WITS RHI

Project Brief: MTN 042

Full Title of Study/Programme	Phase 3B, Randomized, Open Label Safety and Pharmacokinetic Trial of Dapivirine Vaginal Ring (VR) and Oral FTC/TDF Use in Pregnancy
Technical Focus Area	Research (Maternal)
Rationale	The purpose of MTN-042, a multicentre, prospective, open-label, randomized phase 3b is to characterize the safety, adherence, and acceptability of the DPV VR (25 mg), inserted every 4 weeks, and once-daily, Truvada (200 mg FTC/300 mg TDF) tablet used by African women during pregnancy. This study will further elucidate safety during pregnancy by testing the hypothesis that the administration of the DPV VR and Truvada will both be safe and well tolerated by women and their focusses/infants so that women will experience similar rates of adverse pregnancy outcomes with either the DPV VR or Truvada compared to the general population.
Primary Objectives	**Maternal and Infant Safety:** To describe the maternal and infant safety profile associated with study product exposure during pregnancy. **Pregnancy Outcomes:** To describe the pregnancy outcomes associated with study. product exposure during pregnancy
Secondary Objectives	**Pregnancy Complications:** To describe pregnancy complications associated with study product exposure during pregnancy. **Infant Drug Levels:** To describe infant levels of study drugs associated with study product exposure during pregnancy. **Adherence:** To characterize adherence to open label use of the DPV VR (25 mg) and oral Truvada in pregnant women **Acceptability:** To characterize acceptability of open label use of the DPV VR (25 mg) and oral Truvada in pregnant women
Exploratory Objectives	**Genital Microenvironmental:** To describe changes in the genital microenvironment associated with study product exposure during pregnancy.
Primary Endpoint/Outcome	**Maternal Safety (composite)** • All serious adverse events, including maternal deaths

	• All Grade 3 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007]). **Infant Safety (composite)** • All serious adverse events, including infant deaths and congenital anomalies. • All Grade 3 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Corrected Version 2.1, July 2017 **Pregnancy Outcomes** • Frequency of the following pregnancy outcomes: o Full term live birth (≥37 0/7 weeks) o Premature live birth (<37 0/7 weeks) o Pregnancy loss (≥20 0/7 weeks) o Pregnancy loss (<20 0/7 weeks)
Secondary Endpoint/Outcome	**Pregnancy Complications** • Frequency of the following pregnancy complications: o Hypertensive disorders of pregnancy o Chorioamnionitis o Puerperal sepsis and endometritis o Peripartum and postpartum haemorrhage o Preterm premature rupture of membranes (PROM) o Fever of unclear etiology **Infant Drug Levels** • Infant blood TFV-DP and FTC-TP concentrations • Infant plasma DPV concentrations **Adherence** • Maternal blood TFV-DP and FTC-TP concentrations • Maternal plasma DPV concentrations • Participant report of frequency of study product use (e.g. missed doses for oral Truvada and VR removal/expulsions [voluntary and involuntary] and duration without VR in vagina) • Residual drug levels in returned VRs **Acceptability** • Self-reported attitudes about study product attributes and willingness to use study products during pregnancy • Proportion of participants who find the study products to be at least as acceptable as other HIV prevention methods

Study Design	Phase 3b, two-arm, open label, multi-site, randomized (2:1) trial (DPV vaginal ring [VR], Truvada oral tablet), with onset of dosing period to occur within the following gestational age (GA) ranges: Cohort 1: 36 0/7 weeks – 37 6/7 weeks 150 women Cohort 2: 30 0/7 weeks – 35 6/7 weeks 150 women Cohort 3: 20 0/7 weeks – 29 6/7 weeks 150 women Cohort 4: 12 0/7 weeks – 19 6/7 weeks 300 women
Study Population	Healthy, HIV-uninfected pregnant females, 18-40 (inclusive) years old, with an uncomplicated singleton pregnancy who are willing to be randomized to study product, and their infants.
Study Sample Size	Approximately 750 women and their infants
Follow-up/Duration	Approximately 24 months
Study/Programme Sites	• Wits RHI Shandukani Research Centre (SRC) • Other MTN-042 site(s) selected by the MTN Executive Committee
Study/Programme Duration	The total duration of study participation for each participant will vary depending on gestational age at time of enrolment and length of pregnancy prior to pregnancy outcome and will range from approximately 12 weeks or less for Cohort 1 to approximately 36 weeks or less for Cohort 4. Participants who become infected with HIV will continue in study follow-up with a modified study visit/procedure schedule for a minimum of twelve months. Also, infants born to MTN-042 participants will be followed for approximately 52 weeks (i.e. one year).
Investigators	**Dr Lee Fairlie:** Principal Investigator and Protocol Co-chair **Dr Elizea Horne:** Sub-Investigator **Dr Faeezah Patel:** Sub-Investigator **Dr Mrinmayee:** Sub-Investigator **Dr Muneerah Khan:** Sub-Investigator **Dr Muneerah Khan:** Sub-Investigator **Dr Jeanne Coetzee:** Sub-Investigator
Other Partners & Collaborators	Other sites selected by the MTN Executive Committee
Sponsors/Donors	MTN - Microbicides Trials Network Division of AIDS(DAIDS) US National Institute of Mental Health (NIMH) National Institute of Child Health and Human Development (NICHD)

Publications/Key Presentations to Date	None yet.
Progress Update: Mar 2024	MTN-042 Letter of Amendment #2 dated 09 Jun 2020; Site Implementation Date is 30 September 2020. DELIVER cohorts 1 and 2 safety outcomes will be reported in an oral abstract session on Monday 20 February as well as be featured in a CROI press conference later that day. Retention event: This event was held on the 30th of June 2023. The infant participants were given T-shirts with a cartoon and a message written in their home language ("my mom is a hero") Maternal participants were given a cooler bag with a super mom cartoon on it, as a token of appreciation. This event was used as a platform to encourage the participants to ask questions and address any concerns that may hinder their infant's participation in the study. **<u>Cohort: 2</u>** **Total Screened**: 35 **Enrolled**: 28 **Consent Withdrawal**: 4 **In screening pending enrolment**: 0 **On study**: 0 Infant participants, 0 Maternal participants **Screening failures**: total =7 (2: Chlamydia positive, 3Out of province and window closed, 1 No early ultrasound and Asthma) **Pregnancy outcomes**: 27 **Qualitative component cohort 1**: 11 participants were randomly selected for In-depth Interviews and 11 IDIs conducted. **Cohort 2**: 9 participants were purposive selected for In-depth Interviews and 9 IDIs conducted. 2 Special case IDIs (SIDIs) were conducted. **<u>Cohort 3</u>** Approval for Letter of Amendment (LOA) #2 approved and implemented on 15-Dec-2022 **Total Screened:** 63 **Enrolled:** 44 **Consent Withdrawal: 4** **Infant death: 1** miscarriage) **In screening pending enrolment:** 0 **On study:** 18 Infant participants, 0 Maternal participants

	Screening failures: total = 19 (PIH in previous pregnancy, polyhydramnios, HIV positive, Placenta Previa + RPR positive, LTF and etc) **Pregnancy outcomes:** 39 **Qualitative component cohort 3:** 8 participants were selected for In-depth Interviews and 3 IDIs conducted. **Special case IDIs (SIDIs):** 1
Frequency of Donor Narrative Report	Monthly
Overall Study/Project Contact	Dr Hermien Gous Prof. Lee Fairlie
Briefing Owner and Date	Nothando Faith Mtshali Mar 2024