**SUMMARY OF CHANGES**

**INCLUDED IN THE FULL VERSION PROTOCOL AMENDMENT OF**

**MTN-033**

**An Open Label Randomized Phase 1 Pharmacokinetic Study of Dapivirine Gel Administered Rectally to HIV-1 Seronegative Adults**

**DAIDS Protocol #12065**

**IND # 136320**

**THE AMENDED PROTOCOL IS IDENTIFIED AS: Version 2.0 / 8 December 2017**

**Information/Instructions to Study Sites**

The information contained in this protocol amendment impacts the MTN-033 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-033.

**Summary of Revisions**

A summary of revisions is provided below:

* + 1. The IND holder changed from International Partnership for Microbicides (IPM) to DAIDS, resulting in several consequent changes in the document, including, for example, each place the IND Sponsor was mentioned, a change in study designation from MTN-033/IPM 044 to MTN-033, a change in IND# from 69,022 to 136320, limitation of IPM’s protocol-designated role to publication review, and addition of informed consent form review to DAIDS’s protocol-designated responsibilities.
    2. New, clarified, or updated data regarding DPV rings, films and gels was added, including data from FAME-02B, IPM 032, IPM 035, IPM 036, recently released data from MTN-020 (ASPIRE) and IPM 027 (The Ring Study), and updated Investigator’s Brochure (IB) data.
    3. The Male Genital Grading Table for Use in Microbicide Studies (Addendum 2 to the DAIDS AE Grading Table) was added to the list of Grading Tables to be used for AE determination in this study.
    4. Eligibility criteria was edited for clarity as follows:

Rectal product studies added to list of prohibited co-enrollment studies.

“Unprotected RAI” changed to “RAI without a condom”.

Use of all CYP3A inducers and inhibitors will be prohibited, rather than excluding use of strong CYP3A inducers and inhibitors only.

Use of hormone-replacement therapy in tablet, injectable or gel form will be excluded.

* + 1. Study visit procedure language was edited for clarity and consistency as follows:

Rectal enema effluent samples will be collected for pharmacokinetics (PK) as well as pharmacodynamics (PD) at the same visits.

Added asterisk (\*) to physical exam weight assessment in Section 7.7.

* + 1. Edits to Section 11.1 were made to change the data management system used in this study from DataFax to Medidata Rave EDC, an electronic data capture system compliant with US-EU Safe Harbor, the EU Data Protection Directive 95/46/EC, ICH GCP and CFR requirements.
    2. Participant confidentiality language in Section 12, Section 13 and Appendix III was updated to explicitly allow international regulatory authorities to review study-related documents.
    3. The Investigator Signature Form (p. 17) was edited to include newly required language as per DAIDS’s updated policy.
    4. The protocol has been updated to refer to the most recent revision of the DAIDS Table for Grading Adult and Pediatric Adverse Events (now Corrected Version 2.1, July 2017).
    5. Other information has been added or updated for clarity and/or consistency:

Section 6.2 was updated to clarify that participants using the coital simulation device can apply the gel onto the device, the anus, or both.

“Anogenital STIs” changed to “Anorectal STIs” in Section 9.3.

“Reported use of systemic immunomodulatory medications” and “reported use of PEP or PrEP” have been removed from Section 9.3.

Section 10.4 was updated to include the timing of sample collection at dosing visits in the description of the randomization plan.

Risk language for phlebotomy and rectal biopsy collection was updated in Section 13.4.1 and Appendix III, and redundant rectal biopsy collection language was deleted.

Risk language for dapivirine gel was updated in Appendix III and Section 13.4.1 for consistency between the two sections and to coincide with risk language in MTN-026, another Phase 1 study evaluating the same gel formulation as MTN-033.

Other minor updates, corrections, and clarifications are also incorporated into the document, including update of website addresses for NIAID and DAIDS, update of the Protocol Team Roster, and update of protocol document formatting to meet DAIDS-preferred Electronic Common Technical Document (eCTD) guidelines.