SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN

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

MTN-042

Effective Date: Date of last signature

Version: 1.0

STATISTICAL ANALYSIS PLAN

Protocol Name:	Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy
Protocol Number:	MTN-042
Author(s):	Barbra Richardson, PhD Daniel Szydlo, MS
Version:	1.0

Author(s):

Research Professor	
Legal Name	Barbra Richardson
Job Title	Research Professor
Signature & Date	Barbra Richardson Digitally signed by Barbra Richardson Date: 2024.07.03 08:04:35 -07'00'

Statistical Manager	
Legal Name	Daniel Szydlo
Job Title	Statistical Manager
Signature & Date	Daniel Szydlo *Electronically signed by: Daniel Szydlo* *Reason: I am an author of the document.* *Date: Jul 3, 2024 09:30 PDT*

Approvals:

DAIDS Representative	
Legal Name	Dean Follman
Job Title	DAIDS Representative
Signature & Date	Dean A. Follmann -S Digitally signed by Dean A. Follmann -S Date: 2024.07.02 08:26:59 -04'00'

The effective date of this document is the date of the latest signature.

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND ACRONYMS

Term/Abbreviation	Definition
AE	adverse event
AIDS	acquired immune deficiency syndrome
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
CRF	case report form
CSR	Clinical Study Report
CV	coefficient of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DPV	dapivirine
FTC	emtricitabine
GA	gestational age
IQR	interquartile range
IRP	Interim Review Panel
LLOQ	lower limit of quantification
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PO	pregnancy outcome
PPO	post-pregnancy outcome
PrEP	pre-exposure prophylaxis
PROM	premature rupture of membranes
PUEV	product use end/early termination visit
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEV	study exit visit
TFV	tenofovir
TLFs	tables, listings, and figures
VOICE	Vaginal and Oral Interventions to Control the Epidemic

VR	vaginal ring

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to define the analyses that will be conducted to describe mother and infant safety, pregnancy outcomes, pregnancy complications, infant drug levels, adherence, and acceptability for the MTN-042 final protocol analysis.

2.1 General Design Considerations

The following is a summary of Protocol Version 2.0

Short Title: DELIVER: A Phase 3b Safety Study of the Dapivirine Ring and PrEP in Pregnant Women

IND Sponsor: DAIDS

Funders: Division of AIDS, NIAID, NIMH, NICHD, US NIH

Protocol Chair: Katherine Bunge, MD, MPH
Felix Mhlanga, MBChB, MMed

Protocol Co-Chair: Lee Fairlie, MBChB, FCPaeds

Sample Size: Approximately 550 women and their infants

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 Sites: MTN-042 site(s) selected by the MTN Executive Committee

Study Hypotheses:

- Daily use of Truvada oral tablet and dapivirine (DPV) vaginal matrix ring (25 mg) inserted once every 4 weeks will both be generally safe and well-tolerated by the participants and their fetuses/infants.
- Participants who use Truvada oral tablet daily and insert the DPV vaginal matrix ring (25 mg) once every 4 weeks will experience similar distributions of pregnancy outcomes to the general population.

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: 12 0/7 weeks – 29 6/7 weeks 150 women

Study Duration: The total duration of study participation for each participant will vary depending on gestational age at time of enrollment 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 3. 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)

Study Products:

- Silicone elastomer matrix VR containing 25 mg of DPV
- Oral tablets (Truvada) containing 200 mg emtricitabine/300 mg tenofovir disoproxil fumarate (FTC/TDF)

Study Regimen: Within Cohorts 1 and 2, participants will be randomized to the above study products in a 2:1 ratio (VR:tablet). Cohort 3 participants will be randomized to the above study products in a 4:1 ratio (200 VR:50 tablet). Participants randomized to the DPV VR will use one VR continuously for approximately one month, replacing the VR each month. Participants using Truvada tablet will take one tablet orally per day. Participants will use their assigned study product until their pregnancy outcome but no later than 41 6/7 weeks of gestation.

Figure 1: Study Visit Schedule – Cohort 2

The primary objective of the IRP is to monitor the safety of the products being evaluated and make recommendations about the continuation, modification, or termination of either or both arms of the study in the next gestational age cohort.

2.2 Study Objectives and Endpoints

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

Primary Endpoints:

- **Maternal Safety (composite)**

  All serious adverse events, including maternal deaths
  All Grade 3 or higher adverse events (AE) as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric 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 Pediatric Adverse Events, Corrected Version 2.1, July 2017

Pregnancy Outcomes

- Frequency of the following pregnancy outcomes:
  - Full term live birth (≥37 0/7 weeks)
  - Premature live birth (<37 0/7 weeks)
  - Pregnancy loss (≥20 0/7 weeks)
  - Pregnancy loss (<20 0/7 weeks)

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

Secondary Endpoints:

Pregnancy Complications

- Frequency of the following pregnancy complications:
  - Hypertensive disorders of pregnancy
  - Chorioamnionitis
  - Puerperal sepsis and endometritis
  - Antepartum, intrapartum and postpartum hemorrhage
  - Preterm premature rupture of membranes (PROM)
  - Fever of unclear etiology

Infant Drug Levels

- Infant blood tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTCTP) 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

2.3 Randomization

Participants in Cohorts 1 and 2 were randomized in a 2:1 ratio to the two arms of the study, two DPV VR to one FTC/TDF, stratified by study site. Participants in Cohort 3 were randomized in a 4:1 ratio, four DPV VR to one FTC/TDF, also stratified by study site.

2.4 Blinding

This was an open label study. Study staff and participants were blinded to the sequence prior to randomization of the participant.

2.5 Primary Study Hypotheses

- It is hypothesized that daily use of Truvada oral tablet or DPV vaginal matrix ring (25 mg) inserted once every 4 weeks will be generally safe and well-tolerated by the participants and their fetuses/infants.
- It is hypothesized that participants who use Truvada oral tablet daily or insert the DPV vaginal matrix ring (25 mg) once every 4 weeks will experience similar distributions of pregnancy outcomes to the general population.

2.6 Sample Size and Power

For primary analyses of outcomes there will be no direct statistical testing between study arms or between study arms and the data presented in MTN-042B. Instead, the frequency of primary and secondary outcomes from MTN-042 will be viewed in the context of local background pregnancy outcome data compiled in the MTN-042B study, a multi-site, cross-sectional chart review of pregnancy outcome data from the same four African sites. It is hypothesized that participants who use Truvada oral tablet daily and insert the DPV vaginal matrix ring (25 mg) once every 4 weeks will experience distributions of pregnancy outcomes that are qualitatively similar to the general population (i.e. the data compiled in MTN-042B). Comparisons to MTN-042B will not be included in the Clinical Study Report (CSR).

To characterize the statistical properties of this study, the below presents the probability of observing zero, at least one, ten or more, and fifty or more safety endpoints in each group by cohort size and among the total study population for various “true” event rates, ranging from low to high:

Table 1. Probability (%) of observing an event given different "true" event rates by cohort size

"True" event rate	P (0 events)		P ≥ 1 event		P (≥ 10 events)		P (≥ 50 events)	
Cohorts 1-2[a]	**n=100**	**n=50**	**n=100**	**n=50**	**n=100**	**n=50**	**n=100**	**n=50**
1%	36.6	60.50	63.40	39.50	0.00	0.00	0.00	0.00
5%	0.59	7.69	99.41	92.31	1.15	0.00	0.00	0.00
10%	0.00	0.52	100.00	99.48	41.68	0.94	0.00	0.00
15%	0.00	0.03	100.00	99.97	90.06	11.99	0.00	0.00
25%	0.00	0.00	100.00	100.00	99.99	73.78	0.07	0.00
Cohort 3[a]	**n=200**	**n=50**	**n=200**	**n=50**	**n=200**	**n=50**	**n=200**	**n=50**
1%	13.4	60.50	86.6	39.50	0.00	0.00	0.00	0.00
5%	0.00	7.69	100.00	92.31	41.69	0.00	0.00	0.00
10%	0.00	0.52	100.00	99.48	99.19	0.94	0.00	0.00
15%	0.00	0.03	100.00	99.97	100.00	11.99	0.01	0.00
25%	0.00	0.00	100.00	100.00	100.00	73.78	46.21	0.00
Overall[a]	**n=400**	**n=150**	**n=400**	**n=150**	**n=400**	**n=150**	**n=400**	**n=150**
1%	1.80	22.15	90.95	44.30	0.27	0.00	0.00	0.00
5%	0.00	0.05	100.00	99.59	99.06	13.22	0.00	0.00
10%	0.00	0.00	100.00	100.00	100.00	89.40	4.36	0.00
15%	0.00	0.03	100.00	100.00	100.00	99.86	91.06	0.00
25%	0.00	0.00	100.00	100.00	100.00	100.00	100.00	0.85

[a] Sample sizes in the table based on the proposed cohort sizes and study design. For example, Cohort 1 will include approximately 150 participants, with 2:1 randomization, there will be 100 participants in the VR arm and 50 participants in the Truvada arm.

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval for the "true" rate based on the observed data. The table below shows the exact 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate. For example, if none of the 400 participants receiving the VR regimen experience a safety event, the 95% exact 2-sided upper confidence bound for the true rate of such events in a particular arm of the study is 0.92%.

Table 2. Confidence intervals for endpoint rate (proportion of participants with endpoint) given number of endpoints (rows) in with number of participants (columns)

Number of events	Number of participants[a]				
	n=50	n=100	n=150	n=200	n=400
0	0.00, 7.11	0.00, 3.62	0.00, 2.43	0.00, 1.83	0.00, 0.92
1	0.05, 10.65	0.03, 5.45	0.00, 3.66	0.01, 2.75	0.00, 1.38
2	0.49, 13.71	0.24, 7.04	0.16, 4.73	0.12, 3.57	0.06, 1.79
3	1.25, 16.55	0.62, 8.52	0.41, 5.73	0.31, 4.32	0.15, 2.18
4	2.22, 19.23	1.10, 9.93	0.73, 6.69	0.55, 5.04	0.27, 2.54
5	3.33, 21.81	1.64, 11.28	1.09, 7.61	0.82, 5.74	0.41, 2.89

Number of events	Number of participants[a]				
	n=50	n=100	n=150	n=200	n=400
6	4.53, 24.31	2.23, 12.60	1.48, 8.50	1.11, 6.42	0.55, 3.24
8	7.17, 29.11	3.52, 15.16	2.33, 10.24	1.74, 7.73	0.87, 3.90
10	10.03, 33.72	4.90, 17.62	3.24, 11.92	2.42, 9.00	1.21, 4.55
12	13.06, 38.17	6.36, 20.02	4.20, 13.56	3.14, 10.25	1.56, 5.18
15	17.86, 44.61	8.65, 23.53	5.71, 15.96	4.26, 12.07	2.11, 6.11
20	26.41, 54.82	12.67, 29.18	8.34, 19.84	6.22, 15.02	3.08, 7.62
30	45.18, 73.59	21.24, 39.98	13.92, 27.30	10.35, 20.72	5.12, 10.53

[a] Sample sizes in the table based on the proposed cohort size and study design.

Based on pregnancy outcome data from previous studies, we expect certain pregnancy outcomes such as premature live birth and pregnancy loss ≥ 20 weeks to occur at a low frequency (5% and 2-3%, respectively). Among all women who became pregnant in MTN-003 (VOICE) and MTN-020 (ASPIRE), pregnancy loss < 20 weeks was between 19-22%. Given the enrollment criteria for this study, it is expected that the frequency of pregnancy loss < 20 weeks will be lower in enrolled MTN-042 participants. As such, the probability and confidence interval estimates presented in Table 1 and Table 2 also apply to estimates of the frequency of pregnancy outcomes. For example, if there was one stillbirth among the 100 participants in Cohort 1 receiving the VR regimen, the stillbirth frequency would be 1.00% and the 95% exact 2-sided confidence interval would be (0.03, 5.45).

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

The ITT Analysis Set will consist of all enrolled and randomized women, and all enrolled infants. Participant treatment for mothers will be determined according to their randomization arm assignment. Participant treatment for infants will be determined according to their mother's randomization arm assignment.

A secondary Product Exposure Set will be used for some analyses and will differ from the ITT Analysis Set in that participants who never received any study product (per the Pharmacy Dispensation CRF) and endpoints that occur > 7 days after study product discontinuation (per the Discontinuation of Study Product CRF) will be excluded.

A secondary Infant Exposure Set will be used for some analyses and will be the same as the ITT Analysis Set except that infants whose mothers never received study product will be excluded. If all enrolled and randomized mothers in a cohort received study product then the Infant Exposure Set and Infant ITT Analysis Set will be identical, and analyses using the Infant Exposure Set will not be performed.

3.2 Statistical Analysis Issues

All analyses will be descriptive unless otherwise noted.

Background rates of select pregnancy outcomes and complications are available through MTN-042B but are not appropriate for direct comparison as the study populations differed significantly. MTN-042B included all women who presented to the local delivery facility over an eight week period. By design, women who experienced an early loss would not be captured in this cohort. MTN-042 excluded women with complciated pregnancies and as a consequence rates of pregnancy complications and poor obstetric outcomes are likely to be lower in MTN-042 than in MTN-042B.

Study visit numbers for pre-pregnancy outcome visits were defined in relation to enrollment (e.g., visit 10/Week 8 visit occurred 8 weeks after enrollment). Summaries by visit are by study visit unless otherwise noted. Some study procedures were completed at visits corresponding to certain weeks of gestation, and since mothers were enrolled at different gestational ages this means that these procedures were not completed at the same study visit for all participants. Some analyses will be performed by grouping these gestational-week-dependent visits together, instead of summarizing by study visit. Gestational age at enrollment is recorded on the Pregnancy Assessment CRF.

Relevant gestational-week-dependent visits correspond to the following study visits:
4-week visit corresponding to, or immediately before, 36th week of gestation:
- Visit 10 if gestational age 25-28 weeks
- Visit 14 if gestational age 21-24 weeks
- Visit 18 if gestational age 17-20 weeks
- Visit 22 if gestational age 13-16 weeks
- Visit 26 if gestational age 12 weeks

4-week visit corresponding to, or immediately following, the 30th week of gestation:
- Visit 6 if gestational age 26-29 weeks
- Visit 10 if gestational age 22-25 weeks
- Visit 14 if gestational age 18-21 weeks
- Visit 18 if gestational age 14-17 weeks
- Visit 22 if gestational age 12-13 weeks

Visit corresponding to, or immediately following, the 28th week of gestation:
- Visit 10 if gestational age 20-23 weeks
- Visit 14 if gestational age 16-19 weeks
- Visit 18 if gestational age 12-15 weeks

Participants were instructed to use study product until they went into labor. This complicates analyses of laboratory adherence measures (see Section 9.3) taken at the Visit 101 – PPO Visit, since this visit could occur up to 14 days after the pregnancy outcome, i.e., this visit will include time when the participant was expected to not be using study product and drug levels are expected to drop quickly following product discontinuation. This applies to all three laboratory adherence measures, including residual drug levels in VRs since the residual drug measure adjusts for how long the participant had the ring.

Some laboratory adherence measures were tested for a subset of the study population. TFV-DP and FTC-TP were tested for a subset of Cohort 1 mothers (30% of the mothers with a collected sample) (all collected samples were tested for infants, and for mothers in Cohorts 2 and 3). Plasma DPV was tested for a subset of mothers in all three cohorts (50% of the mothers with a collected sample) (all collected samples were tested for infants).

4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

No DSMB oversight was planned for this study. The MTN SMC conducted interim reviews of study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and study or laboratory issues. These reviews took place after all pregnancy outcomes had occurred for Cohort 1, after all pregnancy outcomes had occurred for Cohort 2, and after all mothers had been enrolled for Cohort 3.

An interim review of the safety data by the Interim Review Panel (IRP) was planned and conducted after each cohort completed scheduled participation and prior to beginning accrual in the next scheduled cohort. Planned IRP analyses are documented in the IRP SAP for MTN-042 Cohort 1 and the IRP SAP for MTN-042 Cohort 2.

5. GENERAL ANALYSIS METHODS

When the use of descriptive statistics to assess group characteristics or differences is described, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum).

Descriptions of tabular summaries that are “by study arm and overall” indicate that the table should have columns summarizing each arm as well as a column summarizing the combined arms.

Tabular summaries by visit do not include interim visits, unless otherwise noted. Results from all visits (including interim visits) will be included in listings.

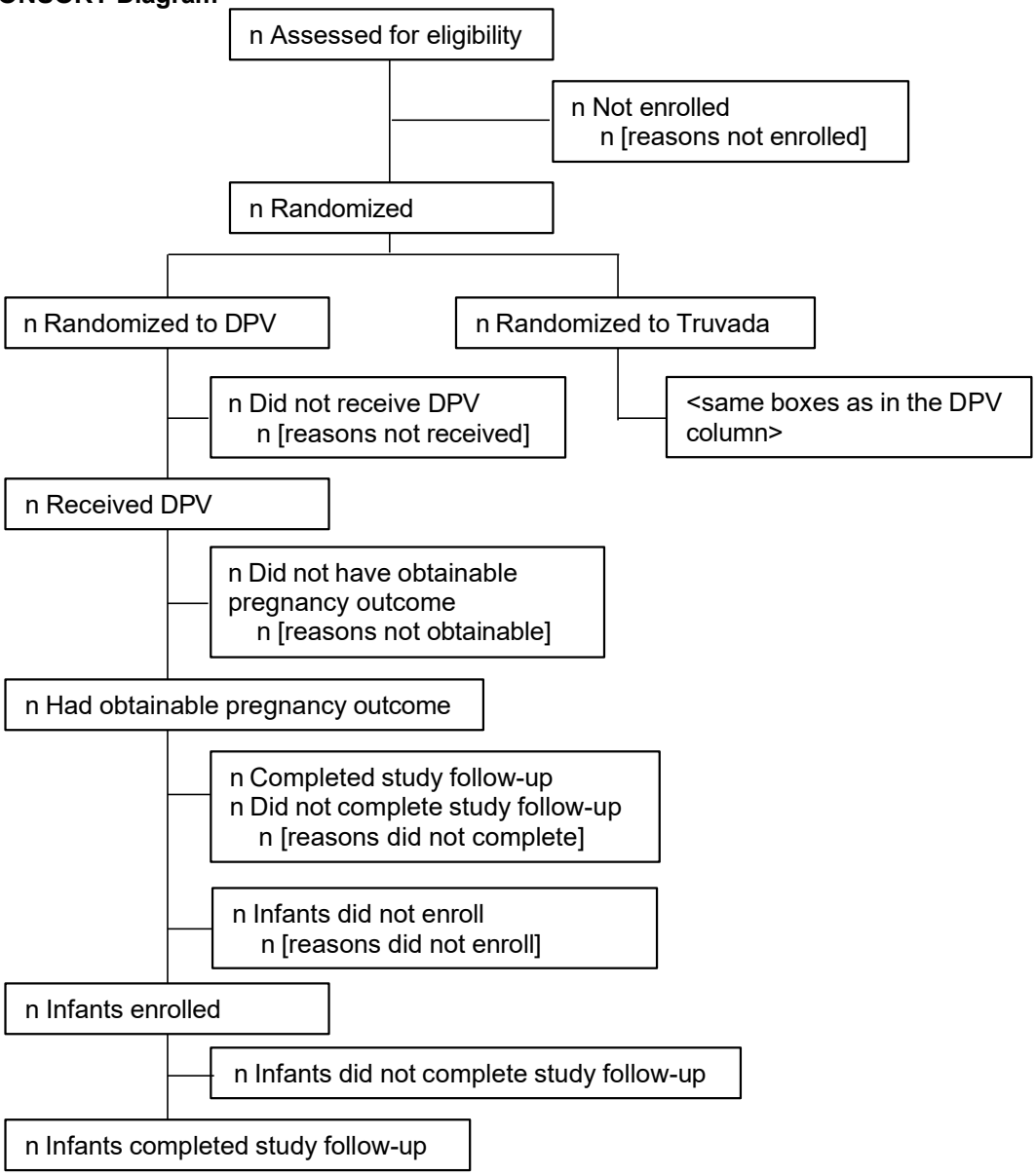
In addition to separate analyses/summaries for each of the three cohorts, an exploratory analysis will split Cohort 3 participants into two groups based on gestational age (20 0/7 weeks through 29 6/7 weeks and 12 0/7 weeks through 19 6/7 weeks) as collected on the Pregnancy Assessment CRF. These ages were originally going to be two separate cohorts in Protocol Version 1.0 before being combined into one cohort in Protocol Version 2.0. These exploratory analyses splitting Cohort 3 will be done only for certain analyses, as specified in this document.

6. TRIAL PARTICIPANT DISPOSITION

6.1 Disposition of Participants

The number of pregnant women screened, screened out (with reasons for not enrolling), randomized to each study arm (with reasons for not receiving assigned intervention), with obtainable pregnancy outcomes (with reasons outcome was not obtainable), completing study follow-up (with reasons study follow-up was not completed), the number of infants enrolled (with reasons not enrolled), and number of infants completing study follow-up (with reasons infant follow-up was not completed) will be presented in a CONSORT flow diagram. Separate diagrams will be used for each cohort.

Figure 1. Mock CONSORT Diagram



6.2 Treatment Exposure

As described in Section 3.1 Analysis Set(s), the Product Exposure analysis set will exclude endpoint data that occurs > 7 days after study production discontinuation, and will exclude participants who never received study product.

Study duration, infant study duration, on product duration, on study pregnancy duration, and estimated gestational age at pregnancy outcome will be summarized as continuous variable in tables, by study arm and overall for each of the three cohorts, and for the three cohorts combined.

Study duration will be calculated as the date of study exit (Study Termination CRF) minus the participant's randomization date + 1 day, unless the participant had a termination reason of "Lost to follow-up". If a participant was lost to follow-up then their study duration will be calculated as the date of their last attended visit minus their randomization date + 1 day. The last attended visit is either the last visit with a completed Follow-up Visit Summary CRF, or the last Interim Visit Summary CRF where at least one study procedure was completed (per Interim Visit Summary CRF, "What study procedures were completed at this visit? Select all that apply" item), whichever occurred last.

Infant study duration will be calculated as the date of study exit (Study Termination CRF) minus the infant's birth date + 1 day, unless the infant had a termination reason of "Lost to follow-up". If an infant was lost to follow-up then their study duration will be calculated as the date of their last attended visit minus their birth date + 1 day. The last attended visit is either the last visit with a completed Infant Follow-up Visit Summary CRF, or the last Infant Interim Visit Summary CRF where at least one study procedure was completed (per Interim Visit Summary CRF, "What study procedures were completed at this visit? Select all that apply" item), whichever occurred last.

On product duration will be calculated as the date of product discontinuation (Discontinuation of Study Product CRF) minus the participant's randomization date + 1 day. Only participants who ever received study product will be included in this summary.

On study pregnancy duration will be calculated as the date of the pregnancy outcome (outcome date on Pregnancy Outcome CRF) minus the participant's randomization date + 1 day. Only participants with an obtainable pregnancy outcome will be included in this summary.

Estimated gestational age at pregnancy outcome will be calculated as the date of the pregnancy outcome minus the date of the participant's pregnancy assessment (Pregnancy Assessment CRF) + 1 day, plus the participant's estimated gestational age (in days) at their pregnancy assessment (Pregnancy Assessment CRF), and will be reported in weeks (e.g., an estimated gestational age of 38 weeks 6/7 days would be treated as 38.86 weeks for this summary). Note that this derivation will be used even if the participant had an available gestational age by best estimation at delivery on the Pregnancy Outcome CRF.

6.3 Protocol Deviations

Protocol deviations will be summarized in tables, overall for each of the three cohorts, and for the three cohorts combined. These tables will summarize the number of protocol deviations, the number and percentage of individuals with at least one protocol deviation (denominator is the number of individuals screened for the study), the number and percentage of deviations reported to local IRB/EC (denominator is number of events), and the number and percentage of each type of deviation (denominator is the number of events). All screened participants will be included.

6.4 Product Discontinuation

Product discontinuation will be summarized in tables, overall and by arm for each of the three cohorts, and overall and by arm for the three cohorts combined. These tables will summarize the number and percentage of responses to the ”Primary reason for completion/discontinuation” item on the Product Discontinuation CRF. The denominator will be the number of participants in the ITT Analysis Set.

6.5 Retention

Study retention will be summarized by type of visit (mothers) or visit (infants) in tables, overall and by arm for each of the three cohorts, and overall and by arm for the three cohorts combined. Separate tables will be prepared for mother participants and infants. These tables will include the number and percentage of visits that were completed, missed, or that occurred after early termination at each visit/type of visit.

For mothers, visit expectation depended on the cohort and gestational age at enrollment of the participant, as well as the timing of their pregnancy outcome. Assuming that their pregnancy outcome had not yet occurred, all mothers were expected to complete the Week 1 phone contact (visit 3), Week 2 bi-weekly visit (visit 4), Week 3 phone contact (visit 5), and Week 4 visit (visit 6). Once the pregnancy outcome occurred, they were also expected to complete the PPO visit (visit 101) and 6-week PPO visit (visit 103). In between these visits the expected visits depended on cohort and gestational age at enrollment, and these expectations are provided in Appendix I.

Infants were expected to complete their PPO visit (visit 201), 1-week PPO visit (visit 202), 6-week PPO visit (visit 203), 6-month PPO visit (visit 204), and 12-month PPO visit (visit 205).

A completed visit is defined as an expected visit where the participant had a Follow-up Visit Summary CRF (or Infant Follow-up Visit Summary CRF for infants) with a non-missing visit date. A visit where the participant had already terminated early is an expected visit where the last date of the visit window was on or after the date of study termination. A missed visit is defined as a visit that was expected but not completed and which occurred prior to study termination. For the purposes of these calculations, a visit will only be included if the last date of the visit window occurred on or prior to the date of the participant’s pregnancy outcome (e.g., a visit will be not counted as missed or expected if it was not attended and the pregnancy outcome occurred while the visit window was still open, and similarly a visit will not be counted as completed or expected if the visit occurred and then the pregnancy outcome occurred during the visit window).

Each study visit had a visit window in which it was to be completed; these windows are provided in Appendix II.

Summaries of mother retention will summarize the number and percentage of visits that were completed, missed, or that occurred after early termination at each visit/type of visit for the following types of visits:

- Phone contact visits (visit 3, visit 5, and others depending on gestational age at enrollment, see Appendix I)
- In-person visits (visit 4, visit 6, and others depending on gestational age at enrollment, see Appendix I
- PPO visits (visit 101)
- 6-week PPO visit (visit 103)

The denominator for the percentages will be the number of expected visits.

Summaries of infant retention will summarize the number and percentage of visits that were completed, missed, or that occurred after early termination at each visit/type of visit for the PPO visit (visit 201), 1-week PPO visit (visit 202), 6-week PPO visit (visit 203), 6-month PPO visit (visit 204), and 12-month PPO visit (visit 205).

7. BASELINE DATA

Unless otherwise noted, all baseline data summaries are restricted to mothers in the analysis set.

7.1 Mother Demographics

Baseline demographic characteristics will include participant age (both as a continuous variable and as the following categories: 18-19 years, 20-24, 25-29, 30-34, and 35-40), enrollment site, ethnic group or tribe, whether or not the participant has a primary partner, number of lifetime sex partners (both as a continuous variable and as the following categories: 1 partner, 2, 3, 4, and 5+), whether or not the participant had a sexual relationship in order to get money, and the HIV status of their primary sex partner. These tables will be presented by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. These items are collected on the Demographics CRF.

7.2 Pregnancy History

Pregnancy history, as collected on the Pregnancy History CRF, will be summarized in tables, by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. These tables will summarize the number and percentage of participants who had any prior pregnancies. Among the participants with a prior pregnancy, the following will be summarized (as continuous variables):

- full term live births (≥37 weeks)
- premature live births (<37 weeks)
- spontaneous fetal deaths and/or still births (≥20 weeks)
- spontaneous abortions (<20 weeks)
- therapeutic/elective abortions
- ectopic pregnancies

7.3 Gestational Age

Participant gestational age at enrollment, as collected on the Pregnancy Assessment CRF, will be summarized in tables, by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. These tables will summarize the estimated gestational age at enrollment (as a continuous variable). Gestational age will be described in weeks, not in weeks and days as it is captured on the CRF (e.g., a gestational age on the CRF of 37 weeks 4 days will be defined as 37.6 weeks for the table summaries).

7.4 Baseline Medical History

Baseline medical history will be summarized in tables, by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. These tables will summarize the following (as categorical variables):

- Number and percentage of randomized participants who had any medical history event (yes or no, from Baseline Medical History Y/N CRF), and the number of events (from the Baseline Medical History Log).
- Number and percentage of participants who had a gradeable event (at least one gradeable event vs. no gradeable events, from “Is condition/event gradable” on the Baseline Medical History Log), with the denominator being the number of participants with a medical history event. The total number of gradeable events will also be summarized.
- Number and percentage of participants with a maximum severity event (Grade 4 is highest severity, Grade 1 is lowest, from “Severity grade” item on the Baseline Medical History Log), with

the denominator being the number of participants who had a gradeable event. The total number of events in each severity will also be summarized.

- Number and percentage of participants with an ongoing event (at least one ongoing event vs. no ongoing events, from “Is the condition ongoing?” item on the Baseline Medical History Log).

7.5 Prior Medication

Prior medication will be summarized in tables, by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. These tables will summarize:

- Number and percentage of randomized participants who had any prior medication (yes or no), and the number of medications.
- Number and percentage of randomized participants with at least one prior medication in each observed ATC Level 3 category, and the total number of prior medications in each ATC Level 3 category.
- Within each ATC Level 3 category, the number and percentage of randomized participants with at least one prior medication in each observed ATC Level 1 category, and the total number of prior medications in each ATC Level 1 category. The denominator for these percentages is the number of participants in the ITT Analysis Set.

Prior medications are defined as medications recorded on the Concomitant Medications Log CRF that had a “Date stopped” prior to the participant’s randomization date.

7.6 Pelvic Exam

Baseline pelvic examination findings will be summarized in tables, by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. These tables will use data collected on the Pelvic Exam CRF at the enrollment visit and will include:

- Number and percentage of participants with a pelvic exam assessment (non-missing value on the “Pelvic exam assessment” item), with the denominator being the number of participants in the ITT Analysis Set.
- Number and percentage of participants with each pelvic exam assessment result (not done, abnormal findings, or no abnormal findings), with the denominator being the number with a non-missing pelvic exam assessment result. Note that a result being missing entirely is treated as different from a result being marked as “not done”.
- Number and percentage of participants with each type of abnormal pelvic exam finding (from vulvar edema through other abnormal findings), with the denominator being the number with a non-missing pelvic exam assessment result.
    - For the abnormal vaginal discharge finding, the number and percentage of participants who had each type of abnormal vaginal discharge (slight, moderate, or pooling) will also be summarized, with the denominator being the number of participants with an abnormal vaginal discharge finding.

8. PRIMARY ENDPOINTS

An intent to treat analysis will be performed to summarize the frequency of primary endpoints (maternal safety, infant safety and pregnancy outcome) by study arm (ITT Analysis Set). An additional analysis will be conducted including only visits in which a participant has been exposed to the study product (Product Exposure Set). Analyses will be conducted separately for each of the three cohorts (including an exploratory analysis that splits Cohort 3 based on gestational age as described in Section 5), with a final aggregate analysis that will include all enrolled participants from each of the three cohorts. The number and the percentages of participants experiencing each primary endpoint will be tabulated by study arm. Each participant will contribute once in each category (i.e., only for highest severity AE for each

participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each primary endpoint. Primary endpoint event rates will be compared to baseline estimates from MTN-042B by checking whether the baseline estimates are included in the exact binomial confidence intervals (this will not be included as part of the CSR). A secondary analysis will be performed to summarize the total number of primary and secondary safety endpoints reported per participant by study arm.

8.1 Primary Maternal Safety

The primary maternal safety endpoint is all maternal adverse events that were either serious adverse events (SAEs) or were Grade 3 or higher. These are referred to in this document as “composite AEs”.

The number and percentage of participants experiencing at least one composite AE and the exact binomial confidence intervals for those proportions will be summarized by study arm and overall for each of the three cohorts (including an exploratory analysis that splits Cohort 3 based on gestational age as described in Section 5), and by study arm and overall for the three cohorts combined. This analysis will include all participants in the ITT Analysis Set.

Secondary analyses will be conducted to further explore maternal safety. These analyses include:

1. The analyses in the preceding paragraph will be repeated using the Product Exposure Set
2. Summaries of the total number of primary maternal safety endpoints reported per participant, by study arm and overall for each of the three cohorts (including a summary of the two Cohort 3 subgroups defined in Section 5), and by study arm and overall for the three cohorts combined. This will use the ITT Analysis Set.
3. A Poisson regression model will be fitted comparing the number of primary maternal safety endpoints per participant by arm, adjusted for site, with an offset of the number of days from randomization to study product discontinuation (see “on product duration” definition in Section 6.2). This model will be fitted for all cohorts combined only, and will use the ITT Analysis Set.

8.2 Primary Infant Safety

The primary infant safety endpoint is all infant adverse events that were either SAEs or were Grade 3 or higher. These are referred to in this document as “composite AEs”.

The number and percentage of infants experiencing at least one composite AE and the exact binomial confidence intervals for those proportions will be summarized by study arm and overall for each of the three cohorts (including an exploratory analysis that splits Cohort 3 based on gestational age as described in Section 5), and by study arm and overall for the three cohorts combined. This analysis will include all infants in the ITT Analysis Set (as appropriate given the cohort/study arm being summarized).

Secondary analyses will be conducted to further explore infant safety. These analyses include:

1. The analyses in the preceding paragraph will be repeated using the Infant Exposure Analysis Set.
2. Summaries of the total number of primary infant safety endpoints reported per infant, by study arm and overall for each of the three cohorts (including a summary of the two Cohort 3 subgroups defined in Section 5), and by study arm and overall for the three cohorts combined. This will use the ITT Analysis Set.
3. A Poisson regression model will be fitted comparing the number of primary infant safety endpoints per participant by arm, adjusted for site, with an offset of the number of days from birth to study termination (see "infant study duration” definition in Section 6.2). This model will be fitted for all cohorts combined only, and will use the ITT Analysis Set.

8.3 Pregnancy Outcomes

The number and percentage of pregnancy outcomes (full term live birth [≥37 0/7 weeks], premature live birth [<37 0/7 weeks], stillbirth/intrauterine fetal demise [≥20 0/7 weeks], and spontaneous abortion [<20 0/7 weeks]) and the exact binomial confidence intervals for those proportions will be summarized by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. This analysis will include all participants in the analysis set who had an obtainable pregnancy outcome. If a participant was found to have a non-singleton pregnancy after enrollment then each outcome from that pregnancy will be included in this analysis.

A secondary analysis will be conducted by repeating the pregnancy outcome summaries for only participants who received study product (i.e., the participants in the Product Exposure Set).

9. SECONDARY ENDPOINTS

9.1 Pregnancy Complications

Pregnancy complications will be summarized in tables by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. This analysis will include all participants in the analysis set who had an obtainable pregnancy outcome.

The summaries of complications will include the following complications, gathered on the Pregnancy Outcome CRF:

- any hypertensive disorders of pregnancy, and the different individual types of hypertensive disorders:
    - chronic
    - gestational
    - pre-eclampsia without severe features
    - pre-eclampsia with severe features
    - eclampsia
    - not specified
- chorioamnionitis
- either of puerperal sepsis or endometritis (combination of the puerperal sepsis and endometritis items), and summaries of both individually:
    - puerperal sepsis
    - endometritis
- either of peripartum and postpartum hemorrhage (Cohort 1 only)
- either of antepartum, intrapartum, or postpartum hemorrhage (Cohorts 2 and 3 only), and summaries of each type of hemorrhage individually:
    - peripartum hemorrhage (Cohort 1 only)
    - antepartum hemorrhage (Cohorts 2 and 3 only)
    - intrapartum hemorrhage (Cohorts 2 and 3 only)
    - postpartum hemorrhage
- preterm premature rupture of membranes (PROM) (the preterm premature rupture of membranes (PPROM) item)
- fever of unclear etiology
- other

The table will include a footnote listing the responses to “If ‘Other’, specify” for complications categorized as other. The number and percentage of participants, and the exact binomial confidence intervals for those proportions, with these complications will be summarized. The denominator will be the number of participants in the analysis set with a pregnancy outcome.

9.2 Infant Drug Levels

The number and percentage of infants with detectable drug levels in each study arm for each sample type will be summarized using descriptive statistics in tables overall for each of the three cohorts, and overall for the three cohorts combined. Participants with a drug level for the assay corresponding to their mother's randomization arm (i.e., plasma DPV concentration for the DPV VR arm, blood TFV-DP and FTC-TP concentration for the FTC/TDF arm) above the lower limit of quantification (LLOQ) at the PPO visit (including interim PPO visits) will be considered to have a detectable drug level for that sample type; otherwise, the participant will be considered to have an undetectable drug level for that sample type. If a participant has multiple concentrations at a visit, they will be considered to have a detectable drug level for that sample type if any of the concentrations are above the LLOQ. The denominator will be the number of infants in the analysis set with at least one valid drug result for the assay corresponding to their mother's randomization arm. Valid drug results are defined as any result that does not have any of the following censor codes: A, D, O, P, X, Z.

Additionally, drug concentration levels at the PPO visit (including interim PPO visits) will be summarized using geometric mean, geometric coefficient of variation (CV), arithmetic mean, standard deviation (SD), median, interquartile range (IQR), and range (minimum, maximum). The CV will be calculated as 100 x standard deviation / Mean of the concentration values. Drug concentrations below the LLOQ will be treated as having a value of half the LLOQ for these summaries. Drug concentrations from assays that do not correspond to the mother's randomization arm, or which have any of the censor code A, D, O, P, X, and/or Z, will be excluded from these summaries.

9.3 Adherence

Laboratory adherence measures (maternal blood TFV-DP and FTC-TP, maternal plasma DPV, and residual drug levels in VRs) will be summarized by visit for each of the three cohorts, and for the three cohorts combined. Residual drug levels in VRs will be reported in terms of the estimated residual drug release rate (see Appendix III for definition). Summaries will include the number of valid results, arithmetic mean, SD, median, IQR, and range.

Laboratory measures that do not correspond to the participant's randomization arm (i.e., maternal blood TFV-DP and/or FTC-TP for a participant randomized to receive the DPV VR, maternal plasma DPV and/or residual drug level in VRs for participants randomized to receive Truvada) will be excluded from all analyses described in this section. TFV-DP, FTC-TP, and plasma DPV measures that have any of the following censor codes will be excluded from all analyses described in this section: A, D, O, P, X, Z. Residual drug level measures that have the censor codes X or Z or for which residual drug release rate is unable to be calculated (see Appendix III) will also be excluded from all analyses described in this section.

By visit summaries will include the visits where the assessment was expected to be collected (e.g., mother blood TFV-DP and FTC-TP will include summaries for the time points where DBS for TFV-DP and FTC-TP drug levels were expected to be collected per protocol). Blood TFV-DP and plasma DPV samples that were collected at other visits will be treated as having been collected at the immediately preceding visit where collection was expected (e.g., a sample collected at an interim visit 4.1 will be treated as having been collected at visit 4). VRs that were returned at other visits will be treated as having been collected at the immediately following visit (see details below).

<u>Residual drug levels in VRs visits</u>
Visit 6 – Week 4: includes all rings returned on or prior to visit 6.0
Visit 10 – Week 8: includes all rings returned after visit 6.0 (i.e., visit 6.1 and later) and on or prior to visit 10.0
Visit 14 – Week 12, Visit 18 – Week 16, etc. are handled similarly.
Visit 101 – PPO Visit: includes all rings returned after last attended bi-weekly visit.

Laboratory adherence will also be categorized as follows:

Residual drug levels:
Red (rate ≤ 0.9 mg/month)
Yellow (0.9 mg/month < rate ≤ 4.0 mg/month)
Green (rate > 4.0 mg/month)

Blood TFV-DP:

- If sample was collected within 6 weeks (i.e., specimen collection date - randomization date + 1 day <= 42 days):
  Red (<150 fmol/punch)
  Yellow (150 fmol/punch – 599 fmol/punch)
  Green (≥600 fmol/punch)

- If sample was collected more than 6 weeks (i.e., specimen collection date – randomization date + 1 day > 42 days) after randomization date:
  Red (<200 fmol/punch)
  Yellow (200 fmol/punch – 649 fmol/punch)
  Green (≥650 fmol/punch)

Plasma DPV:
Red (<LLOQ (i.e., < 20 pg/mL))
Yellow (LLOQ – 95 pg/mL, inclusive)
Green (> 95 pg/mL)

These categories will be summarized in terms of the number and percentage of participant visits, by visit (including all visits combined) and study arm for each of the three cohorts, and by visit and study arm for the three cohorts combined. The denominator will be the number of valid samples at the visit.

Adherence will also be summarized at a participant level for all three measures, with participants categorized as either “ever exposed” (if they have at least one measure in the Yellow or Green category) or “never exposed” (if they have no measures in the Yellow or Green categories). These categories will be summarized by number and percentage of participants by study arm for each of the three cohorts, and by study arm for the three cohorts combined. The denominator will be the number of participants with at least one valid sample.

Additional exploratory analyses of Blood TFV-DP categories may be done if additional information regarding adherence cutoffs becomes available. These exploratory analyses would not be part of the CSR.

Participant report of frequency of study product use will be summarized by visit for each of the three cohorts, and for the three cohorts combined. For participants randomized to the FTC/TDF arm this will be the responses to the “In the past 4 weeks, how often did you miss taking the pills” item on the Tablet Adherence CRF (possible responses are “never”, “rarely”, or “often”). For participants randomized to the DPV VR arm this will be the responses to the “in the past 4 weeks, how often was the ring out of your vagina for any extended period of time, that is more than 12 hours in a row?”, “in the past 4 weeks, how often was the ring out of your vagina, even for just a minute excluding expected instances when a ring was briefly removed and replaced with a new ring?”, and “was the ring ever removed (in the past 4 weeks)?” items on the Ring Adherence CRF.

9.4 Acceptability

Acceptability questions were asked of participants in Cohorts 2 and 3.

Self-reported attitude about study product and willingness to use study products during pregnancy will be assessed by summarizing the "would you be willing to use the [pills/ring] for HIV prevention when pregnant in the future?" item from the Follow-up Behavioral Assessment and Post-PO Behavioral Assessment CRFs. The responses from these two CRFs will be summarized separately for each of the visits where responses were expected to be collected (including interim visits for those expected visits): Visit 6 Follow-up Behavioral Assessment (both cohorts), Follow-up Behavioral Assessment from the 4-week Visit corresponding to, or immediately before, 36th week gestation (Cohort 3 only, see Section 3.2 Statistical Analysis Issues), and the Visit 103 6-week PPO Post-PO Behavioral Assessment, by study arm and overall for each of Cohorts 2 and 3. Responses at Visit 6 and Visit 103 will also be summarized by study arm and overall for these cohorts combined.

The proportion of participants who find the study products to be at least as acceptable as other HIV prevention methods will be assessed by summarizing the "overall, how much do you like or dislike male condoms for HIV prevention?", "overall, how much do you like or dislike the [pills/ring] for HIV prevention?", and "overall, how satisfied have you been with the [pills/ring] for preventing HIV?" items on the Follow-up Behavioral Assessment CRF. The responses from Visit 6 will be summarized by study arm and overall for each of Cohorts 2 and 3, and by study arm and overall for these cohorts combined. Responses from the 4-week Visit corresponding to, or immediately before, 36th week gestation (see Section 3.2 Statistical Analysis Issues) will be summarized by study arm and overall for Cohort 3. The denominator for each proportion will be the participants in the analysis set who responded to the item.

10. SAFETY ANALYSES

10.1 Maternal Adverse Events

In addition to the summaries of the primary maternal safety endpoint detailed in Section 8.1, maternal adverse event summaries will include:

- the total number and percentage of participants with an SAE
- the total number of SAEs by severity grade and relationship to study product
- the total number of composite AEs by severity grade and relationship to study product
- the number and percentages of composite AEs for each level of relationship to study product (not related, related) for the most causal relationship per participant overall and by system organ class and preferred term.
- the number and percentage of participants with any AE, and number and percentage of AEs by body system, preferred term, and severity
- the number and percentage of participants with any AE, and number and percentage of AEs by body system, preferred term, and relationship to study product
- listing of all AEs, including participant ID, cohort, randomization arm, site, whether or not the AE was an SAE, whether or not the AE was a composite AE, preferred term, severity, relationship to study product, visit of AE report, AE onset date, AE outcome date, AE duration, AE outcome, and associated comments.
- the above summaries will be repeated using the Product Exposure Set

The denominator for all percentages described above is the number of participants in the analysis set. All summaries will be presented by arm across all cohorts, and by arm within each cohort. No statistical comparisons are planned.

10.2 Infant Adverse Events

In addition to the summaries of the primary infant safety endpoint detailed in Section 8.2, infant adverse event summaries will include:

- the total number and percentage of infants with an SAE
- the total number of infant SAEs by severity grade and relationship to study product
- the total number of infant composite AEs by severity grade and relationship to study product
- the number and percentages of infant composite AEs for each level of relationship to study product (not related, related) for the most causal relationship per participant overall and by system organ class and preferred term.
- the number and percentage of participants with any AE, and number and percentage of AEs by body system, preferred term, and severity
- the number and percentage of participants with any AE, and number and percentage of AEs by body system, preferred term, and relationship to study product
- listing of all infant composite AEs, including participant ID, cohort, mother's randomization arm, site, whether or not the AE was an SAE, preferred term, severity, relationship to study product, visit of AE report, AE onset date, AE outcome date, AE duration, AE outcome, and associated comments.
- the above summaries will be repeated using the Infant Exposure Analysis Set

The denominator for all percentages described above is the number of infants in the analysis set. All summaries will be presented by arm across all cohorts, and by arm within each cohort. No statistical comparisons are planned.

10.3 Product Holds

The number and percentage of participants who had at least one product hold, the total number of product holds, the number and percentage of reasons for product hold, the number and percentage of the instructions whether to resume study product use, and the duration of product hold (for those holds where the participant was instructed to resume use) will be summarized in tables. These tables will be presented by arm and overall for each of the three cohorts, and by arm and overall for the three cohorts combined. Product holds are collected on the Product Hold CRF.

The denominator for the percentage of participants with at least one product hold will be the number of mothers in the analysis set. The denominator for the other percentages will be the total number of product holds. The duration of product hold will be summarized as a continuous variable (see Section 5 General Analysis Methods).

10.4 Mother Laboratory Evaluations

Results of mother laboratory evaluations will be summarized for the following tests: hemogram (hemoglobin, hematocrit, MCV, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophiles, and basophils) test results as collected on the Hematology CRF, chemistries (AST, ALT, creatinine, and creatinine clearance) test results as collected on the Chemistry Panel CRF, and dipstick urinalysis (leukocyte esterase, nitrites, protein, and glucose) test results as collected on the Urine Test Results CRF. Boxplots (for continuous variables, i.e., hemogram and chemistries) and tables with summary statistics (for all) will be reported for laboratory evaluations performed at expected visits. These summaries will be by visit, by arm and overall for each of the three cohorts, and by visit, by arm and overall for the three cohorts combined. Results from non-expected visits, including interim visits, will not be summarized in the boxplots or summary tables.

Expected visits for hemogram, chemistries (AST and ALT), and dipstick urinalysis are the following:

- Screening (visit 1)
- Enrollment (visit 2)
- first 4-week visit (visit 6; this visit only for Cohorts 2 and 3)

- the visit corresponding to, or immediately following, the 28th week of gestation (only for Cohort 3; this is visit 10 if the participant had a gestational age of 20-23 weeks at enrollment, visit 14 if the gestational age was 16-19 weeks, or visit 18 if the gestational age was 12-15 weeks, all according to the Pregnancy Assesment CRF, see Section 3.2 Statistical Analysis Issues)
- 6-week PPO visit/SEV/early SEV (visit 103)

The results for the 28th week of gestation visit will be reported as one visit (i.e., not reported separately for visit 10, visit 14, and visit 18).

Expected visits for creatinine and creatinine clearance are the following:

- Screening (visit 1)
- Enrollment (visit 2)
- second bi-weekly visit/first 4-week visit (visit 6)
- 4-week visit 12 weeks after first 4-week visit (Cohorts 2 and 3 only; visit 18)
- 6-week PPO visit/SEV/early SEV (visit 103)

10.5 Infant Laboratory Evaluations

Boxplots and tables with summary statistics will be reported for infant creatinine results at expected visits. These summaries will be by visit, by mother randomization arm and overall for each of the three cohorts, and by visit, by arm and overall for the three cohorts combined. Results from non-expected visits, including interim visits, will not be summarized in the boxplots or summary tables. Creatine test results were expected at the PPO visit (visit 201) and at the 6-week PPO visit (visit 203).

10.6 Mother HIV-1

Tables summarizing the number and percentage of participants with post-enrollment HIV-1 diagnosis will be prepared. A participant will be considered to have been diagnosed with HIV-1 if they have an HIV Confirmatory Results CRF with a “Final HIV Status” of HIV infected at any visit after Enrollment. The denominator will be the number of participants in the analysis set with at least one post-Enrollment visit HIV Test Results CRF indicating that a rapid HIV test sample collected for testing. These tables will be presented by study arm and overall for each of the three cohorts, and by arm and overall for the three cohorts combined.

10.7 Infant HIV-1

Tables summarizing the number and percentage of infants with an HIV-1 diagnosis will be prepared. An infant will be considered to have been diagnosed with HIV-1 if they have an Infant HIV Confirmatory Results CRF with a “Final HIV Status” of HIV infected. The denominator will be the number of infants in the analysis set. These tables will be presented by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined.

10.8 Sexually Transmitted Infections

The number and percentage of participants diagnosed with syphilis, trichomonas, gonorrhea, or chlamydia, as well as the number and percentage diagnosed with any of those four STIs during follow-up will be summarized in tables, by arm and overall for each of the three cohorts, and by arm and overall for the three cohorts combined. These will be summarized using the STI Test Results CRF from follow-up visits (e.g., Week 1 Phone Contact/Visit 3 or later).

A positive result for trichomonas, gonorrhea, or chlamydia is defined as having a value of “Positive” for “Trichomonas test”, “N. gonorrhea”, or “C. trachomatis” respectively, and a negative result as having a value of “Negative”. A positive result for syphilis is defined as having a value of “Reactive” for “Syphilis

screening test" and a value of "Positive" for "Syphilis confirmatory test", and a negative result if the syphilis test was done but did not meet the above definition for positivity. If "Was a vaginal sample collected for NAAT for GC/CT/Trich testing?" is "No" or the response to "Trichomonas test" is "Not done" or missing the participant will not be counted in the denominator for trichomonas. If "Was a vaginal sample collected for NAAT for GC/CT/Trich testing?" is "No" or the response to "N. gonorrhea" is "Not done" or missing the participant will not be counted in the denominator for gonorrhea, and if "Was a vaginal sample collected for NAAT for GC/CT/Trich testing?" is "No" or the response to "C. trachomatis" is "Not done" or missing the participant will not be counted in the denominator for chlamydia.

Participants will be categorized as a positive result if they ever had a positive result during follow-up (e.g., participants will only be counted once per STI). Participants will be categorized as a negative result for each if they had at least one test result during follow-up and no positive results.

10.9 Concomitant Medications

Concomitant medications will be summarized in tables, by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined. These tables will summarize:

- Number and percentage of randomized participants who had any concomitant medications (yes or no), and the number of medications.
- Number and percentage of randomized participants with at least one concomitant medication in each observed ATC Level 3 category, and the total number of concomitant medications in each ATC Level 3 category.
- Within each ATC Level 3 category, the number and percentage of randomized participants with at least one concomitant medication in each observed ATC Level 1 category, and the total number of concomitant medications in each ATC Level 1 category. The denominator for these percentages is the number of participants in the ITT Analysis Set.

Concomitant medications are defined as medications recorded on the Concomitant Medications Log CRF that overlapped with a participants' time on study; i.e., that had a "Date stopped" on or after the participant's randomization date, or that were marked "Ongoing".

10.10 Infant Concomitant Medications

Infant concomitant medications will be summarized in tables, by study arm and overall for each of the three cohorts, and by study arm and overall for the three cohorts combined.

- Number and percentage of enrolled infants who had any concomitant medications (yes or no), and the number of medications.
- Number and percentage of enrolled infants with at least one concomitant medication in each observed ATC Level 3 category, and the total number of concomitant medications in each ATC Level 3 category.
- Within each ATC Level 3 category, the number and percentage of enrolled infants with at least one concomitant medication in each observed ATC Level 1 category, and the total number of concomitant medications in each ATC Level 1 category. The denominator for these percentages is the number of infants in the ITT Analysis Set.

Infant concomitant medications are defined as medications recorded on the Concomitant Medications Log CRF that overlapped with an infant's time on study; i.e., that had a "Date stopped" on or after the infant's birth date, or that were marked "Ongoing".

10.11 Physical Examination

Tables summarizing physical examination findings will be prepared. These summaries will be by visit, by arm and overall for each of the three cohorts, and by visit, by arm and overall for the three cohorts combined. These will be summarized for visits where the physical examination was expected to be performed.

Expected visits for physical examinations are the following:

- Screening (visit 1)
- 4-week visits (e.g., visit 6, visit 10, visit 14, etc.; these visits only for Cohorts 2 and 3) (targeted exam only, i.e., only general appearance)
- PPO visit (visit 101) (targeted exam only, i.e., only general appearance)

These tables will use data collected on the Physical Examination CRF and will include:

- Number and percentage of participants with a physical exam (non-missing value on the “Physical exam” item), with the denominator being the number of participants in the ITT Analysis Set who completed the visit.
- Number and percentage of participants with each physical exam result (not done, normal, or abnormal findings), with the denominator being the number with a physical exam. Note that a result being missing entirely is treated as different from a result being marked as “not done”
    - The "General appearance” item will be summarized for all expected visits. The remaining items will only be summarized for Screening.

10.12 Infant Physical Exam

Tables summarizing infant physical examination findings will be prepared. These summaries will be by visit, by arm and overall for each of the three cohorts, and by visit, by arm and overall for the three cohorts combined. These will be summarized for visits where the infant physical examination was expected to be performed.

Expected visits for physical examinations are the following:

- PPO visit (visit 201)
- 6-week PPO visit (visit 203)
- 6-month PPO visit (visit 204)
- 12-month PPO visit/early SEV (visit 205)

These tables will use data collected on the Physical Examination CRF and will include:

- Number and percentage of infants with a physical exam (non-missing value on the “Physical exam” item), with the denominator being the number of infants in the ITT Analysis Set who completed the visit.
- Number and percentage of infants with each physical exam result (not done, normal, or abnormal findings), with the denominator being the number with a physical exam. Note that a result being missing entirely is treated as different from a result being marked as “not done”
    - The “Heart/Cardiovascular”, “Lung/Respiratory”, and "General appearance” items will be summarized for all expected visits. The remaining items will only be summarized for the PPO visit.

10.13 Infant Ages and Stages Assessment

Tables summarizing infant ages and stages will be prepared. These summaries will be by visit, by arm and overall for each of the three cohorts, and by visit, by arm and overall for the three cohorts combined. These will be summarized for visits where the infant ages and stages assessment was expected to be collected, which are the 6-month PPO visit (visit 204) and the 12-month PPO visit/early SEV (visit 205).

These tables will use data collected on the Infant Ages and Stages Assessment CRF and will include:

- Number and percentage of infants with an Ages and Stages Assessment completed (non-missing value on the "Was the Ages and Stages Assessment Completed?" item), with the denominator being the number of infants in the ITT Analysis Set who completed the visit.
- Summaries of the "Communication total", "Gross Motor total", "Fine Motor total", "Problem solving total", and "Personal-Social total" items as continuous variables.
- Number and percentage of infants with abnormalities observed for communication, gross motor, fine motor, problem solving, personal-social, and other abnormalities, with the denominator being the number of infants with the Ages and Stages Assessment completed.
- Summary of the sum of the communication, gross motor, fine motor, problem solving, and person-social totals, as a continuous variable.
- Number and percentage of infants with any abnormality observed (across communication, gross motor, fine motor, problem solving, personal-social, and other), and the total number of abnormalities.

10.14 Edinburgh Postnatal Depression Scale

Tables summarizing results from the Edinburgh Postnatal Depression Scale will be prepared. These summaries will be by visit, by arm and overall for each of the three cohorts, and by visit, by arm and overall for the three cohorts combined. These will be summarized for visits where the questionnaire was expected to be administered.

Expected visits for the Edinburgh Postnatal Depression Scale are the following:

- Enrollment visit (visit 2)
- 4-week visit corresponding to, or immediately following, the 30th week of gestation (only for Cohort 3; this is visit 6 if the gestational age at enrollment was 26-29 weeks, visit 10 if the GA was 22-25 weeks, visit 14 if the GA was 18-21 weeks, visit 18 if the GA was 14-17 weeks, or visit 22 if the GA was 12-13 weeks)
- 6-week PPO visit (visit 103)

These tables will use data collected on the Edinburgh Postnatal Depression Score CRF and will include:

- Number and percentage of participants with an assessment performed ("Was this assessment performed?" was "Yes"), with the denominator being the number of participants in the ITT Analysis Set who completed the visit.
- Number and percentage of participants with each response to the 10 items on the questionnaire ("I have been able to laugh and see the funny side of things", "I have looked forward with enjoyment to things", "I have blamed myself unnecessarily when things went wrong", "I have been anxious or worried for no good reason", "I have felt scared or panicky for no very good reason", "Things have been getting on top of me", "I have been so unhappy that I have had difficulty sleeping", "I have felt sad or miserable", "I have been so unhappy that I have been crying", "The thought of harming myself has occurred to me"), with the denominator being the number of participants in the ITT Analysis Set with an assessment performed.
- Number and percentage of participants who were subsequently referred for further evaluation and/or management ("Following completion of this questionnaire, was the mother subsequently referred for further evaluation and/or management"), with the denominator being the number of participants in the ITT Analysis Set with an assessment performed.
- Summary of the EPDS Score as a continuous variable.

10.15 Infant Demographics

Tables summarizing infant sex at birth will be prepared and will be by arm and overall for each of the three cohorts, and by arm and overall for the three cohorts combined. These will be summarized using the "sex at birth" item on the Infant Demographics CRF.

10.16 Social Benefits

Tables summarizing social benefits will be prepared and will be by arm and overall for each of the three cohorts, and by arm and overall for the three cohorts combined. These summaries will include responses from the Social Benefits CRF collected at the 6-week PPO visit (visit 103), including interim 6-week PPO visits for participants who did not have the Social Benefits CRF collected at their scheduled 6-week PPO visit.

These tables will include:

- Numbers and percentages of participants with each possible response to items under "From your perspective, what are all the benefits of participating in this study?" (i.e., from "The financial reimbursement", "Free health care from the study",…, "To help my relationship with my partner and/or family", and "Other"), with the denominators being the number of participants in the ITT Analysis Set.
- Number and percentage of participants with each response to "What is the most important benefit or reason for your participation in this study?", with the denominator being the number of participants in the ITT Analysis Set.

10.17 Social Impacts

Tables summarizing social impacts will be prepared and will be by arm and overall for each of the three cohorts, and by arm and overall for the three cohorts combined. These tables will include:

- Number and percentage of participants who reported a social impact during the study (any Social Impact Y/N CRF with a "Has the participant reported a social impact during the study?" of "Yes"), with the denominator being the number of participants in the ITT Analysis Set.
- Number and percentage of participants with each type of social impact ("Social impact type" from the Social Impact Log CRF) and the total number of each type of impact. The denominator will be the number of participants who reported a social impact.
- Number and percentage of participants who reported an impact involving physical harm ("Did this involve physical harm to the participant?") and the total number of impacts involving physical harm. The denominator will be the number of participants who reported a social impact.
- Number and percentage of participants who reported an impact involving harm to children ("Did this involve physical or other harm to participant's child(ren)?") and the total number of impacts involving harm to children. The denominator will be the number of participants who reported a social impact.
- The total number of impacts with each level of impact ("What impact did this situation have on the participant's quality of life?", responses of "minimal disturbance", "moderate disturbance; no significant impact", and "major disturbance with significant impact").
- The total number of impacts with each current status ("Current status", responses of "unresolved", "unresolved at end of study", "unable to resolve; no further action taken", "resolved).

11. CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		
1.0	Date of last signature	All	New document

12. APPENDIX I Mother Expected Visits from Week 5 until Pregnancy Outcome

Table 3: Cohort 1 Mother Expected Visits from Week 5 until Pregnancy Outcome

GA (wks) at Enrollment	Week 5 (phone contact)
37	
36	Visit (GA 41)

Cells shaded blue represent expected phone contact visits. The parenthetical "GA x" displays the gestational age in weeks of the participant at that visit. Visits in this table are only considered expected up until the participant's pregnancy outcome.

Note that the 37 weeks gestational age at enrollment group did not have any expected visits between Visit 6 – Week 4 and their pregnancy outcome.

Table 4: Cohort 2 Mother Expected Visits from Week 5 until Pregnancy Outcome

GA (wks) at Enrollment	Week 5 (phone contact)	Week 6 (in-person	Week 7 (phone contact)	Week 8 (in-person)	Week 9 (phone contact)	Week 10 (in-person)	Week 11 (phone contact
35	Visit 7 (GA 40)	Visit 8 (GA 41)					
34	Visit 7 (GA 39)	Visit 8 (GA 40)	Visit 9 (GA 41)				
33	Visit 7 (GA 38)	Visit 8 (GA 39)	Visit 9 (GA 40)	Visit 10 (GA 41)			
32	Visit 7 (GA 37)	Visit 8 (GA 38)	Visit 9 (GA 39)	Visit 10 (GA 40)	Visit 11 (GA 41)		
31	Visit 7 (GA 36)	Visit 8 (GA 37)	Visit 9 (GA 38)	Visit 10 (GA 39)	Visit 11 (GA 40)	Visit 12 (GA 41)	
30		Visit 8 (GA 36)	Visit 9 (GA 37)	Visit 10 (GA 38)	Visit 11 (GA 39)	Visit 12 (GA 40)	Visit 13 (GA 41)

Cells shaded blue represent expected phone contact visits. Cells shaded yellow represent expected in-person visits. The parenthetical "GA x" displays the gestational age in weeks of the participant at that visit. Visits in this table are only considered expected up until the participant's pregnancy outcome.

Table 5: Cohort 3 GA 24-29 weeks Mother Expected Visits from Week 5 until Pregnancy Outcome

Cells shaded blue represent expected phone contact visits. Cells shaded yellow represent expected in-person visits. The parenthetical "GA x" displays the gestational age in weeks of the participant at that visit. Visits in this table are only considered expected up until the participant's pregnancy outcome.

GA (wks) at Enroll	Week 7 (phone contact)	Week 8 (in-person)	Week 9 (phone contact)	Week 10 (in-person)	Week 11 (phone contact	Week 12 (in-person)	Week 13 (phone contact)	Week 14 (in-person)	Week 15 (phone contact)	Week 16 (in-person)	Week 17 (phone contact)
29	Visit 9 (GA 36)	Visit 10 (GA 37)	Visit 11 (GA 38)	Visit 12 (GA 39)	Visit 13 (GA 40)	Visit 14 (GA 41)					
28		Visit 10 (GA 36)	Visit 11 (GA 37)	Visit 12 (GA 38)	Visit 13 (GA 39)	Visit 14 (GA 40)	Visit 15 (GA 41)				
27		Visit 10 (GA 35)	Visit 11 (GA 36)	Visit 12 (GA 37)	Visit 13 (GA 38)	Visit 14 (GA 39)	Visit 15 (GA 40)	Visit 16 (GA 41)			
26		Visit 10 (GA 34)		Visit 12 (GA 36)	Visit 13 (GA 37)	Visit 14 (GA 38)	Visit 15 (GA 39)	Visit 16 (GA 40)	Visit 17 (GA 41)		
25		Visit 10 (GA 33)			Visit 13 (GA 36)	Visit 14 (GA 37)	Visit 15 (GA 38)	Visit 16 (GA 39)	Visit 17 (GA 40)	Visit 18 (GA 41)	
24		Visit 10 (GA 32)				Visit 14 (GA 36)	Visit 15 (GA 37)	Visit 16 (GA 38)	Visit 17 (GA 39)	Visit 18 (GA 40)	Visit 19 (GA 41)

Note that these gestational ages at enrollment groups did not have any expected visits after Visit 6 and prior to Visit 9 and these visits are omitted from Table 5.

Table 6: Cohort 3 GA 18-23 weeks Mother Expected Visits from Week 5 until Pregnancy Outcome

GA (wks) at Enroll	Wk 8	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21	Wk 22	Wk 23
23	V10 (GA 31)	V14 (GA 35)	V15 (GA 36)	V16 (GA 37)	V17 (GA 38)	V18 (GA 39)	V19 (GA 40)	V20 (GA 41)					
22	V10 (GA 30)	V14 (GA 34)		V16 (GA 36)	V17 (GA 37)	V18 (GA 38)	V19 (GA 39)	V20 (GA 40)	V21 (GA 41)				
21	V10 (GA 29)	V14			V17(GA 36)	V18 (GA 37)	V19 (GA 38)	V20 (GA 39)	V21 (GA 40)	V22 (GA 41)			
20	V10 (GA 28)	V14 (GA 32)				V18 (GA 36)	V19 (GA 37)	V20 (GA 38)	V21 (GA 39)	V22 (GA 40)	V23 (GA 41)		
19	V10 (GA 27)	V14 (GA 31)				V18 (GA 35)	V19 (GA 36)	V20 (GA 37)	V21 (GA 38)	V22 (GA 39)	V23 (GA 40)	V24 (GA 41)	
18	V10 (GA 26)	V14 (GA 30)				V18 (GA 34)		V20 (GA 36)	V21 (GA 37)	V22 (GA 38)	V23 (GA 39)	V24 (GA 40)	V25 (GA 41)

Cells shaded blue represent expected phone contact visits. Cells shaded yellow represent expected in-person visits. The parenthetical “GA x” displays the gestational age in weeks of the participant at that visit. Visits in this table are only considered expected up until the participant’s pregnancy outcome.

Note that these gestational age at enrollment groups did not have any expected visits after Visit 6 and prior to Visit 10, and after Visit 10 and prior to Visit 14, and these visits are omitted from Table 6.

Table 7: Cohort 3 GA 12-17 weeks Mother Expected Visits from Week 5 until Pregnancy Outcome

GA (wks) at Enroll	Wk 8	Wk 12	Wk 16	Wk 19	Wk 20	Wk 21	Wk 22	Wk 23	Wk 24	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29
17	V10 (GA 25)	V14 (GA 29)	V18 (GA 33)	V21 (GA 36)	V22 (GA 37)	V23 (GA 38)	V24 (GA 39)	V25 (GA 40)	V26 (GA 41)					
16	V10 (GA 24)	V14 (GA 28)	V18 (GA 32)		V22 (GA 36)	V23 (GA 37)	V24 (GA 38)	V25 (GA 39)	V26 (GA 40)	V27 (GA 41)				
15	V10 (GA 23)	V14 (GA 27)	V18 (GA 31)		V22 (GA 35)	V23 (GA 36)	V24 (GA 37)	V25 (GA 38)	V26 (GA 39)	V27 (GA 40)	V28 (GA 41)			
14	V10 (GA 22)	V14 (GA 26)	V18 (GA 30)		V22 (GA 34)		V24 (GA 36)	V25 (GA 37)	V26 (GA 38)	V27 (GA 39)	V28 (GA 40)	V29 (GA 41)		
13	V10 (GA 21)	V14 (GA 25)	V18 (GA 29)		V22 (GA 33)			V25 (GA 36)	V26 (GA 37)	V27 (GA 38)	V28 (GA 39)	V29 (GA 40)	V30 (GA 41)	
12	V10 (GA 20)	V14 (GA 24)	V18 (GA 28)		V22 (GA 32)				V26 (GA 36)	V27 (GA 37)	V28 (GA 38)	V29 (GA 39)	V30 (GA 40)	V31 (GA 41)

Cells shaded blue represent expected phone contact visits. Cells shaded yellow represent expected in-person visits. The parenthetical “GA x” displays the gestational age in weeks of the participant at that visit. Visits in this table are only considered expected up until the participant’s pregnancy outcome.

Note that these gestational ages at enrollment groups did not have any expected visits after Visit 6 and prior to Visit 10, after Visit 10 and prior to Visit 14, after Visit 14 and prior to Visit 18, and after V18 and prior to Visit 21, and these visits are omitted from Table 7.

13. APPENDIX II Visit Timing Requirements

Table 8: Visit Timing Requirements for Mothers in Cohort 1

Visit	Target Day	Window Opens	Window Closes
Visit 1 - Screening	N/A	N/A	
Visit 2 - Day 0 Enrollment	0	Up to 35 days after screening informed consent date	
Visit 3 - Week 1 Phone Contact	7	6 days prior to target	2 days after target
Visit 4 - Week 2 Bi-weekly Visit	14	4 days prior to target	4 days after target
Visit 5 - Week 3 Phone Contact	21	2 days prior to target	2 days after target
Visit 6 - Week 4 Bi-weekly Visit	28	4 days prior to target	4 days after target
Visit 7 - Week 5 Phone Contact (women who enroll at 36 weeks GA only)	35	2 days prior to target	2 days after target
PPO Visit	as soon after the PO as possible	Pregnancy Outcome	14 days after target
1-Week PPO Phone Contact*	7 days after PO	6 days prior to target	7 days after target
6-Week PPO Visit/SEV	42 days after PO	13 days prior to target	13 days after target

*The 1-Week PPO Phone Contact may be skipped if the PPO Visit occurs within the visit window for this phone contact

Table 9: Visit Timing Requirements for Mothers in Cohort 2

Visit	Target Day	Window Opens	Window Closes
Visit 1 - Screening	N/A	N/A	
Visit 2 - Day 0 Enrollment	0	Up to 35 days after screening informed consent date	
Visit 3 - Week 1 Phone Contact	7	6 days prior to target	2 days after target
Visit 4 - Week 2 2w Visit	14	4 days prior to target	4 days after target
Visit 5 - Week 3 Phone Contact	21	2 days prior to target	2 days after target
Visit 6 - Week 4 4w Visit	28	4 days prior to target	4 days after target
Visit 7 - Week 5 Phone Contact	35	2 days prior to target	2 days after target
Visit 8 - Week 6 Bi-weekly Visit	42	4 days prior to target	4 days after target
Visit 9 - Week 7 Phone Contact	49	2 days prior to target	2 days after target
Visit 10 - Week 8 Bi-weekly Visit	56	4 days prior to target	4 days after target
Visit 11 - Week 9 Phone Contact	63	2 days prior to target	2 days after target
Visit 12 - Week 10 Bi-weekly Visit	70	4 days prior to target	4 days after target
Visit 13 - Week 11 Phone Contact	77	2 days prior to target	2 days after target
Visit 101 - PPO Visit	as soon after the PO as possible	Pregnancy Outcome	14 days after target
Visit 102 - 1-Week PPO Phone Contact*	7 days after PO	7 days prior to target	7 days after target
Visit 103 - 6-Week PPO Visit/SEV	42 days after PO	13 days prior to target	13 days after target

*The 1-Week PPO Phone Contact may be skipped if the PPO Visit occurs within the visit window for this phone contact

Table 10: Visit Timing Requirements for Mothers in Cohort 3

Visit	Target Day	Window Opens	Window Closes
Visit 1 - Screening	N/A	N/A	
Visit 2 - Day 0 Enrollment	0	Up to 35 days after screening informed consent date	
Visit 3 - Week 1 Phone Contact	7	6 days prior to target	2 days after target
Visit 4 - Week 2 2w Visit	14	4 days prior to target	4 days after target
Visit 5 - Week 3 Phone Contact	21	2 days prior to target	2 days after target
Visit 6 - Week 4 4w Visit	28	4 days prior to target	4 days after target
Visit 7	N/A	N/A	
Visit 8	N/A	N/A	
Visit 9 - Week 7 Phone Contact	49	2 days prior to target	2 days after target
Visit 10 - Week 8 Bi-weekly Visit (participants enrolled at 29 weeks gestation)	56	4 days prior to target	4 days after target
Visit 10 - Week 8 4w Visit (participants enrolled at 12-28 weeks gestation)	56	4 days prior to target	4 days after target
Visit 11 - Week 9 Phone Contact	63	2 days prior to target	2 days after target
Visit 12 - Week 10 Bi-weekly Visit	70	4 days prior to target	4 days after target
Visit 13 - Week 11 Phone Contact	77	2 days prior to target	2 days after target
Visit 14 - Week 12 Bi-weekly Visit (participants enrolled at 25-29 weeks gestation)	84	4 days prior to target	4 days after target
Visit 14 - Week 12 4w Visit (participants enrolled at 12-24 weeks gestation)	84	4 days prior to target	4 days after target
Visit 15 - Week 13 Phone Contact	91	2 days prior to target	2 days after target
Visit 16 - Week 14 Bi-weekly Visit	98	4 days prior to target	4 days after target

Visit 17 - Week 15 Phone Contact	105	2 days prior to target	2 days after target
Visit 18 - Week 16 Bi-weekly Visit (participants enrolled at 21-25 weeks gestation)	112	4 days prior to target	4 days after target
Visit 18 - Week 16 4w Visit (participants enrolled at 12-20 weeks gestation)	112	4 days prior to target	4 days after target
Visit 19 - Week 17 Phone Contact	119	2 days prior to target	2 days after target
Visit 20 - Week 18 Bi-weekly Visit	126	4 days prior to target	4 days after target
Visit 21 - Week 19 Phone Contact	133	2 days prior to target	2 days after target
Visit 22 - Week 20 Bi-weekly Visit (participants enrolled at 17-21 weeks gestation)	140	4 days prior to target	4 days after target
Visit 22 - Week 20 4w Visit (participants enrolled at 12-16 weeks gestation)	140	4 days prior to target	4 days after target
Visit 23 - Week 21 Phone Contact	147	2 days prior to target	2 days after target
Visit 24 - Week 22 Bi-weekly Visit	154	4 days prior to target	4 days after target
Visit 25 - Week 23 Phone Contact	161	2 days prior to target	2 days after target
Visit 26 - Week 24 Bi-weekly Visit (participants enrolled at 13- 17 weeks gestation)	168	4 days prior to target	4 days after target
Visit 26 - Week 24 4w Visit (participants enrolled at 12 weeks gestation)	168	4 days prior to target	4 days after target
Visit 27 - Week 25 Phone Contact	175	2 days prior to target	2 days after target
Visit 28 - Week 26 Bi-weekly Visit	182	4 days prior to target	4 days after target
Visit 29 - Week 27 Phone Contact	189	2 days prior to target	2 days after target

Visit 30 - Week 28 Bi-weekly Visit	196	4 days prior to target	4 days after target
Visit 31 - Week 29 Phone Contact	203	2 days prior to target	2 days after target
Visit 101 - PPO Visit	as soon after the PO as possible	Pregnancy Outcome	14 days after target
Visit 102 - 1-Week PPO Phone Contact*	7 days after PO	7 days prior to target	7 days after target
Visit 103 - 6-Week PPO Visit/SEV	42 days after PO	13 days prior to target	13 days after target

*The 1-Week PPO Phone Contact may be skipped if the PPO Visit occurs within the visit window for this phone contact

Table 11: Visit Timing Requirements for Infants

Visit	Target Day	Window Opens	Window Closes
V201 - PPO Visit	as soon after the PO as possible	Pregnancy Outcome	14 days after target
V202 - 1-Week PPO Phone Contact	7 days after PO	6 days prior to target	7 days after target
V203 - 6-Week PPO Visit	42 days after PO	13 days prior to target	13 days after target
V204 - 6-Month PPO Visit	183 days after PO	28 days prior to target	28 days after target
V205 - 12-Month PPO Visit	365 days after PO	28 days prior to target	28 days after target

*The 1-Week PPO Phone Contact may be skipped if the PPO Visit occurs within the visit window for this phone contact

14. APPENDIX III Residual Drug Levels Calculation

The DPV release rate per 28 days of use is calculated as:

$$rate = \frac{(conc_m - conc_r)}{days} \times 28$$

With $conc_m$ being the amount of residual drug in the manufacturer lot, $conc_r$ being the amount of residual drug in the returned ring, and *days* being the number of days the participant should have been using the ring.

An individual ring is identified in the lab residual DPV data using the `guspec` identifier, with each individual ring having it's own unique identifier. Some rings were tested multiple times and will have multiple observations with the same `guspec` value. Observations with censor values of "(A)X", "(A) X", "(B)X", "(B) X", "(B)Z", "(B) Z", or "Z" should not be analyzed. The amount of residual dapivirine in the ring ($conc_r$ above) is indicated by the value of `conc`.

Rings from the lab residual DPV data are linked to the clinical data through the Ring Insertion and Removal CRF, using the participant ID (`ptid`) and specimen collection date (`spcdt`) from the lab data and participant ID and the "Date ring returned" from the CRF data. For participants with multiple rings collected on the same date (i.e., two observations with same `ptid` and `spcdt` and different `guspec`), one ring needs to be assigned to correspond to "ring #1" in the Ring Return section of the CRF, and one to "ring #2". In this case, the lab observation with the smaller value of `recnum` will be linked to the earlier ring return date on the CRF, and the larger value of `recnum` will be linked to the later ring return date.

The number of days (*days* in the above equation) is calculated by taking the specimen collection date – "date returned ring #1 was provided" + 1 day (or "date returned ring #2 was provided"), unless the specimen collection date is after the participant's pregnancy outcome date, in which the duration is calculated as the pregnancy outcome date – "date returned ring #1 was provided" + 1 day.

Ring lot number is determined by linking the "date returned ring #1/#2 was provided" to the Pharmacy Dispensation CRF "date study product dispensed" and taking the "vaginal ring #1 lot number" or "vaginal ring #2 lot number", as appropriate. That lot number is linked to the manufacturer record of the concentration for that lot ($conc_m$ above).