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LETTER OF AMENDMENT

DATE: September 24, 2018

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5369 Protocol Team

SUBJECT: Letter of Amendment # 1 for Protocol A5369, Version 1.0, 03/09/18, entitled "HIV-1-Gag Conserved-Element DNA Vaccine (p24CE) as Therapeutic Vaccination in HIV-Infected Persons with Viral Suppression on Antiretroviral Therapy"

The following information affects the A5369 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.

This LOA is being implemented for the following reasons:

1. The FDA, requested that Permanent and Premature Treatment Discontinuation section be changed. In response, the following section has been updated: 9.1.
2. The FDA requested that the team change the Study Suspension Rule be modified to include study-stopping criteria. In response, the following section has been updated: 10.5.
3. A team decision has been made to make the protocol consistent with the electroporation device instructions. In response, the following sections have been updated: 4.2.5, 4.2.18, 4.2.19, 5.1, 5.2, 6.3.5, 6.3.10, 10.7.3, and the Sample Informed Consent.

4. A team decision has been made to comply with the specimen requirements for the advanced flow assay. In response, the following section has been updated: 6.1.
5. A team decision has been made to clarify adverse event collection requirements. In response, the following section has been updated: 7.2.
6. A team decision has been made to correct the language in sections 5.2 and 13.4.
7. A team decision has been made to confirm that both the HIV vaccines and the injection device are experimental. In response, section 5.2 and the “WHY IS THIS STUDY BEING DONE?” section of the Sample Informed Consent has been updated.
8. A team decision has been made to modify the lay language to make it easier to understand. In response the “WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?” section of the Sample Informed Consent has been updated.
9. A team decision has been made to correct the volumes of blood to be collected. In response the “WHAT DO I HAVE TO DO IF I AM IN THIS STUDY” section of the Sample Informed Consent has been updated.

The following are changes (noted in bold or strikethrough) to A5369, Version 1.0, 03/09/18. These changes will be included in the next version of the A5369 protocol if it is amended at a future date.

TABLE OF CONTENTS

1. Section 4.2.5

   To be consistent with the electroporation device instructions the team decided to change the language in section 4.2.5 to: A skin-fold measurement of the cutaneous and subcutaneous tissue for eligible injection sites (on the medial deltoid or **vastus lateralis** muscles) that **does not** exceed~~s~~ ~~40~~ **50** mm.

2. Section 4.2.18

   To be consistent with the electroporation device instructions the team decided to change the language in section 4.2.18 to: Extensive tattoos covering the site of administration (upper left and right medial deltoid muscles and **left and right vastus lateralis muscles**).

3. Section 4.2.19

   To be consistent with the electroporation device instructions the team decided to change the language in section 4.2.19 to: Presence of any surgical or traumatic metal implants at the site of administration (medial deltoid or **vastus lateralis** muscles).

4. Section 5.1

   To be consistent with the electroporation device instructions for the team decided to change the language in section 5.1 to:

   ARM 1: p24CE1/2 pDNA 4 mg administered by one injection/electroporation **in the medial deltoid or vastus lateralis muscles** at week 0 and week 4

   Then
   p24CE1/2 pDNA 2 mg admixed with full-length p55gag pDNA 2 mg administered by one injection/electroporation **in the medial deltoid or vastus lateralis muscles** at week 12, and week 24.

   ARM 2: full-length p55gag pDNA 4 mg administered by one injection/electroporation **in the medial deltoid or vastus lateralis muscles** at week 0, week 4, week 12, and week 24.

   ARM 3: Placebo (Sodium Chloride for Injection, USP 0.9%) 1 mL administered by one injection/electroporation **in the medial deltoid or vastus lateralis muscles** at week 0, week 4, week 12, and week 24.

5. Section 5.2

   The language in the third paragraph after the “Placebo section” is updated to include the following language indicating that the electroporation device is experimental:

   Intramuscular TriGrid Delivery System (TDS-IM v2.0) (ICHOR Medical Systems, San Diego, California), a device for electroporation mediated intramuscular administration of

DNA based-biologic candidates. **The injection device is experimental and has not been approved by the FDA.** TDS-IM v2.0 Stimulator and Applicator which are reusable components, will be provided to the clinic by arrangement with the ACTG Leadership and Operations Center.

The language in the 4th paragraph under ARM 1 Week 12 and Week 24, second sentence is revised to include a missing word:

Withdraw 0.6 mL from the vial of p55gag pDNA (4 mg/mL) with a 1 mL low void 25 Ga syringe and inject this into the mixing **vial**.

The language in the 4th paragraph under ARM 2: Week 0, Week 4, Week 12, and Week 24 p55gag pDNA is corrected read:

Remove syringe cap from the glass syringe and add a slip-tip needle. Using aseptic technique, withdraw sufficient quantity fluid from each of the two vials of **p55gag pDNA** (4 mg/mL) to load the glass syringe with 1 mL.

6. Section 6.1

To comply with the requirement that advanced flow analysis requires that a WBC with differential be obtained at the same time protocol section 6.1 Schedule of Evaluations will be updated to include a WBC with differential to the Pre-Entry and Week 6 study visits.

Evaluation	Screening	Pre-Entry	Entry (Week 0)	Post-Entry Evaluations (Weeks)												Premature Treatment/ Study Discontinuation Evaluations
				Post Vaccination #1	4	Deferred Week 4 (See section 6.3.10)	Post Vaccination #2	6	12	Deferred Week 12 (See section 6.3.10)	Post Vaccination #3	24	Deferred Week 24 (See section 6.3.10)	Post Vaccination #4	26	48	
Hematology	X	**X**	X		X	X		**X**	X	X		X	X		X	X	X

7. Section 6.1

To comply with the requirement that advanced flow analysis requires that CD4/CD8 be obtained at the same time protocol section 6.1 Schedule of Evaluations will be updated to include a CD4/CD8 at the Week 6, 26, and 48 study visits.

Evaluation	Screening	Pre-Entry	Entry (Week 0)	Post-Entry Evaluations (Weeks)												Premature Treatment/ Study Discontinuation Evaluations
				Post Vaccination #1	4	Deferred Week 4 (See section 6.3.10)	Post Vaccination #2	6	12	Deferred Week 12 (See section 6.3.10)	Post Vaccination #3	24	Deferred Week 24 (See section 6.3.10)	Post Vaccination #4	26	48	
CD4+/CD8+	X	X	X					**X**	X	X		X	X		**X**	**X**	X

8. Section 6.3.5

   To be consistent with the electroporation device instructions the team decided to change the language in section 6.3.5 Skin Pinch to: The skin pinch test measures the thickness of the cutaneous and subcutaneous tissue at the injection site of both upper arms (medial deltoid **or vastus lateralis** muscles).

9. Section 6.3.10

   To be consistent with the electroporation device instructions for use the team decided to change the language in section 6.3.10 Study Vaccine/Placebo Administration and Evaluation Vaccine Administration will be changed to: All vaccinations including modifications and permanent discontinuations must be documented. The vaccine is to be administered via IM injection in the outer aspect of the upper arm (deltoid) **or thigh (vastus lateralis)**. Details of all vaccinations, including the time the vaccine vial is removed from the freezer, reconstituted, administered, and route of administration are to be documented in the source documents.

10. Section 7.2

    The following NOTE will be added to section 7.2 Adverse Event Collection Requirements for this Protocol:

    NOTE: All AEs relating to the vaccine must be recorded on an eCRF and keyed within 2 days.

11. Section 9.1

    The FDA recommends that section 9.1 Permanent and Premature Treatment Discontinuation be changed to include: **A plasma HIV-1 RNA >1,000 copies/mL confirmed by a second consecutive reading.**

12. Section 10.5

    The FDA recommends that section 10.5 Study Suspension Rule be modified to include a third bullet: **Study Stopping Criteria: Two or more participants experience a viral load rebound plasma HIV-1 RNA >1,000 copies/mL confirmed by a second consecutive reading.**

13. Section 10.7.3

    To be consistent with the electroporation device instructions the team decided to change the language in the last sentence in the last paragraph in section 10.7.3 Secondary Analyses to: Also, the participant ratings of pain will be described a) when the device was placed on the participant's skin and the vaccine/placebo was injected, b) at the time of the electrical stimulation and muscle contraction, c) 10 minutes and 30 minutes after the procedure was completed, by treatment arm, and the left and right deltoid **or left and right vastus lateralis** separately.

14. Section 13.4

The language in section 13.4 will be corrected to:

~~This protocol was submitted to the Office of Biotechnology Activities (OBA) in accordance with Appendix M of the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines 2009) http://oba.od.nih.gov/rdna/nih_guidelines_oba.html. The protocol (#1004-1038) was reviewed by the NIH Recombinant DNA Advisory Committee (RAC) as notified by the OBA on May 4, 2010.~~

Because this study is evaluating products containing recombinant or synthetic DNA, it must comply with regulations set forth in the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (April 2016). Information about the study must be submitted to site Institutional Biosafety Committees (IBCs) and Institutional Review Boards/Ethics Committees (IRBs/ECs) Investigators at each site are responsible for obtaining IBC approval per NIH Guidelines section IV-B7-a-(1). IBC review and approval must be documented by the investigator and submitted as part of DAIDS's initial protocol registration for this trial before participants are enrolled at the site. If this protocol is amended, investigators should follow the requirements of their IBC.

Based on Appendix M-III-A of the NIH Guidelines, DAIDS has determined that the vaccine products used in this clinical trial are exempt from the requirements of submission of the protocol to the NIH Office of Science Policy and subsequent review by and reporting to OSP (Appendix M-I of the NIH Guidelines).

~~The Principal Investigators and the institution are responsible for ensuring that no research subjects are enrolled in the protocol until Institutional Biosafety Committee (IBC) approval, IRB approval and all applicable regulatory authorizations have been obtained.~~

~~The current reporting requirements set forth in Appendix M-I-C-1 of the NIH Guidelines require the Principal Investigator to submit additional documentation as specified to the OBA.~~

~~Within 20 working days of enrolling the first participant in the trial, the investigator at the first site must provide OBA with the documents and information listed below (per Appendix M-I-C-1 of the NIH Guidelines).~~

- ~~A copy of the protocol approved by the IBC and IRB~~
- ~~A copy of the informed consent approved by the IRB~~
- ~~A copy of the IBC approval of the clinical site~~
- ~~A document outlining the responses to the RAC's recommendations (if any) and any modification to the protocol required by the FDA~~
- ~~The IND number~~
- ~~The NIH grant number~~
- ~~The date of the initiation of the trial~~

~~The guidelines allow for formal delegation of all or part of the investigator reporting~~

~~requirements (Appendix M-I-C-4 of the NIH Guidelines).~~

~~When adding new sites to the clinical trial, no research participant should be enrolled at the site until the following documentation has been submitted to the OBA:~~

- ~~IBC approval from the clinical site~~
- ~~IRB approval~~
- ~~IRB-approved informed consent document~~
- ~~Curriculum vitae of the Principal Investigator(s) – no more than two pages in biographical sketch format~~
- ~~NIH grant number(s) if applicable~~

~~During the conduct of the study, the principal investigator is responsible for providing OBA with safety reports and annual report. In such cases, OBA requires that these documents follow the timelines for submission and format of the homologous FDA mandatory reports.~~

~~All information communicated to the OBA is publically available unless it is clearly labeled as confidential. Since annual reports to the FDA may contain proprietary information, the product manufacturer will edit the annual report to remove any proprietary information prior to submission to OBA. The DAIDS medical officer will sign off on the redacted annual report before submission to OBA.~~

~~The safety reports can be sent simultaneously to the FDA and OBA by the RSC SAE Office.~~

15. Appendix I, Sample Informed Consent

    The **language in the** second paragraph in the “WHY IS THIS STUDY BEING DONE?” section is changed to read:

    The HIV vaccines **and injection device** used in this study **are** experimental. This means that neither the vaccines **nor the injection device** have been approved by the Food and Drug Administration (FDA).

16. Appendix I, Sample Informed Consent

    To be consistent with the electroporation device instructions for use the team decided to change the language in the fourth bullet in the “WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?” “At the screening visit” section to read:

    You will have a skin pinch test to measure the thickness of the skin on your upper arm **or upper thigh** muscles. This test will also measure the right depth when giving the injections in the upper arm **or upper thigh** muscles.

17. Appendix I, Sample Informed Consent

    The first paragraph in the “WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?” “Study Injections” section is changed to read:

When you enter the study, you will be placed into one of the three groups. You will be randomized 2:1:1 (by chance) to receive either the p24CE1/2 pDNA vaccine (an HIV vaccine **that contains the gene that makes parts of the HIV protein that are the same in all samples of HIV virus**) followed by p24CE1/2 + full-length Gag pDNA vaccine (a different HIV vaccine **that contains the gene for the whole HIV protein, which can be slightly different from one HIV virus to the next**), OR the full-length Gag pDNA vaccine alone, OR placebo (the placebo is a salt solution that does not contain any vaccine, medicine, or drugs).

18. Appendix I, Sample Informed Consent

To be consistent with the electroporation device instructions for use the team decided to change the language in the first sentence in the "WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?" "Electroporation EP Procedure" section to read: To improve the effectiveness of the vaccine, instead of a regular needle and syringe, a small, hand-held device will be used to inject the vaccine or placebo into your upper arm **or thigh** muscle.

19. Appendix I, Sample Informed Consent

To correct the volume of blood to be collected the first bullet in the "WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?" "At the pre-entry visit" section is changed to read: You will have a total of about ~~3~~ **14** tablespoons of blood drawn from a vein in your arm. To clarify that participants having leukapheresis performed at this visit will not have this blood collection the following is added:

NOTE: If you are having leukapheresis performed at this visit, you will have a reduced volume of additional blood collected.

20. Appendix I, Sample Informed Consent

To correct the volume of blood to be collected the fourth bullet in the "WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?" "At the entry visit" section is change to read: You will have a total of about ~~4~~ **11** tablespoons of blood drawn from a vein in your arm.

21. Appendix I, Sample Informed Consent

To correct the volume of blood to be collected the last sentence in the third paragraph in the "WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?" "During the study" section is changed to read: You will have between 2 and **14** tablespoons of blood drawn at each visit. To clarify that participants having leukapheresis performed at the week 26 visit will not have blood collected at that visit the following is added:

NOTE: If you are having leukapheresis performed at the week 26 visit, you will have a reduced volume of blood collected at that visit.

22. Appendix 1, Sample Informed Consent

To be consistent with the electroporation device instructions for use the team decided to update the language in the Risks of Injections:

- Arm discomfort
- Bleeding or bruising at the spot where the needle enters your body
- Small risk of fainting or infection
- Stinging, pain, soreness, redness, itching, swelling, burning, warmth at injection site
- Induration (hardness under the skin) at the site where the vaccine/placebo is given
- **Brief twitching/contraction of the upper arm or thigh muscle where the injection is given.**

23. Appendix I, Sample Informed Consent

    To be consistent with the electroporation device instructions for use the team decided to change the language in the first bullet of the Risks of EP Procedure to: Brief twitching/contraction of the upper arm **or thigh** muscle where the vaccination is given will occur during the ~~the~~ EP procedure. This may result in a painful sensation, which should last only a few seconds.

24. Appendix I, Sample Informed Consent

    In the “WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?” section based on FDA recommendations the team added the following bullet: You have **a plasma HIV-1 RNA >1,000 copies/mL confirmed by a second consecutive reading.**

25. Protocol Signature Page

    Per a new regulatory requirement by the Division of AIDS (DAIDS), a Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

HIV-1-Gag Conserved-Element DNA Vaccine (p24CE) as Therapeutic Vaccination in HIV-Infected Persons with Viral Suppression on Antiretroviral Therapy

SIGNATURE PAGE

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 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.

Principal Investigator: _____
Print/Type

Signed: _____Date: _____
Name/Title