

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

MTN-042

**Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral
TRUVADA® Use in Pregnancy**

DAIDS Protocol #38544

IND #139,598

THE AMENDED PROTOCOL IS IDENTIFIED AS: Version 2.0/ May 20, 2021

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-042 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-042.

Rationale

The HIV prevention landscape has changed substantially since the MTN-042 study protocol was approved. Recent years have seen an increased call for better drug safety data during pregnancy and for ethical inclusion of pregnant women in clinical research. Furthermore, the DPV VR has received a positive scientific opinion from the EMA under Article 58 for use as an HIV prevention method by cisgender women ages 18 and older in low- and middle-income countries, and the WHO has included the DPV VR on its prequalification list of medicines as well as formulated a conditional recommendation supporting offering of the DPV VR as an HIV prevention option. IPM is seeking regulatory approval of the ring in several African countries through WHO's Stringent Regulatory Authorities Collaborative Review process, and the first in-country decisions are likely to be issued as early as mid-2021. Prescribing information for the DPV VR will likely indicate a preference to avoid the use of the DPV VR during pregnancy, but still allow the healthcare provider to exercise their discretion if they consider that the woman and/or her unborn child are at high risk of HIV-1 infection.

Should the ring be approved, there will likely be women exposed to the DPV VR during pregnancy either due to not yet realizing they are pregnant or because they are at high risk of HIV acquisition and they and their providers agree the benefits of ring use outweigh the potential risks. Providing safety data on DPV VR use by pregnant women is therefore more urgent, and the long pause between Cohorts 3 and 4 is a concern. While the 4-step design was optimal when the protocol was first developed, it is now unnecessarily complex, and if the DPV VR is approved, the delay between Cohorts 3 and 4 will needlessly postpone the availability of data during DPV VR rollout in African countries. Recently published results

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from the DPV VR open-label studies and MTN-023 have added to the existing literature on its use for HIV prevention, providing further evidence of its favorable safety profile.

This protocol modification will collapse Cohorts 3 and 4 into a new combined Cohort 3, with 200 participants randomized to the DPV VR and 50 participants randomized to oral Truvada. This combined Cohort 3 would encompass the gestational ages at enrollment (12-29 6/7 weeks) originally included in both Cohorts 3 and 4 so would provide safety data covering all of the initially planned gestational ages. Efforts will be made to ensure that entire gestational age range is represented among the enrollments. There are no changes to safety monitoring included in this modification. The proposed changes should allow the study to enroll and complete follow-up for all participants through delivery by early 2023. This will expedite the availability of safety data for DPV VR use by pregnant women, which will be critical to inform product rollout should the DPV VR be approved for HIV prevention. To further that goal, the team also proposes publishing safety data from each of the two earlier Cohorts as soon as they are available.

Summary of Revisions

A summary of revisions is provided below:

1. Merged Cohorts 3 and 4 into Cohort 3 – Sample Size, Study Design, Study Duration, Study Regimen, and Figures 3 and 4 in Protocol Summary; Section 4.1 (Identification of Study Design); Section 4.3 (Description of Study Population); Section 4.4 (Time to Complete Accrual); Section 4.5 (Expected Duration of Participation); Section 5.1 (Selection of the Study Population); Section 6.1 (Regimen) and Figure 5 in Section 6.1 (Regimen); Figures 8 and 9 in Section 7 (Study Procedures); Table 3 in Section 7.3 (Visit 2: Enrollment Visit [Day 0]); Section 7.4.2 (Bi-weekly Visits After 36th Week of Gestation) and Table 5 in Section 7.4.2 (Bi-weekly Visits After 36th Week of Gestation); Section 7.4.3 (2-week Visit [Cohorts 2-4]) and Table 6 in Section 7.4.3 (2-week Visit [Cohorts 2-4]); Section 7.4.4 (4-week Visit[s][Cohorts 2-4]) and Table 7 in Section 7.4.4 (4-week Visit[s][Cohorts 2-4]); Table 8 in Section 7.5.1 (Post-Pregnancy Outcome [PPO] Visit); Section 7.9 (Behavioral Evaluations); Section 10.1 (Overview and Summary of Design); Section 10.4 (Sample Size and Power Calculations); Section 10.4.1 (Primary Endpoints – Maternal and Infant Safety) and Tables 17 and 18 in Section 10.4.1 (Primary Endpoints – Maternal and Infant Safety); Section 10.5 (Participant Accrual, Follow-up and Retention); Section 10.6 (Randomization); Section 10.8.1 (Primary Analyses); Appendix I (Table of Visits and Study Procedures – Mothers); “Who will be in this research study?” section in Appendix V (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 1), Appendix VI (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 2), Appendix VIII (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 4) and Appendix IX (Sample Informed Consent Form [Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography] –Infant); “What will I be asked to do if I join this research study?” section in Appendix VIII (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 4); Deletion of Appendix VII (Sample Informed

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Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 3)

- Removed references to Cohort 4
 - Extended the combined Cohort 3 and Cohort 4 gestational age eligibility window from 12-19 6/7 weeks to 12-29 6/7 weeks
 - Reduced the combined Cohort 3 and Cohort 4 sample size from 450 to 250 participants and overall study sample size from 750 to 550 participants
 - Modified the combined Cohort 3 and Cohort 4 product arm randomization from 2:1 (VR:tablet) to 4:1 (VR:tablet)
 - Updated expected overall study duration from 38-50 months (49-61 months including one-year infant follow-up) to 37-45 months (48-56 months including one-year infant follow-up)
2. Updated rationale of study design to justify merging of Cohorts 3 and 4 and modified product arm randomization for the combined Cohort 3 and Cohort 4 – Section 2.9 (Rationale for Study Design)
 3. Updated information on DPV VR licensing status – Section 2.2.1 (DPV VR); Section 2.9 (Rationale for Study Design); Section 13.4.2 (Benefits); “Study Products” section in Appendix V (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 1), Appendix VI (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 2), Appendix VIII (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 4) and Appendix IX (Sample Informed Consent Form [Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography] –Infant)
 4. Updated information on DPV VR and Truvada use during pregnancy – Section 2.1 (Pregnancy and HIV in Sub-Saharan Africa); Section 2.5 (Clinical Studies – DPV); Section 2.5.3 (Phase 3 Studies of DPV); Section 2.6.2 (Phase 3 Studies of FTC with TDF); Section 2.8.1 (DPV VR)
 5. Corrected the visit window for 1-week PPO Phone Contact to align with the visit window for Post-Pregnancy Outcome Visit – Section 7.5.2 (1-week PPO Phone Contact)
 6. Extended the window for conducting in-depth interviews (IDI) for Cohort 2 and the combined Cohort 3 and Cohort 4 to align with the IDI window for Cohort 1 – Legend in Table 7 in Section 7.4.4 (4-week Visit[s] [Cohorts 2-4]); Section 7.9 (Behavioral Evaluations); Legend in Appendix I (Table of Visits and Study Procedures – Mothers)
 7. Corrected the instruction to participants to bring the ring to the delivery facility with them when they go to deliver – Section 7.4.2 (Bi-weekly Visits After 36th Week of Gestation)
 8. Clarified the follow-up visit procedures for participants who discontinue product use due to pregnancy loss – Section 7.7.2 (Participants Who Experience a Pregnancy Loss)
 9. Clarified that lochia during the post-partum period will not be reportable as an adverse event – Section 8.3.1 (Adverse Events)
 10. Clarified that pregnancy loss and report of admission to care for labor and delivery management are considered scheduled product discontinuations rather than early product discontinuations – Section 9.3 (General Criteria for Temporary/Permanent Discontinuation of Study Product)

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11. Updated references to “Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials” and “Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites” with references to “Site Clinical Operations and Research Essentials (SCORE) Manual” per recent DAIDS guidance – Section 11.2 (Source Documents and Access to Source Data/Documents); Section 11.3 (Quality Control and Quality Assurance); Section 13.5 (Informed Consent Process)
12. Updated description of clinical site monitoring to allow remote site monitoring per recent DAIDS guidance – Section 12 (Clinical Site Monitoring)
13. Revised pregnancy complication secondary endpoint of “peripartum and postpartum hemorrhage” to align with Medical Dictionary for Regulatory Activities (MedDRA) categories of “antepartum, intrapartum and postpartum hemorrhage” – Secondary Endpoint of Pregnancy Complications in Protocol Summary; Secondary Endpoint of Pregnancy Complications in Section 4.2 (Summary of Major Endpoints); Pregnancy Complications in Section 10.2.2 (Secondary Endpoints); Section 10.7 (Data and Safety Monitoring Procedures)
14. Reconciled inconsistencies between protocol sections per DAIDS Amendment Regulatory Review – Section 2.5.2 (Phase 1 and 2 Studies of DPV); Table 3 in Section 7.3 (Visit 2: Enrollment Visit [Day 0]); Section 9.5 (Other Clinical Findings); “Study Supplies/Products” section in Appendix I (Table of Visits and Study Procedures – Mothers); “Clinical” section in Appendix II (Table of Visits and Study Procedures – Infants)
15. Reconciled inconsistencies between the protocol sections and the protocol informed consent forms per DAIDS Amendment Regulatory Review – “Study Products” and “Risks and/or Discomforts” sections in Appendix V (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 1), Appendix VI (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 2), Appendix VIII (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 4) and Appendix IX (Sample Informed Consent Form [Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography] –Infant); “Why you may stop taking the study drug early or be asked to leave the study” section in Appendix V (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 1), Appendix VI (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 2) and Appendix VIII (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 4); “What will I be asked to do if I join this research study?” section in Appendix VI (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 2) and Appendix VIII (Sample Informed Consent Form – [Screening, Enrollment, Long-Term Storage and Off-Site Visit], MOTHER – Cohort 4)

Also, please note that the citations and protocol roster have been updated and that all changes made with LoA#1 (clarified eligibility criteria, study hypotheses, dapivirine vaginal ring [DPV VR] product descriptions, and HIV testing procedures for infants, modified reporting criteria, product hold criteria and serum creatinine assessment frequency, specified blood volume amounts drawn from infants and which visit procedures will be the Early Termination Visit procedures for the infants, reduced frequency of social benefits behavioral assessments, added explicit mention of

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mental health assessments to the protocol and consent forms, and updated information about DPV VR studies), LoA#2 (added consent language emphasizing that neither study product guarantees protection from HIV and behavioral assessments after participants' pregnancy outcome for all Cohorts as well as a baseline behavioral assessment for Cohort 1, allowed retrospective HIV RNA testing on enrolled participants who acquire an HIV infection and retrospective testing related to COVID-19 infection on enrolled participants if such testing becomes available in the future, clarified requirements related to participants' release of medical records, and included IMPAACT 2009 study results and information related to COVID-19's impact on study implementation), CM#1 (corrected the infant blood draw volume amounts expected for research purposes from the Truvada and DPV VR group infants and updated the Truvada tablet package insert version), and CM#2 (clarified that the MTN Laboratory Center can approve alternate STI testing methodologies to be used as backup in the event of laboratory supply chain disruptions) have been included in v2.0, as well as other minor grammatical edits.