and Toxicity Management and Resolution**

   Fifth paragraph
   Following required consultation with the CMC, and improvement or resolution of the exclusionary condition (if applicable), study product may be administered. Whenever possible, infants should be re-scheduled to return to the clinic for product administration within the allowable visit window. If the allowable window elapses **before adverse event and toxicity management requirements are met**, the site investigator should consult with the CMC~~, which may approve product administration after the allowable window~~.

7. Protocol Section 11.2 and the sample informed consent forms in Appendices II-V are updated to reflect ICH GCP E6 4.8.10(n) and current DAIDS requirements pertaining to review of study records, as follows:

   Section 11.2, fourth paragraph, first sentence
   All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, the VRC, the US Food and Drug Administration, site drug regulatory authorities, site IRBs/ECs, OHRP, and other ~~applicable~~ **US, local, and international** regulatory entities.

   Appendix II, item 22, and Appendix III, item 9
   Groups that oversee the study include:

   - *[insert name of site IRBs/ECs]*
   - *[insert name of site drug regulatory authority]*
   - *[insert name of other site drug entities that may review records]*
   - The United States National Institutes of Health and its study monitors
   - The United States Food and Drug Administration
   - The United States Office for Human Research Protections
   - The IMPAACT Network that is coordinating the study
   - **Other US, local, and international regulatory entities**

Appendix IV, item 7, and Appendix V, item 7
These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research
- **Other US, local, and international regulatory entities**

Appendix I
IMPAACT 2008 Schedule of Evaluations: Screening through Week 14

Study Visit	Screen	Entry	Entry +3d	Week 1	Week 2	Week 2+3d	Week 3	Week 6	Week 6+3d	Week 7	Week 10	Week 10+3d	Week 11	Week 14[9]
Visit Window	-30 d	Day 0	-1/+3 d	±3 d	±3 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	**-7/+14 d**
Informed consent	X													
Maternal Evaluations *(for mothers of enrolled infants who consent to blood collection)*														
Stored plasma and PBMCs for exploratory evaluations		10 mL												
Stored serum for exploratory evaluations		10 mL												
Infant Evaluations														
HIV-related testing history	X	X												
Medical/medications history	X	X		X	X		X	X		X	X		X	X
ARV history	X	X			X			X			X			X
Immunization history	X	X			X			X			X			X
Feeding history	X	X			X			X			X			X
cART adherence assessment		X			X			X			X			X
Physical examination	X	X		X	X		X	X		X	X		X	X
VRC01 administration[1] (Arm 1 only)		***X***			***X***			***X***			***X***			
Reactogenicity assessment[2]		X	X	X	X	X	X	X	X	X	X	X	X	
Confirmatory HIV nucleic acid test (if needed)	0-3 mL													
Complete blood count with differential and platelets	1 mL			1 mL			1 mL			1 mL			1 mL	1 mL
ALT, AST, ALP, creatinine	1 mL			1 mL			1 mL			1 mL			1 mL	1 mL
CD4 and CD8 cell count and percentage[3]	1 mL													1 mL
HIV-1 RNA in plasma[4] (real time)		1 mL[4]		3 mL[4]				3 mL[4]			3 mL[4]			3 mL[4]
Urinalysis		X		X										X

Appendix I
IMPAACT 2008 Schedule of Evaluations: Screening through Week 14

Study Visit	Screen	Entry	Entry +3d	Week 1	Week 2	Week 2+3d	Week 3	Week 6	Week 6+3d	Week 7	Week 10	Week 10+3d	Week 11	Week 14[9]
Visit Window	-30 d	Day 0	-1/+3 d	±3 d	±3 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	-7/+14 d
Infant Evaluations (continued)														
Stored plasma and PBMCs for primary, secondary, and other evaluations		3-5 mL[5]			1 mL			1 mL			1 mL			5 mL
VRC01 resistance (plasma)		**X**												
VRC01 level (plasma)		X			X			X			X			X
Anti-VRC01 antibodies (plasma)		X												X
HIV-1 DNA (PBMC)		X												X
HIV-1 RNA (spliced/ unspliced; PBMC)		X												X
HIV-1 RNA (inducible; PBMC)		X												
Neutralization (plasma)		X												X
ARV levels (plasma, adherence)														X
Stored serum for **ADCC**		1 mL												1 mL
Stored plasma and PBMCs for exploratory evaluations[6]		0-2 mL[6]			X[6]			X[6]			X[6]			0-2 mL[6]
Cerebral spinal fluid storage for exploratory evaluations														
Total Infant Blood Volume	**3-6 mL**	**5-9 mL**	**—**	**5 mL**	**1 mL**	**—**	**2 mL**	**4 mL**	**—**	**2 mL**	**4 mL**	**—**	**2 mL**	**12-14 mL**

Appendix I
IMPAACT 2008 Schedule of Evaluations: Week 16 through Week 48

Study Visit	Week 16[9]	Week 20	Week 24	Week 36	Week 48	Early D/C[7]	CSF Collection[8]
Visit Window	-7 to +14 d	±14 d	±14 d	±14 d	±14 d	NA	NA
Informed consent							
Maternal Evaluations ***(for mothers of enrolled infants who consent to specimen collection)***							
Stored plasma and PBMCs for exploratory evaluations							
Stored serum for exploratory evaluations							
Infant Evaluations							
HIV-related testing history							
Medical/medications history	X	X	X	X	X	X	X[8]
ARV history	X	X	X	X	X	X	
Immunization history	X	X	X	X	X	X	
Feeding history	X	X	X	X	X	X	
cART adherence assessment	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	
VRC01 administration (Arm 1 only)							
Reactogenicity assessment							
Confirmatory HIV nucleic acid test (if needed)							
Complete blood count with differential and platelets		1 mL	1 mL	0-1 mL[3]	0-1 mL[3]	1 mL[7]	
ALT, AST, ALP, creatinine		1 mL	1 mL				
CD4 and CD8 cell count and percentage[3]			1 mL	1 mL[3]	1 mL[3]	1 mL[7]	
HIV-1 RNA in plasma[4] (real time)	3 mL[4]		3 mL[4]	3 mL[4]	3 mL[4]	3 mL[4,7]	
Urinalysis			X			[X][7]	

Appendix I
IMPAACT 2008 Schedule of Evaluations: Week 16 through Week 48

Study Visit	Week 16[9]	Week 20	Week 24	Week 36	Week 48	Early D/C[7]	CSF Collection[8]
Visit Window	-7 to +14 d	±14 d	±14 d	±14 d	±14 d	NA	NA
Infant Evaluations (continued)							
Stored plasma and PBMCs for primary, secondary, and other evaluations	1 mL		7 mL		7 mL	5-7 mL[7]	
VRC01 resistance (plasma)							
VRC01 level (plasma)	X					X	
Anti-VRC01 antibodies (plasma)			X		X	X	
HIV-1 DNA (PBMC)			X		X	X	
HIV-1 RNA (spliced/ unspliced; PBMC)			X		X	X	
HIV-1 RNA (inducible; PBMC)			X		X		
Neutralization (plasma)			X		X	X	
ARV levels (plasma, adherence)			X		X	X	
Stored serum for **ADCC**			1 mL		1 mL	1 mL[7]	
Stored plasma and PBMCs for exploratory evaluations[6]	X[6]		2 mL	5 mL	7 mL	2 mL[7]	2 mL[8]
Cerebral spinal fluid storage for exploratory evaluations							X[8]
Total Infant Blood Volume	**4 mL**	**2 mL**	**16 mL**	**9-10 mL**	**19-20 mL**	**13-15 mL**	**2 mL**

Appendix I Footnotes

1. At Entry and Weeks 2, 6, and 10, for infants in Arm 1, blood collection must precede administration of VRC01.
2. Refer to Section 6.16.
3. CD4 and CD8 cell counts and percentages are generally expected to require 1 mL of blood. At sites where a complete blood count (CBC) is needed to obtain both cell counts and percentages, 1 mL may be collected to perform the CBC at Week 36 and Week 48 (at other sites, the CBC is not required at these visits).
4. At Entry, collect 1 mL and dilute as needed to perform the HIV-1 RNA assay. At all other time points, collect 3 mL and process specimen for storage of PBMCs in addition to plasma for the RNA assay, if possible.
5. At Entry, collect 3 mL for storage for primary, secondary, and other evaluations if the infant weighs <3 kg; collect 5 mL if the infant weighs ≥3 kg.
6. At Entry and Week 14, collect 2 mL for storage for exploratory evaluations only if the infant weighs ≥ 3 kg at the visit; otherwise, do not collect any blood for exploratory evaluations at these visits. At Weeks 2, 6, 10, and 16, no additional blood is collected for exploratory evaluations but any plasma and PBMCs remaining from specimens collected for primary, secondary, and other evaluations will be stored for exploratory purposes (indicated with "X^6").
7. Refer to Section 6.13. Infants who are withdrawn or terminated before completing the Week 24 Visit should have urinalysis performed and 5 mL of blood drawn for storage for primary, secondary, and other evaluations; infants who are withdrawn or terminated after the Week 24 Visit should not have urinalysis performed and should have 7 mL of blood drawn for storage for primary, secondary, and other evaluations. For all infants, laboratory evaluations that have been performed within the two weeks prior to the Early D/C Visit need not be repeated.
8. Refer to Section 6.12.
9. **The Week 14 Visit is targeted to take place on Day 98, with a preferred window of ±7 days and an allowable window of -7 to +14 days. Every effort should be made to conduct this visit as close as possible to the target date and within the preferred window. If the visit cannot be conducted within the preferred window, the visit may be conducted within the allowable window with approval in advance from the CMC. Also note that the Week 14 and Week 16 allowable visit windows overlap by a period of seven days. The Week 14 Visit should preferably be conducted before this period of overlap. However, if this is not possible, the Week 14 Visit may be conducted during the period of overlap and, in this case, the Week 14 and Week 16 Visits may be combined (i.e., all Week 14 and Week 16 visit procedures may be performed on one day)**