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LETTER OF AMENDMENT

DATE: April 16, 2019

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators at A5369 Protocol-Specific Sites

FROM: A5369 Protocol Team

SUBJECT: Letter of Amendment #2 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 Division of AIDS (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:

- To revise the requirement for leukapheresis evaluation; to update other sections and the sample informed consent accordingly.
- To revise the plasma HIV-1 RNA inclusion criterion.
- To clarify the preferred method and options for urinalysis testing.
- To remove the Immunology Quality Assurance (IQA) requirement for CD4/CD8 T cell testing.
- To allow for additional pre-leukapheresis testing as needed.

1. Section 3.0, STUDY DESIGN, is revised as shown below. The protocol is limiting enrollment to three participants per site until 60 days after the last participating site is activated. Noting the importance of leukapheresis evaluation for this study, the protocol is updated to note that the first three participants enrolled at each site are required to have leukapheresis at pre-entry and at week 26 until at least 60 days after the last participating site is activated and at least 50% of the target accrual has agreed to the leukaphereses.

   A5369 is a phase I/IIa, randomized, double-blinded, placebo-controlled study in which 40 study participants will be randomized 2:1:1 to the p24CE/full-length *gag*DNA vaccine arm versus full-length *gag*DNA vaccine arm versus placebo arm. HIV-specific immunologic assays will be done at baseline and after the last dose of vaccine. Cells and plasma will also be obtained after the second prime vaccine dose, processed, and stored. Immunologic assays may be performed at this timepoint depending on the results of the assays done at baseline and after the last dose of vaccine. HIV-1 reservoir assays will be done at baseline and after the last dose of vaccine. ~~Enrollment slots for participants agreeing to have leukaphereses will be reserved for a minimum of 20 participants. These participants are required to have leukapheresis at both the pre-entry and week 26 visit~~. **Until 60 days after the last participating site is activated, each site will be limited to three participants in screening/enrollment at any given time. During this time period, these first three participants at each site will be required to agree at the screening visit to undergo the leukaphereses at the pre-entry and week 26 timepoints. Once the 60 day period after the last participating site is activated has passed, and at least 50% of the target accrual has agreed to undergo the leukaphereses, a study participant agreeing to the leukaphereses will be optional but highly recommended. The study team will inform the participating sites when this leukapheresis-optional period has begun.**

2. Section 4.1.5 is revised as shown below. This revision is to allow sites to enroll participants who meet other eligibility criteria except for the HIV-1 RNA value unavailable for one of the two windows mentioned below.

   4.1.5 One documented plasma HIV-1 RNA that is below the limit of detection of an FDA-approved assay between 24 and 36 months prior to the screening HIV-1 RNA **and/or** one documented plasma HIV-1 RNA that is below the limit of detection of an FDA-approved assay between 12 and 24 months prior to the screening HIV-1 RNA, and one documented HIV-1 RNA that is below the limit of detection of an FDA-approved assay collected fewer than 12 months prior to the screening HIV-1 RNA (see section 4.1.6).

   NOTE: A single, unconfirmed plasma HIV-1 RNA above the limit of detection but <400 copies/mL is allowed if followed by an HIV-1 RNA below detectable limits, but not in the 6 months prior to screening.

   NOTE: One documented plasma HIV-1 RNA that is below the limit of detection between 24 and 36 months prior to the screening HIV-1 RNA and one

between 12 and 24 months prior to the screening HIV-1 RNA are preferred. However, in cases where a plasma HIV-1 RNA is not available in one of these windows, but there has been uninterrupted ART during the window and suppressed HIV-1 RNA before and after the window, the participant may be enrolled.

3. Section 4.1.16 is revised as shown below.

   4.1.16 Indication of willingness to have the leukapheresis procedure.

   NOTE: **Until 60 days after the last participating site is activated, each site will be limited to three participants in screening/enrollment at any given time. During this time period, these first three participants at each site will be required to agree at the screening visit to undergo the leukaphereses at the pre-entry and week 26 timepoints. Once the 60 day period after the last participating site is activated has passed, and at least 50% of the target accrual has agreed to undergo the leukaphereses, a study participant agreeing to the leukaphereses will be optional but highly recommended. The study team will inform the participating sites when this leukapheresis-optional period has begun.** ~~Leukapheresis will be required if the study has reached 50% of the accrual target and less than 20 participants have agreed to have the leukapheresis procedure.~~

4. Section 4.2.5, updated via LOA #1, is revised to make a wording error correction as shown below.

   4.2.5 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** 50 mm.

5. Section 6.1, Schedule of Evaluations, is updated as shown below.

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	
Leukapheresis (~~Optional~~ **see section 6.3.14**)		X													X		

6. Under section 6.3.7, Laboratory Evaluations, Urinalysis is revised as shown below.

   Urinalysis
   Dipstick ~~only~~ **alone is acceptable; other methodologies are also acceptable. Sites may perform a laboratory urinalysis if needed to meet site-specific requirements.**

7. Under section 6.3.8, Immunologic Studies, CD4/CD8 is revised as shown below.

   CD4/CD8
   Obtain absolute CD4/CD8 T cell count and percentages within 60 days prior to entry from a laboratory that possesses a CLIA certification or equivalent.

   For entry and post-entry evaluations, all laboratories must possess a CLIA certification or its equivalent ~~and must be certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program~~.

8. Section 6.3.14, Leukapheresis (Optional), is revised as below. In addition, a NOTE is added to this section.

   6.3.14 Leukapheresis ~~(Optional)~~

   Leukapheresis will be performed at pre-entry and week 26. **Until 60 days after the last participating site is activated, each site will be limited to three participants in screening/enrollment at any given time. During this time period, these first three participants at each site will be required to agree at the screening visit to undergo the leukaphereses at the pre-entry and week 26 timepoints. Once the 60 day period after the last participating site is activated has passed, and at least 50% of the target accrual has agreed to undergo the leukaphereses, a study participant agreeing to the leukaphereses will be optional but highly recommended. The study team will inform the participating sites when this leukapheresis-optional period has begun.** ~~Enrollment slots for participants agreeing to have leukapheresis will be reserved for a minimum of 20 participants. Participants agreeing to have leukapheresis performed at pre-entry are also required to have leukapheresis performed at week 26.~~

   NOTE: Sites may perform additional pre-leukapheresis testing (e.g., PT/INR) to meet site-specific requirements.

9. Several sections in APPENDIX I, SAMPLE INFORMED CONSENT, are revised as shown below.

   Screening
   If you decide to take part in this research study, you will be asked to sign this consent form. You will come to the clinic to have a screening visit. Tests will be done at the screening visit to see if it is safe for you to join the study. The screening visit will take about 1 hour, but it may be shorter or longer. **Prior to**

screening or at Screening visit, the site staff will inform you whether leukapheresis is required.

Pre-Entry
If you qualify for the study, you will return to the clinic ~~about 2 weeks~~ after your screening visit **for a Pre-Entry visit**. The visit is expected to last between 3 to 4 hours

At the pre-entry visit:

- You will have a total of about 3 tablespoons of blood drawn from a vein in your arm.
- You will have blood collected and stored for future immunologic testing (to measure the body's ability to fight infection).
- You will have a pregnancy test done, if you are a woman able to become pregnant.
- You will have blood collected to measure CD4/CD8 T cell counts (the number of white blood cells that fight infection).
- You will have blood collected for human leukocyte antigen (HLA) typing and testing.
- You will have blood stored for future tests.
- If you ~~agree~~ **are one of the first 3 participants to be enrolled at your site** you may be required to have leukapheresis performed (your site can tell you if you will be required to have leukapheresis). You will also be required to have a leukapheresis performed at the week 26 visit. By collecting blood using this procedure, researchers are able to get many more white blood cells than is usually possible. **If you are not required to have leukapheresis, this procedure is optional but highly recommended.**
- If you agree, you will have stool samples collected to study the different kind of bacteria in your stool. These samples will be stored and will be tested after the study is over. You will not be given the results. (This test is optional)

10. Protocol Signature Page

Per a regulatory requirement by the DAIDS, a Protocol Signature Page (PSP) is appended for submission to the 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