EMA/597357/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of indication variation

Procedure No. EMEA/H/W/002168/II/0027

Invented name: Dapivirine Vaginal Ring 25 mg

International non-proprietary name: dapivirine

Scientific opinion Holder (SOH): International Partnership for Microbicides Belgium AISBL

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Status of this report and steps taken for the assessment		
Current step	**Description**	**Actual Date**
☐	Start of procedure	02 Nov 2024
☐	CHMP Rapporteur Assessment Report	19 Dec 2024
☐	PRAC Rapporteur Assessment Report	03 Jan 2025
☐	PRAC members comments	08 Jan 2025
☐	Updated PRAC Rapporteur Assessment Report	09 Jan 2025
☐	PRAC endorsed relevant sections of the assessment report	16 Jan 2025
☐	CHMP members comments	20 Jan 2025
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 Jan 2025
☐	Request for supplementary information	30 Jan 2025
☐	Submission of Responses	16 Apr 2025
☐	Re-start of procedure	21 Apr 2025
☐	CHMP Rapporteur Assessment Report	21 May 2025
☐	PRAC Rapporteur Assessment Report	21 May 2025
☐	PRAC members comments	27 May 2025
☐	Updated PRAC Rapporteur Assessment Report	28 May 2025
☐	PRAC endorsed relevant sections of the assessment report	05 Jun 2025
☐	CHMP members comments	10 Jun 2025
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	n/a
☒	Opinion	19 Jun 2025

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List of abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AEOI	Adverse event of interest
AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
CAB LA	Cabotegravir long-acting (injection)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
CTM	Clinical Trial Manufacturing
CYP	Cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug-drug interaction
DSMB	Data and Safety Monitoring Board
DVR-004	Dapivirine Vaginal Ring 25 mg
EMA	European Medicines Agency
EoI	Extension of the Indication
EU	European Union
FDA	(US) Food and Drug Administration
FTC	Emtricitabine
HIV	Human immunodeficiency virus
HIVdb	HIV database
HIV-1	Human immunodeficiency virus type 1
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational product
IPM	International Partnership for Microbicides
LPUV	Last Product Use Visit
m-ITT	Modified intent-to-treat
NA	Not applicable
NGS	Next generation sequencing

NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside or nucleotide reverse transcriptase inhibitor
PrEP	Pre-exposure prophylaxis
RAM	Resistance-associated mutation
RNA	Ribonucleic acid
RT	Reverse transcriptase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
STI	Sexually transmitted infection
SVF	Simulated vaginal fluid
TasP	Treatment-as-prevention
TDF	Tenofovir disoproxil fumarate
TEAE	Treatment-emergent adverse event
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UNAIDS	Joint United Nations Programme on HIV/AIDS
US(A)	United States (of America)
V	Volume of distribution
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
YOA	Years of age

1. Background information on the procedure

Pursuant to section 10 of the CHMP "Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organisation (WHO) for the evaluation of medicinal products intended exclusively for markets outside the community" (EMEA/CHMP/5579/04), International Partnership for Microbicides Belgium AISBL submitted to the EMA on 15 October 2024 an application for a variation[1] to the CHMP Scientific Opinion. The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 16 years and older for Dapivirine Vaginal Ring 25 mg, based on final results from study MTN-034 (REACH) listed as a category 3 study in the RMP; this is a Phase 2a crossover trial evaluating the safety of and adherence to a vaginal matrix ring containing dapivirine and oral emtricitabine/tenofovir disoproxil fumarate in an adolescent and young adult female population. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 1.5 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Scientific advice

The SOH did not seek Scientific advice at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

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☒is recommended for approval.

[1] Which corresponds, by analogy, to a Type II variation pursuant to Commission Regulation (EC) 1234/2008

Amendments to the scientific opinion

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

3. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

International Partnership for Microbicides Belgium AISBL submitted to the EMA on 15 October 2024 an application for an extension of indication to include reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 16 years and older for Dapivirine Vaginal Ring 25 mg, based on final results from study MTN-034 (REACH) listed as a category 3 study in the RMP; this is a Phase 2a crossover trial evaluating the safety of and adherence to a vaginal matrix ring containing dapivirine and oral emtricitabine/tenofovir disoproxil fumarate in an adolescent and young adult female population. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC were updated. The Package Leaflet was updated accordingly. Version 1.6 of the RMP was endorsed.

4. Scientific discussion

4.1. Introduction

4.1.1. Problem statement

Disease or condition

The proposed extension of the therapeutic indication is:

"Reducing the risk of HIV1 infection via vaginal intercourse in HIV-uninfected women **16**~~18~~ years and older in combination with safer sex practices when oral PrEP is not/cannot be used or is not available."

Epidemiology

Since the beginning of the epidemic, more than 70 million people have been infected with HIV, of which about 35 million people have died. Globally, an estimated 39 million people are living with HIV. An estimated 0.8% [0.7-0.9%] of adults and adolescents aged 15-49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 25 adults (4.2%) living with HIV

and accounting for nearly two-thirds of the people living with HIV worldwide (WHO Global Health Observatory (GHO) data).

Adolescent girls and young women still have to contend with extraordinarily high risks of HIV infection in many parts of sub-Saharan Africa, as do people from key populations everywhere. Women and girls (of all ages) accounted for 63% of all new HIV infections in sub-Saharan Africa in 2022. Gender and other inequalities, along with violence, stigma, discrimination and harmful laws and practices, sabotage their abilities to protect themselves from HIV.

Globally, only 3 in every 10 adolescent girls and young women aged 15-24 years have comprehensive and accurate knowledge about HIV. The lack of information on HIV prevention and the power to use this information in sexual relationships, including in the context of marriage, undermines women's ability to negotiate condom use and engage in safer sex practices.

For more information, please refer to https://www.unaids.org/sites/default/files/media_asset/2023-unaids-global-aids-update-summary_en.pdf.

Biologic features, aetiology and pathogenesis

HIV-1 infection is a blood-born infection. HIV is a retrovirus that infects and replicates primarily in human CD4+ T cells and macrophages. HIV can be transmitted via blood, blood products, sexual fluids, other fluids containing blood, and breast milk. Most individuals are infected with HIV through sexual contact, before birth or during delivery, during breast-feeding, or when sharing contaminated needles and syringes (intravenous drug users). Sexual intercourse is the most common mode of HIV transmission. The risk of transmission per exposure is low; estimates are on the order of 0.1% per contact for heterosexual transmission, but this varies considerably and increases with concurrent ulcerative STDs and high HIV viral load in the infected partner, e.g. due to no or non-efficient antiretroviral therapy.

Clinical presentation, diagnosis and prognosis

Acute HIV-1 infection is often missed, as it usually presents with nonspecific signs and symptoms (including fever, rash, or diarrhoea), or goes without clinical symptoms. If symptoms are present, these generally emerge approximately 2 weeks following HIV infection. Among those presenting with symptoms, the number of symptoms correlates with higher pre-seroconversion peak plasma viral load.

Diagnosis most often occurs during chronic infection. Recent estimates suggest that even in high-income settings; about 25-35% of people living with HIV starting ART have a CD4 cell count of less than 200 cells/mm3. In some settings, up to half of the people present to care with advanced HIV disease – defined by WHO as having a CD4 cell count <200 cells/mm3 or a WHO clinical stage 3 or 4 disease. Leading causes of mortality among adults with advanced HIV disease globally include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia.

Diagnostic tests for HIV-1 infection include assays for HIV-1 RNA, p24 antigen, and HIV-1 and HIV-2 antibodies.

Management

HIV prevention strategies have long been focussed on increasing correct condom use, and voluntary medical male circumcision (VMMC). More recently, treatment as prevention (TasP) and oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil (TDF) have been recognised as valuable HIV prevention strategies.

As of June 2016, the WHO recommends to offer PrEP as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches. As such, the recommendation to offer PrEP is no longer limited to specific populations (see WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, second edition):

Oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence).

For oral PrEP using emtricitabine+tenofovir disoproxil (FTC/TDF), efficacy against HIV-1 infection has convincingly been shown to be related to the level of adherence of individual subjects. The better the adherence to daily administration the better is the protection that is afforded. Regular monitoring of an individual on PrEP for HIV-1 infection, other sexually transmitted infections (STIs) and adverse drug reactions, as well as counselling the subject to strictly adhere to the recommended dosing schedule, are considered important for the correct use of oral PrEP in daily practice.

Many women in sub-Saharan Africa live in highly patriarchal societies where they have very limited economic options. Because of this gender and social inequality, they cannot reliably negotiate the use of protective methods during sexual encounters, leaving them vulnerable to sexually transmitted infections, including HIV. The fact that many currently available biomedical prevention methods require partner participation/consent or may be associated with the stigma of HIV infection is a key obstacle to consistent use. This, together with the continued high risk of HIV transmission to women in sub-Saharan Africa makes it especially important to develop additional options that enable women to reduce their risk of HIV infection without the need for male partner negotiation. An effective vaginal microbicide could offer an additional urgently needed female-initiated option for prevention of HIV-infection.

4.1.2. About the product

The applicant has developed a silicone elastomer ring as a vaginal delivery system that provides sustained release of dapivirine (a non-nucleoside inhibitor of HIV-1 reverse transcriptase [NNRTI]) over a 28-day period to reduce transmission of HIV-1 to at-risk women through vaginal intercourse.

NNRTIs have antiviral activity against HIV-1 infection, achieved via allosteric binding to HIV-1 reverse transcriptase (RT) to block RT activity, thereby preventing viral replication.

Silicone elastomer vaginal rings are currently used to deliver hormones for contraception and hormone replacement therapy.

The proposed use of Dapivirine Vaginal Ring 25 mg (also referred to as DVR-004) is as follows:

One Dapivirine Vaginal Ring 25 mg containing 25 mg dapivirine is inserted into the vagina and kept in until replaced each month with a new ring. Reduced risk of HIV-1 infection is achieved after 24 hours of ring insertion. To maintain efficacy, a new Dapivirine Vaginal Ring 25 mg is recommended by the Applicant to be inserted immediately after the previous ring is removed.

The dapivirine molecule was originally developed as an oral ARV drug in the late 1990s for the treatment of HIV-1 infection. The anti-HIV-1 activity of dapivirine has been evaluated in a variety of models and against a range of HIV-1 strains from multiple subtypes including subtype C and other subtypes prevalent in sub-Saharan Africa. The oral clinical development program consisted of eleven Phase I/II trials including more than 200 participants who were exposed to oral doses of dapivirine ranging from 50 to 1000 mg daily. The maximum tolerated oral dose was established as 300 mg twice daily for multiple doses. According to the applicant, based on its in vitro and in vivo efficacy and favourable safety profile shown in the nonclinical studies and clinical trials, as well as its physical and chemical properties,

dapivirine was further developed as a topical microbicide for the prevention of HIV-1 infection.

4.1.3. The development programme/compliance with CHMP guidance/scientific advice

Dapivirine Vaginal Ring 25 mg received a positive scientific opinion under the EU-M4all procedure (based on Article 58 of Regulation (EC) No 726/2004) on 23 July 2020 and has been included in the updated WHO Consolidated Guidelines on HIV prevention, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach in July 2021. No scientific advice has been provided in the context of this EoI.

4.1.4. General comments on compliance with GLP, GCP

The Applicant states that the trial was conducted according to the protocol and in full compliance with the principles of the revision of the Declaration of Helsinki that was current at the time of trial conduct, the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) in clinical trials and other applicable regulatory requirements.

However, there were issues identified on the conduct of the clinical trial MTN-034 regarding Good Clinical Practise (GCP) compliance. First, the analyses of several exploratory endpoints such as data on vaginal microbiota and evaluation of candidate biomarkers of safety and efficacy in mucosal secretions, described in the SAP and protocol, were either not performed or the data were not collected. No clarification of the omission of these exploratory endpoints is provided. Although not in compliance with GCP, this issue was not further pursued as these endpoints are considered of little clinical significance in the context of this extension of the indication. Second, it was not clear if the power calculations for the sample size were based on the original 300 participants described in the protocol or on the 250 participants mentioned in the SAP. Similarly to the first issue, this was not further pursued as all provided primary analyses are descriptive and the actual sample size is considered sufficient for descriptive comparisons.

There were however also some GCP issues identified that could be of clinical significance to the benefit/risk analysis and these were further addressed by the Applicant (see also section 'Annex I – Request for Supplementary Information). These issues concerned the absence of description of a database lock for MTN-034, a SAP dated several months after last participant last visit of the clinical trial, provision of more information regarding the nature of ten deviations that required notification of the sponsor as critical events, and clarifications on study populations included in the primary and secondary analyses. The Applicant provided more information which resulted in reassurance that these had no impact on the B/R analysis.

4.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

4.3. Clinical aspects

4.3.1. Introduction

The scope of this Type II, Category C.I.6.a, variation is for an extension of the indication to include adolescent girls of 16 years and older in addition to women of 18 years and older for Dapivirine Vaginal Ring 25 mg, based on final results from study MTN-034 (REACH). This trial was a two sequence open-

label crossover trial of Truvada and Dapivirine Vaginal Ring 25 mg use followed by a product choice period which evaluated the adherence and safety of the two study products in healthy, HIV negative, sexually active adolescent girls and young women from South Africa, Uganda and Zimbabwe. This dossier is submitted for an evaluation under Article 58 of Regulation (EC) No 726/2004 and therefore there is no requirement to provide results in accordance with agreed paediatric investigation plans (PIPs). Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC for Dapivirine Vaginal Ring 25 mg are updated.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the SOH.

- Tabular overview of clinical studies

Trial number	Description	Age	Duration	Number of participants	Countries	Status
MTN-034	Phase IIa, crossover trial evaluating the safety of and adherence to a vaginal matrix ring containing dapivirine and oral emtricitabine / tenofovir disoproxil fumarate in a healthy, adolescent, and young adult, HIV-negative, female population.	16 to 21	76 weeks	239	South Africa, Kenya, Uganda, Zimbabwe	Completed

4.3.2. Pharmacokinetics

Bioanalytical methods

In study MTN-034, no plasma or vaginal fluid concentrations of dapivirine were determined. Therefore, the bioanalytical method description is limited to determining residual dapivirine ring levels. The Applicant submitted bioanalytical report (**230373**) and bioanalytical method validation report (**VAL 195/01, Parexel 206594**) to support the adequacy of the determination of residual dapivirine ring levels. The validation report has been submitted previously.

A total of 2293 post-use intra-vaginal rings from **MTN-034** were received and stored at room temperature (15 – 30°C) upon date of sample receipt. Long term stability under these conditions was demonstrated over a period of 1510 days. Sample analysis was conducted using HPLC between 10-04-2019 and 24-08-2021 at the bioanalytical services division (BASD) FARMOVS (Pty) Ltd. Of the University of the Free State (South Africa). The method was partially validated to determine the values of the quality control ring (QC_{CR}) samples.

Special populations

No plasma or vaginal fluid concentrations of dapivirine were determined.

4.3.3. Discussion on clinical pharmacology

Pharmacokinetics

The method for determining residual dapivirine ring levels post-use was validated in a bioanalytical validation study (VAL195/01, 206594), which has been considered acceptable previously during initial

scientific opinion application. The used bioanalytical method for **MTN-034** was considered acceptable and properly validated during sample analysis.

In the initial scientific opinion procedure, it was concluded that there is no clear correlation between plasma dapivirine concentrations and residual dapivirine ring levels. Therefore, variability in the residual dapivirine ring levels cannot be used to investigate a potential difference in plasma concentrations in patients between 16 and 18 years of age (YOA). However, no deviation in the pharmacokinetic profile is to be expected in patients 16 to 18 years old versus patients above 18 years.

4.3.4. Conclusions on clinical pharmacology

Pharmacokinetics

No new pharmacokinetic data was submitted in this procedure. Based on theoretical considerations, no deviation in the pharmacokinetic profile is to be expected in patients 16 to 18 years old versus patients above 18 years.

4.4. Clinical efficacy

4.4.1. Main study

MTN-034

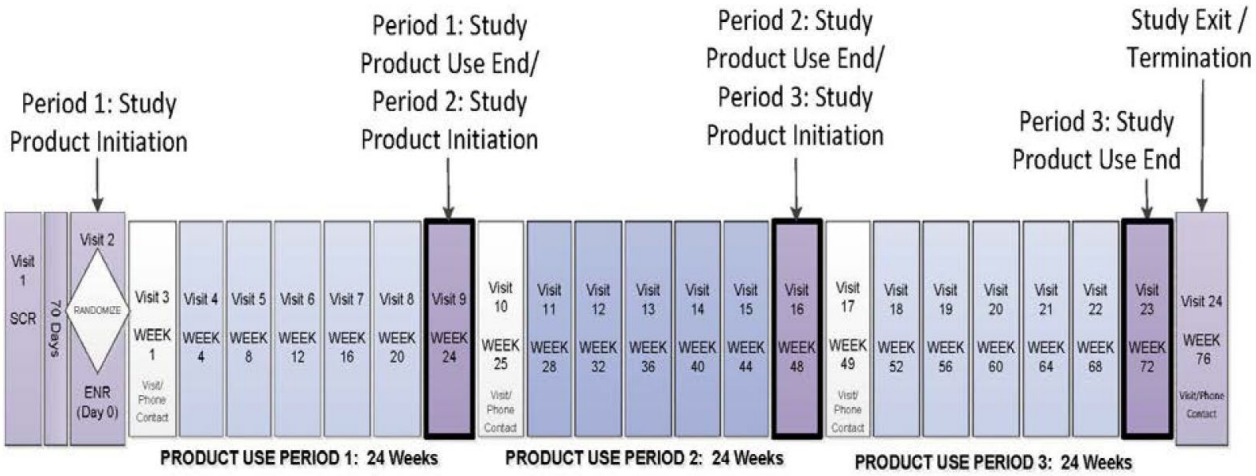
The results of study MTN-34 have been submitted in support of this application for extension of the indication to adolescents 16 YOA and older.

MTN-034 is a phase 2a, open-label, multi-site, two-sequence, crossover, randomized trial evaluating the safety of, and adherence to, Dapivirine Vaginal Ring 25 mg (DVR-004) and Truvada (emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF)) in an adolescent and young adult female population.

Methods

The trial population included healthy HIV-uninfected adolescent girls and young women aged 16-21 years at enrolment and was aimed to evaluate the safety of and adherence to DVR-004 and Truvada in this population. Each participant attended the trial for approximately 76 weeks, as illustrated in Figure 1 below:

Figure 1. Trial Visit Schedule



At visit/phone contact 3, 10 and 17 (week 1, 25 and 49, respectively) AEs were collected and reproductive tract infections (RTIs), urinary tract infections (UTIs) and sexually transmitted infections (STIs) were treated per local standard or care.

Study participants

The main inclusion criteria for study MTN-034 were:

- Aged ≥16 through ≤ 21 years (inclusive) at enrollment;
- HIV-uninfected based on testing performed at screening and enrollment;
- History of at least one episode of sexual intercourse in participant's lifetime
- Negative pregnancy test at screening and enrolment;
- Use of an effective method of contraception for at least two months prior to enrolment, and intended to continue use for the duration of trial participation.

The main exclusion criteria to study MTN-034 were:

- Access/use of oral PrEP outside the context of trial participation
- A positive HIV test at screening or enrolment
- Diagnosed with urinary tract infection (UTI), pelvic inflammatory disease (PID), STI or reproductive tract infection (RTI) requiring treatment per World Health Organization (WHO) guidelines at screening or enrollment;
- At enrollment, had a clinically apparent Grade 2 or higher pelvic exam finding (per Female Genital Grading Table for Use in Microbicide Studies Addendum 1 (dated November 2007) to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017);
- Positive for hepatitis B surface antigen (HBsAG) at screening visit.

Assessor's comment:
The population eligible for participation in MTN-034 corresponds to a population that is considered relevant for the sought indication. It is not entirely understood what is implied with the exclusion criterium of 'diagnosed UTI, PID, STI or RTI requiring treatment per WHO guidelines at screening or enrolment;', as it is stated that these infections were 'treated per local standard of care'. However, as this

is considered of little clinical relevance to the study methodology and the validity of the included study population, this issue is not further pursued.

Treatments

Table 1. Study Product Regimen

	N (Planned)	Study Product Use Period 1: 24 Weeks	Study Product Use Period 2: 24 Weeks	Study Product Use Period 3: 24 Weeks
Sequence A	150	Vaginal (monthly DVR-004)	Oral (daily Truvada tablets)	Free Choice (monthly DVR-004 or daily Truvada tablets or neither)
Sequence B	150	Oral (daily Truvada tablets)	Vaginal (monthly DVR-004)	Free Choice (monthly DVR-004 or daily Truvada tablets or neither)

Participants were randomly assigned in a 1:1 ratio to one of two sequences of two study product use periods: DVR-004 inserted vaginally monthly for 24 weeks and Truvada taken daily for 24 weeks:

• Sequence A: DVR-004 inserted monthly for 24 weeks (study product use Period 1), followed by one Truvada oral tablet (200 mg FTC + 300 mg TDF) taken daily for 24 weeks (study product use Period 2).

• Sequence B: one Truvada oral tablet (200 mg FTC + 300 mg TDF) taken daily for 24 weeks (study product use Period 1), followed by one DVR-004 inserted monthly for 24 weeks (study product use Period 2).

There was no washout period between product use periods. After completing the randomized sequence, participants selected between the two study products, DVR-004 and Truvada, to use in the final 24 weeks of the trial (study product use Period 3). Participants were able to choose either or neither study product at any time during the third study product use period. Prior to the initiation of a new study product use period (period 2 and 3), all AEs that resulted in study product holds had to be managed. If requirements were not met for product use resumption, a Protocol Safety Review Team (PSRT) had to be consulted regarding progression into the next dosing period. If a participant was scheduled to initiate DVR-004 use during her menses, she had the option to choose to delay study product initiation until the completion of her menses.

Objectives

The objectives for study MTN-034 were as followed:

Primary Objectives:

• Safety:

- To compare the safety profiles of FTC/TDF oral tablet administered daily and dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population.

• Adherence:

- To compare adherence to the FTC/TDF oral tablet administered daily and to the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population.

Secondary Objectives:

• Acceptability:

- To compare the acceptability of the FTC/TDF oral tablet administered daily and the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population.

• Adherence:

- To compare study product adherence during the **third study product use period** when study product was chosen, against the study product use period during which the same study product was randomly assigned.

• Study Product Preference:

- Participant preference between dapivirine ring and FTC/TDF oral tablets over the course of trial participation.

Exploratory Objectives:

The most important exploratory objective was:

• Human Immunodeficiency Virus (HIV) Incidence:

- To assess the incidence of HIV-1 infection over the course of dapivirine vaginal ring use and FTC/TDF oral tablet use.

Outcomes/endpoints

Primary Endpoints:

• Safety:

- Grade 2 or higher adverse events (AEs) as defined by DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017 and/or Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies, dated November 2007).

• Adherence during the randomized Crossover Period (Period 1 and 2):

- Detectable drug levels in blood

- Residual drug levels in returned used rings

Secondary Endpoints:

• Acceptability:

- Participant self-report of acceptability

• Adherence during the Product Choice Period (Period 3):

- Detectable drug levels in blood (FTC/TDF)

- Residual drug levels in returned used rings

• Study Product Preference:

- Participant product selection during third product use period

- Participant self-report of product preference

Main Exploratory Endpoints:

• HIV Incidence:

- HIV-1 infection by rapid test

Adherence
The primary analysis of adherence is restricted to adherence data based on intraerythrocytic tenofovir diphosphate (TFV-DP) concentrations in blood via dried blood spots (DBS) for Truvada, and residual drug levels in returned used rings for DVR-004 during the randomized Crossover Period (i.e. during product use Periods 1 and 2). These analyses are based on samples collected during visits taking place every 4 weeks for 24 weeks, for each of the 3 product use periods (see Figure 1). The number of rings returned versus dispensed were calculated only among rings that were returned and dispensed in the first two product use periods (e.g., a ring that was dispensed in Period 1 but not returned until Period 3 was counted as a dispensed ring but not as a returned ring for this analysis).
Dapivirine ring release rates have not been verified using directly observed dosing (DOD) and have never been calibrated to TFV-DP; therefore, these two adherence measures and the resulting categorizations are not directly comparable. The categories of adherence defined in this study for the two products are as follows:

Truvada (TFV-DP):

- No quantifiable use (< 16.6 fmol/punch)
- Some use (≥ 16.6 < 700 fmol/punch)
- High use (≥ 700 fmol/punch)

As steady-state concentrations for Truvada were not reached until 6 weeks of use, for the first month of Truvada use (week 4 for participants randomized to sequence B and week 28 for participants randomized to sequence A) the categories 'some use' were defined as ≥ 16.6 <500 fmol/punch and 'high use' as ≥ 500 fmol/punch.

DVR-004 (Dapivirine Vaginal Ring 25 mg):

- Very low/no use (release rate ≤ 0.9 mg/month)
- Some use (0.9 mg/month < release rate ≤ 4.0 mg/month)
- High use (release rate > 4.0 mg/month).

Primary analysis of safety
Regarding the safety assessment as part of the primary analysis, the following specifications were made concerning the recording of adverse events (AEs):

- Asymptomatic bacterial vaginosis and asymptomatic candidiasis were not reportable AEs, but were captured on the STI case report form (CRF)
- Fetal losses (e.g. spontaneous abortions, spontaneous fetal deaths, stillbirths) were not reported as AEs, but were captured on the Pregnancy Outcome CRF
- Untoward maternal conditions that either resulted in or resulted from fetal losses were reported as reproductive system AEs
- Genital bleeding clinically assessed as expected (i.e., changes in genital bleeding judged to be related to a woman's contraceptive use, irregular bleeding judged to be related to the adolescent menstrual cycle, bleeding at the time of speculum insertion/removal or

cervicovaginal specimen collection that is judged by the clinician to be within the range of normally anticipated for that procedure) was not reported as an AE.

Acceptability

Regarding the secondary acceptability endpoint evaluation, the primary analysis population was used for the acceptability analysis and was restricted to scheduled visits during Periods 1 and 2 where the Audio Computer-assisted self-interview (ACASI) was expected to be completed and the endpoint question expected to be answered (i.e., Week 12, 24, 36 and 48 Visits). Two analyses were completed to accommodate social desirability bias:

1. Responses were collapsed into two categories; "like" (responses of "like" and "like very much") and "did not like" (responses of "dislike very much", "dislike", and "neither like nor dislike").

2. Responses were collapsed into two categories; "like" (responses of "like" and "like very much", and "neither like nor dislike") and "did not like" (responses of "dislike very much", "dislike").

Product preference and selection

Participant reports of product preference was defined as the participant's response to the question "would you prefer to use the ring of the tablets for HIV prevention?" on the Product Preference and Acceptability CRF completed at Week 72, or at an interim visit for Week 72 if the visit was missed.

Product selection, composed of product choice and product change (if applicable), were collected. Product choice was collected at the week 48 visit (visit 16), product change was collected at week 49-68 visits if the participant decided to switch study products or stop product use altogether.

Assessor's comment:

In general the objectives and endpoints are acceptable. The following comments should however be noted:

No estimands have been described. The Applicant is urged to include estimands in any future submissions including clinical trial data.

The adherence categories used for Truvada as measured in DBS is an accepted method. The high use category for Truvada is defined on a cut-off of ≥ 700 fmol/punch from DOD studies, which has been demonstrated to equate to >4 doses per week.

Some exploratory endpoints are mentioned, but are also referred to as not being analysed and/or provided in the CSR (such as vaginal microbiota data, evaluation of candidate biomarkers of safety and efficacy in mucosal secretions, participant self-report of product use and persistence with chosen product during the third product use period). Considering the purpose of the study in support of the extension of the indication to adolescents from 16 YOA, omission of these exploratory endpoints is considered of little clinical significance and are therefore not further pursued.

With regard to attempting to measure adherence by way of measuring residual dapivirine levels in used rings, the measurement of residual dapivirine ring levels is not a very sensitive measure for adherence, as only a small proportion of the drug load is released during 28 days of ring use, even with full adherence. As a consequence, residual ring levels provide very limited discriminative power to detect short periods of non-adherence. Furthermore, as stated by the Applicant, the COVID-19 pandemic during the follow-up of the trial interrupted scheduled trial visits due to pandemic restrictions. Dapivirine rings could be returned at any visit, but it cannot be excluded that a ring returned during e.g. study product use period 3 (choice period) might reflect use of rings from both periods 1 and 2 (randomized crossover period). There was no ring identifier that allowed direct linkage between returned and dispensed rings. In

conclusion, the clinical relevance of residual dapivirine levels in returned rings is limited, and no clinically relevant conclusions can be drawn from the adherence data to dapivirine vaginal rings as compared to adherence to Truvada or as an indication of DVR-004 efficacy. However, adherence data of DVR-004 in both adolescent women 16-17 YOA and adult women can be considered sufficiently suitable to provide an indication of (similar) dapivirine ring use between these two age groups. The proposed secondary endpoints such as product choice and acceptability, may provide relevant information on DVR-004 use by 16-17 year old vs adult women and are acceptable.

Sample size

The original sample size was 300 participants, randomized in a 1:1 ratio to one of two sequences of two study product use periods: DVR-004 inserted monthly for 24 weeks (N = 150) and Truvada taken daily for 24 weeks (N = 150). The sample size and power calculations were based on the primary comparisons of safety and adherence between the first and second periods of the study (i.e., the randomized Crossover Period).

For the primary safety endpoint, if there was no intra-participant correlation for safety outcomes, the trial had 80% power to detect a minimum difference of 5.8% to 9.2% depending on the rate of AEs in the treatment regimen with the lower AE rate. If the intra-participant correlation was moderately high (i.e., 0.5), the minimum detectable difference range was 4.1% to 6.5%. For the primary adherence outcome, the trial had >80% power to detect a difference of 8.4% (with an intra-participant correlation of 0.5) to 11.9% (with an intra-participant correlation of 0.0), assuming that 60% of participant visits with lower adherence would have low levels of TFV-DP or high residual dapivirine levels in returned rings.

Assessor's comment:

The power calculation for the sample size is not understood, as it is not clear if the proposed power of 80% is based on the original 300 participants, or on the 250 participants mentioned in the SAP. The discrepancies between the protocol and the SAP, as well as the consequences of the actual sample size being smaller than described here, are not addressed. Furthermore, the purpose of these power calculations in the context of descriptive statistics are also not clear. However, as the primary analyses are all descriptive these issues are not further pursued.

Randomisation

Prior to site activation, SCHARP (CRO) will configure the randomisation within the Medidata Balance system and upload into this system a permuted block randomisation schedule. The database (via the Medidata Balance module) will assign the participant to a product sequence and the randomisation date and time will appear automatically on the Randomisation eCRF.

Participants will be randomised in a 1:1 ratio to one of the two treatment sequences (A or B). Randomisation was stratified by site.

Assessor's comment:

The description of the randomisation was not included in the Protocol nor in the SAP, but was part of the randomisation listing.

The randomisation listing lacked the randomisation date and time. Therefore the Applicant is urged to, in future submissions, present a randomisation listing including the used stratification factor(s),

randomisation Date and Time, patient number/randomisation number, the randomised sequence and the received sequence. The listing should be sorted by site, randomisation Date and Time.

Blinding

Study staff and participants will be blinded to the treatment sequence prior to randomisation of the participant.

The study MTN-034 is an open-label trial.

Assessor's comment:

The study is an open-label study. This means that after randomisation the study was unblinded. This is acceptable.

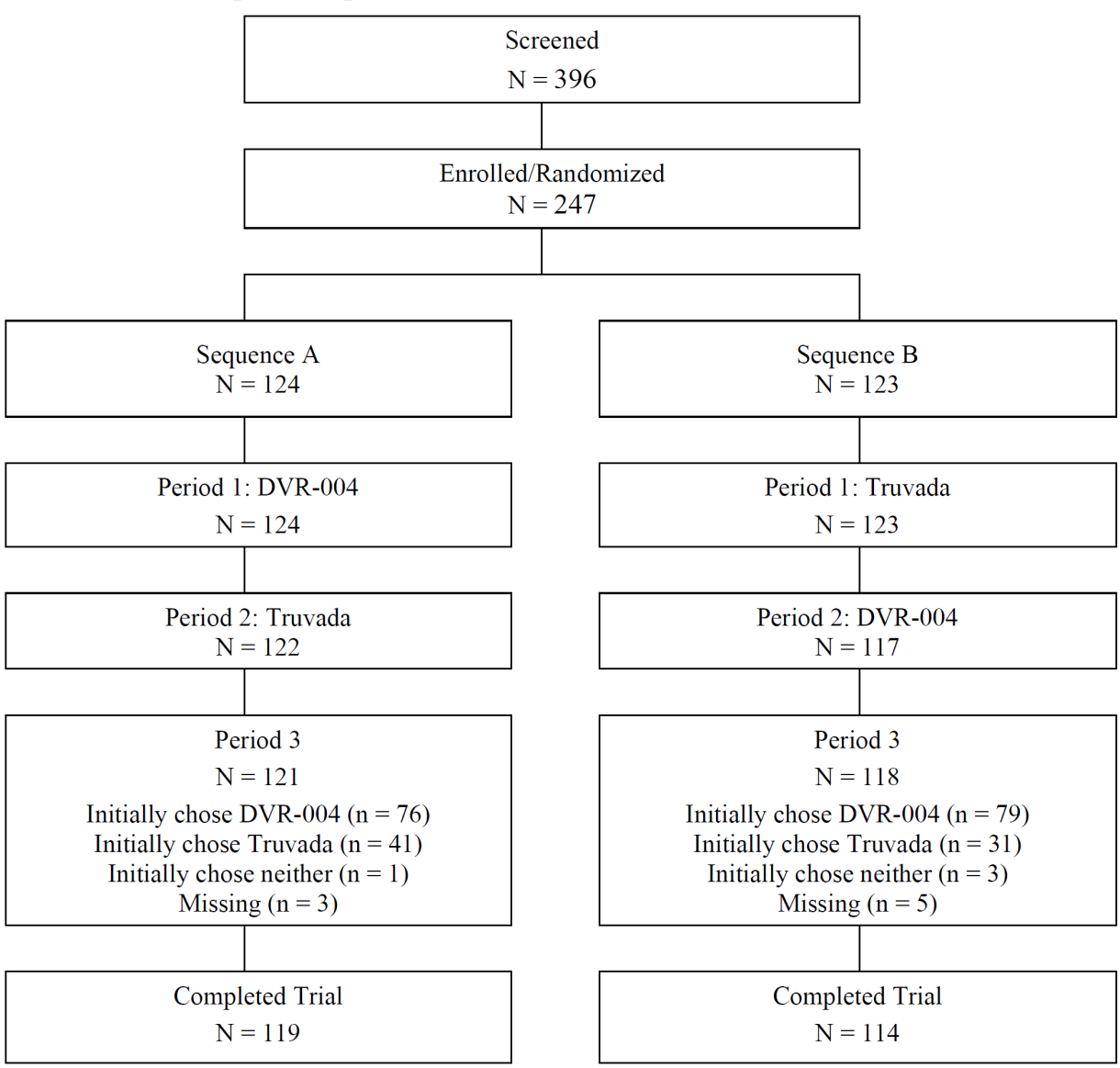
Statistical methods

Descriptive statistics were used to summarize continuous (mean and standard deviation, median, quartiles, range and number of missing data values) and categorical (frequencies, relative frequencies, percentages, and number of missing data values) variables. Descriptive analyses were summarized overall and stratified by trial site and by randomization sequence unless otherwise noted. Summaries by trial site used the site at which the participant was enrolled. A two-sided significance level of 0.05 was used for all statistical tests unless otherwise noted. Data from both regularly scheduled and unscheduled (referred to as "interim") visits were used in analyses as appropriate. Unless otherwise noted, data from interim visits did not contribute to summaries by visit but contributed to summaries that were combined across all visits.

Results

Participant flow

Figure 2. Participant disposition



N = number of participants; n = number of participants in each category
Source: Section 14, Table 14.1.1.1

A total of 396 participants were screened across the four research centres in three African countries (South Africa, Uganda and Zimbabwe). A total of 247 participants enrolled: 124 participants were randomized to Sequence A [24 weeks (6 months) of DVR-004 followed by 24 weeks (6 months) of Truvada] and 123 to Sequence B [24 weeks (6 months) of Truvada followed by 24 weeks (6 months) of DVR-004] (Figure 1).

A total of 233 (94%) participants completed the clinical trial (Figure 2): 119 (96%) participants randomized to Sequence A group and 114 (93%) randomized to Sequence B group. Of the 14 (6%) participants who terminated the trial early, 5 participants were randomized to Sequence A and 9 to Sequence B. Reasons for early trial termination were withdrawal of consent (overall 5 participants;

Sequence A, n = 2; Sequence B, n = 3), lost to follow-up (overall 8 participants, Sequence A, n = 3; Sequence B, n =5) and Investigator decision (overall 1 participant; Sequence B, n = 1).

Table 2. Participant Disposition by Randomisation Sequence

	Treatment, n (%)		
	Sequence A	**Sequence B**	**Overall**
Disposition			
Enrolled	124 (100%)	123 (100%)	247 (100%)
Completed	119 (96.0%)	114 (92.7%)	233 (94.3%)
Did not complete trial	5 (4.0%)	9 (7.3%)	14 (5.7%)
	Treatment, n (%)		
	Sequence A	**Sequence B**	**Overall**
Reasons for trial non-completion, n (%)			
Withdrawal of consent	2 (40.0%)	3 (33.3%)	5 (35.7%)
Lost to follow-up	3 (60.0%)	5 (55.6%)	8 (57.1%)
Investigator decision	0	1 (11.1%)	1 (7.1%)
Discontinued study product use			
Period 1	4/124 (3.2%)	5/123 (4.1%)	9/247 (3.6%)
Period 2	3/122 (2.5%)	2/117 (1.7%)	5/239 (2.1%)
Period 3	2/121 (1.7%)	5/118 (4.2%)	7/239 (2.9%)

Sequence A = DVR-004/Truvada; Sequence B = Truvada/DVR-004

n = number of participants in each category (the percentage calculation is based on the total number of participants in the sections denoted by indent)

Source: Section 14, Tables 14.1.1.1, 14.1.1.4.1, 14.1.1.3.1

Recruitment

Participants enrolled in the MTN-034 were healthy, HIV-negative, sexually active adolescent girls and young women from Sub-Saharan Africa. Enrollment of study participants was expected to have been completed by April 30 2020, but was stopped mid march 2020 due to the pandemic. Although the pause in trial enrolment was lifted on may 15 2020, it was decided to forego resumption of participant enrolment to allow the trial research centres to focus efforts on protecting safety of currently enrolled participants and staff. 247 of the expected 300 participants were already enrolled, including 85 of the target 100 participants under the age of 18 years.

The clinical trial was conducted at four research centres in three African Countries (South Africa, Uganda and Zimbabwe). Although originally one research centre located in Kenya was meant to participate in the trial, due to concerns with performance issues of this centre, the trial was not initiated at this location. The number of potential participants allocated to this research centre were distributed across the remaining four trial sites.

Assessor's comment

The statement of the Applicant concerning recruitment difficulties due to the COVID-19 pandemic and subsequent stopping of participant enrollment as well as removal of the fifth research centre, are acknowledged. The size of the enrolled population is considered sufficient for descriptive comparisons and therefore this issue is not further pursued.

Conduct of the study

Date first participant first visit: 06 February 2019

Date last participant last visit: 09 September 2021

Date of latest protocol (v 2.0): 07 December 2017

Database lock occurred on 2 March 2022.

Date of latest SAP (v 1.0): 26 April 2022

CSR: 27 February 2024

Several changes in the planned statistical analysis have been made, predominantly regarding the exploratory endpoints. These concern measurements/evaluations of the vaginal microbiota (collected but not analysed), evaluations of candidate biomarkers of safety and efficacy in mucosal secretions (collected, not analysed), markers of sexual exposure (not collected) and the exploratory endpoints of adherence, for which participant self-reports of product use and persistence with chosen product during the third use period are collected and analysed but not provided in the report.

In total, there were 693 protocol deviations impacting 227 (92%) enrolled participants. Lockdowns and social distancing requirements due to the COVID-19 pandemic, starting in March 2020, required deviations to the protocol (e.g., visits or visit procedures that were conducted by phone instead of in-person, or study product that was not returned). However, because the trial was ongoing at the start of the pandemic, there was no deviation specific to COVID-19. As a result, pandemic-related deviations were categorized as "Other," with COVID- 19 or pandemic lockdown included within the description of the event. Of the 693 deviations reported during the study, 504 of these were categorized as "Other," and the majority of these were described as pandemic related. None of the deviations were considered by the Applicant to impact participant eligibility so no adjustments to the analysis set were performed. Ten deviations required notification of the sponsor, DAIDS, as a critical event.

There were 13 (5%) product holds (Sequence A, n = 5; Sequence B, n = 8) during the trial. Reasons for product hold included reactive HIV rapid test (n = 6), pregnancy (n = 5), breastfeeding (n = 4), inability to comply with trial procedures or be at risk due to study product use (n = 1) and reported PEP use (n = 1).

Assessor's comment:

Several issues regarding study conduct were identified and subsequently addressed by the Applicant. This included submission of additional information regarding modifications to product adherence counselling which were implemented when the study was already ongoing, information on critical deviations requiring notification of the sponsor, and clarification that although final signatures were applied to the SAP after study results had been collected and after database lock, there was no analysis done prior to the final signatures on the SAP in accordance with the data management vendor's SOP on SAP development. Based on assessment of the provided information, it was concluded that the identified issues are considered resolved.

Baseline data

The overall mean (SD) age of participants was 18.2 (1.42) years: 34% (85/247) were 16-17 years old, 46% (114/247) were 18-19 years old and 19% (48/247) were 20-21 years old. The majority (87%) were single and 89% reported a primary sex partner. About 40% of participants reported that they were very or somewhat worried about their HIV risk in the next year.

Table 3. Demographic and Baseline Characteristics

Parameter	Sequence A N = 124	Sequence B N = 123	Total N = 247
Demographics			
Age (years)			
Mean (±SD)	18.2 (±1.44)	18.1 (±1.40)	18.2 (±1.42)
Median (Q1, Q3)	18.0 (17, 19)	18.0 (17, 19)	18.0 (17, 19)
Min, Max	16, 21	16, 21	16, 21
Age category, n (%)			
16-17 years old	41 (33.1)	44 (35.8)	85 (34.4)
18-19 years old	57 (46.0)	57 (46.3)	114 (46.2)
20-21 years old	26 (21.0)	22 (17.9)	48 (19.4)
Marital status, n (%)			
Single	106 (85.5)	108 (87.8)	214 (86.6)
Married	7 (5.6)	3 (2.4)	10 (4.0)
Cohabitating	9 (7.3)	11 (8.9)	20 (8.1)
Separated or divorced	2 (1.6)	1 (0.8)	3 (1.2)
Currently attending school, n (%)	51 (41.1)	41 (33.3)	92 (37.2)
Ever attended school, n (%)	71 (97.3)	82 (100.0)	153 (98.7)
Age left School, years, mean (±SD)	16.4 (±2.18)	16.2 (±2.19)	16.3 (±2.18)
Highest level of education, n (%)			
Primary	15 (12.3)	18 (14.6)	33 (13.5)
Secondary	92 (75.4)	97 (78.9)	189 (77.1)
College or university	15 (12.3)	8 (6.5)	23 (9.4)
Earns own income	22 (17.7)	31 (25.2)	53 (21.5)
Behavioral characteristics			
Perceived HIV risk in next year, n (%)			
Very worried	38 (30.6)	33 (26.8)	71 (28.7)
Somewhat worried	18 (14.5)	11 (8.9)	29 (11.7)
A little worried	30 (24.2)	38 (30.9)	68 (27.5)
Not at all worried	38 (30.6)	41 (33.3)	79 (32.0)

SD = standard deviation

Sequence A = DVR-004/Truvada; Sequence B = Truvada/DVR-004

N = Total number of participants; n = Number of participants in each category (the percentage calculation is based on the total number of participants in the sections denoted by indent)

Source: Section 14, Table 14.1.2.1.1

Assessor's comment

The Applicant clarified that the question about "ever attending" school was only asked to participants who were not currently attending school. As a consequence, the numbers presented for the characteristics 'currently attending school' and 'ever attended school' were based on different denominators.

Numbers analysed

Approximately 300 participants were planned to be enrolled at four clinical research centers: 396 participants were screened, of whom 247 of the expected and planned participants were enrolled: 124 participants were randomized to Sequence A and 123 to Sequence B (randomized Crossover Period). A total of 239 participants continued to the non-randomized Choice Period (121 of Sequence A participants and 118 of Sequence B participants). In total, all participants randomized into the trial and assessed evaluable by meeting all the eligibility criteria were included in the primary and secondary analyses. The safety, adherence and drug detection analyses consisted of all 247 eligible participants (Sequence A, N = 124, Sequence B, N = 123). The analyses sets were defined as followed:

Primary Analysis Set: All participants randomized and enrolled into the trial were included in the primary safety and adherence analyses and secondary acceptability analysis. During the first two study product use periods participants were analyzed according to the product the participant was randomized to receive [i.e., intent-to-treat (ITT)].

Choice Period Adherence Analysis Set (Choice Population): All participants randomized and enrolled into the trial who completed visits in study product use Period 3 (i.e., from Week 48 Visit through Week 72 Visit) were included in the adherence analysis during study product use Period 3 (i.e., Choice Period).

Outcomes and estimation

Adherence to the Study Products

Adherence was a primary and secondary endpoint of the trial. Residual drug levels in returned used vaginal rings and TVF-DP concentrations in DBS were used to assess adherence to DVR-004 and Truvada, respectively, during the randomized Crossover Period (primary endpoint) and Choice Period (secondary endpoint). All participants randomized and enrolled into the trial who had at least one post-enrollment drug concentration/level result (N = 247) were included in the primary adherence analysis. All participants who were still enrolled during the Choice Period (N = 239) were included in the secondary adherence analysis.

Adherence categories for DVR-004 use were defined using residual dapivirine levels in returned used rings with the following categories: high use (dapivirine release rate > 4.0 mg/month); some use (dapivirine release rate > 0.9 mg/month and ≤ 4.0 mg/month); and very low/no use (dapivirine release rate ≤ 0.9 mg/month). Adherence categories for Truvada use were defined using TFV-DP concentrations in DBS with the following categories: no quantifiable use (<16.6 fmol/punch), some use (16.6 - <700 fmol/punch) and high use (≥ 700 fmol/punch).

Primary endpoint: adherence during the randomized Crossover Period

Overall, during the randomized crossover period, 210/238 (88%) participants had all observed levels of dapivirine suggesting at least some use and 229/242 (95%) participants had all observed TFV-DP concentrations in DBS indicating at least some use. This difference was statistically significant and assignment to Truvada was associated with higher odds of having all laboratory assay values indicating at

least some use than assignment to DVR-004 [odds ratio (OR): 1.16, 95% CI (1.091, 1.228), p < 0.0001].

Based on pooled results from *all* trial visits of all participants during the randomized crossover period, 603 (45%) participant-visits had levels indicating high use, 688 (51%) participant-visits had levels indicating some use, and 46 (3%) participant-visits had levels of dapivirine suggesting very low/no use during DVR-004 visits. Overall, based on TFV-DP concentrations in DBS, 754 (58%) participant-visits had concentrations indicating high use, 535 (41%) participant-visits had concentrations indicating some use and 17 (1%) participant-visits had concentrations indicating no quantifiable use during Truvada visits.

Secondary endpoint: adherence during the Choice Period

Regarding the secondary adherence endpoint, during the Choice Period, 131/164 (80%) participants had all observed levels of dapivirine suggesting at least some use. The odds of having all residual drug laboratory assay values indicating at least some use of DVR-004 during the Choice Period was not different than during the Crossover Period [OR 1.003 (95% CI 0.909, 1.106), p = 0.9590]. Similarly, 74/87 (85%) participants had all observed TFV-DP concentrations in DBS indicating at least some use.

The odds of having all TFV-DP laboratory assay values indicating at least some use of Truvada during the Choice Period was not different than during the Crossover Period [OR 1.002 (95% CI 0.895, 1.121), p = 0.9758]. Overall, based on residual dapivirine levels in returned rings across all trial visits during the Choice Period, 333 (39%) participant-visits had levels indicating high use, 456 (54%) participant-visits had levels indicating some use and 58 (7%) participant-visits had levels of dapivirine suggesting very low/no use during DVR-004 visits. Overall, based on TFV-DP concentrations in DBS, 198/400 (50%) participant-visits had concentrations indicating high use, 183 (46%) participant-visits had concentrations indicating some use and 19 (5%) participant visits had concentrations indicating no quantifiable use during Truvada visits.

Assessor's comment:

A directly observed dosing (DOD) study has not been conducted for DVR-004, so the categories of adherence between DVR-004 and Truvada cannot be directly compared. This is also acknowledged by the Applicant. Instead, a comparison between adherence to DVR-004 of participants 16 and 17 YOA and adults (in whom efficacy has been established) is considered more relevant in the context of this extension of the indication. This analysis was requested and provided by the Applicant. The available information confirms that the residual dapivirine levels in used rings were very similar between adult women from 18 YOA and those 16-17 YOA. Hence, the efficacy of DVR-004 can also be expected to be similar in these age categories.

Ancillary analyses

Study product selection

Of the 239 participants who were enrolled in the trial during Choice Period, 231 participants made a choice at the Week 48 Visit (i.e., Truvada, DVR-004 or no product) as recorded on the Product Choice eCRF. During study product Period 3, as reported on the Product Choice and Product Change eCRFs, the majority of participants chose the ring: 137 (59%) participants chose the DVR-004 at each attended visit, while 62 (27%) participants chose Truvada at each attended visit, 30 (13%) participants switched between DVR-004, Truvada and/or neither product and 2 (1%) never chose any product (See Table 4).

Table 4. Product Selection During Choice Period by Randomization Sequence - Choice Population

Description	Sequence A N = 124 n (%)	Sequence B N = 123 n (%)	Total N = 247 n (%)
Product selected	118 (95.2)	113 (91.9)	231 (93.5)
Always choosing ring	66 (55.9)	71 (62.8)	137 (59.3)
Always choosing tablets	35 (29.7)	27 (23.9)	62 (26.8)
Switching between the ring/tablets/neither	17 (14.4)	13 (11.5)	30 (13.0)
Never choosing either	0	2 (1.8)	2 (0.9)

Sequence A = DVR-004/Truvada; Sequence B = Truvada/DVR-004

N = Total number of participants; n = Number of participants in each category (the percentage calculation is based on the total number of participants in the sections denoted by indent)

Source: Section 14, Table 14.1.3.3.1

Study product preference

At the start of the Choice Period (i.e., at the Week 48 Visit), 227 participants reported their product preference: 150 (66%) participants preferred DVR-004, 67 (30%) preferred Truvada, 7 (3%) participants preferred either product equally and 3 (1%) participants preferred neither product or didn't provide a response. Six months later, at the end of Period 3 (i.e., at the Week 72 Visit), 223 participants reported their choice/preference again. Preferences were relatively similar to those at Week 48: 133 (60%) of participants preferred DVR-004, 68 (31%) preferred Truvada, 18 (8%) preferred either product equally and 4 (2%) preferred neither product.

Study product acceptability

Acceptability was based on participants' self-report and answers to the following questions provided in the self-interview conducted during the randomized Crossover Period, at Week 12, 24, 36, and 48 Visits: "Please rate how much you like using the ring for HIV prevention"(administered during DVR-004 use periods) or "Please rate how much you like using the tablets for HIV prevention" (administered during Truvada use periods).

Overall, most participants found both the DVR-004 and Truvada acceptable: the majority liked (liked or very much liked) both products during trial visits where the endpoint question was expected to be answered during the randomized Crossover Period for both randomization sequences. For DVR-004, the proportion of participants that liked or very much liked the product were > 80% for the week 12, 24, and 48 week visits for both sequence groups. The odds of Truvada being liked or very much liked during periods of Truvada use were significantly lower than the odds of DVR-004 being liked or very much liked during periods of DVR-004 use (OR: 0.27, 95% CI 0.18-0.40, p < 0.0001).

HIV seroconversion

Four participants seroconverted to HIV during the trial:

• One participant randomized to Sequence B (Truvada/DVR-004) had a positive HIV rapid test and confirmatory test from samples collected at the Week 28 Visit (Visit 11) (Crossover Period). Note: at Week 28 Visit participant was at the DVR-004 use period. Viral load at diagnosis (Visit 11) was 932,232 copies/mL, CD4+ = 13.0%.

At the preceding Week 24 Visit (Visit 9), the last visit of the Truvada use period during Period 1, viral load was 21,382 copies/mL. Therefore, the Applicant concluded that this participant was most likely infected with HIV during Period 1, during the Truvada use period.

• One participant randomized to Sequence B (Truvada/DVR-004) had a positive HIV rapid test and confirmatory test from samples collected at the Week 52 Visit (Visit 18) (Choice Period). Note: During the Choice Period the study product of choice was Truvada. Viral load at diagnosis Week 52 (Visit 18) was 201 copies/mL, CD4+ = 37.2%.

At the preceding visit at Week 48 (Visit 16), the study product use end visit of the DVR-004 use period, viral load was 1,433,873 copies/mL. Therefore, the Applicant concluded that this participant was most likely infected with HIV during the DVR-004 use period.

• One participant randomized to Sequence B (Truvada/DVR-004) had a positive HIV rapid test and confirmatory test from samples collected at Week 56 Visit (Visit 19) (Choice Period). Note: During the Choice Period the study product of choice was Truvada. Viral load at diagnosis was 3,073,349 copies/mL, CD4+ count = 20.2%.

At the preceding Week 48 Visit, the end of the DVR-004 use period, HIV RNA was undetectable. As quantifiable HIV RNA (with very high viral load) were detected at the Week 56 Visit while using Truvada, the Applicant concluded that the participant was likely infected during Truvada use during the Choice Period.

• One participant randomized to Sequence B (Truvada/DVR-004), had a positive HIV rapid test and confirmatory test from samples collected at Week 68 Visit (Choice Period), 20 weeks after last DVR-004 use. Note: During the Choice Period the study product of choice was Truvada. Viral load at diagnosis was 89,927 copies/mL, CD4+ count = 26.3%.

No samples were available for quantifiable HIV RNA testing from preceding visits during Truvada use in Choice Period (i.e., Week 52 and 56 Visits) as well as from the Week 48 Visit (last visit of DVR-004 use period). HIV RNA sample from Week 36 Visit (Visit 13) was undetectable for HIV. Thereby the timing of HIV infection cannot be determined. HIV rapid tests remained unreactive until the Week 68 Visit.

Assessor's comment

Generally, it appears that both DVR-004 and Truvada are perceived as acceptable product choices for PrEP in the investigated population overall. For product choice, preference and acceptability of the product there was no notable difference between the 16-17 YOA and young adult women 18-21 YOA. A majority of women in both age categories chose DVR-004 at week 48 as their preferred PrEP method. At the end of the Choice period, the preference for DRV-004 was slightly declined. This was somewhat more notable in the younger women. Acceptability remained relatively stable and high over time, and comparable in both age groups across the two study sequences.

Four HIV-1 seroconversions were detected during the study, of which the Applicant concluded that two were likely to have occurred while the participant was using Truvada for PrEP, one was likely to have occurred during DVR-004 use and in one participant the timing of HIV infection could not be established. The conclusions of the Applicant can be followed. As the study was not formally designed for the analysis of (prevention of) HIV-1 seroconversion, the provided information is considered exploratory. The results however do not raise concerns on the expected efficacy of DVR-004 in adolescent girls from 16 YOA.

4.4.2. Discussion on clinical efficacy

The extension of the indication, to include HIV-uninfected women/girls 16 years and older for Dapivirine Vaginal Ring 25 mg, is based on final results from study MTN-034 (REACH) listed as a category 3 study in

the RMP. This is a Phase 2a crossover trial evaluating the safety of, and adherence to, a vaginal matrix ring containing dapivirine and oral emtricitabine/tenofovir disoproxil fumarate in an adolescent and young adult female population.

Design and conduct of the clinical study

This study was performed in healthy adult girls and women 16-21 YOA, living in sub-Saharan Africa. In total four research centres in three African countries (South Africa, Uganda and Zimbabwe) were involved in the trial. The population included in the trial corresponds to a population that is considered relevant for the sought indication. The trial consisted of three periods of 24 weeks, of which the first two periods were randomized crossover periods between DVR-004 and Truvada. Period 3, also referred to as the Choice Period, consisted of 24 weeks in which the participant could choose use of Truvada or DVR-004. At each monthly visit, a new vaginal ring was dispensed with instructions to continuously use it for the next 28 days. Throughout the trial, all participants received pre- and post-test HIV counselling, protocol adherence counselling, product adherence disclosure counselling, contraceptive counselling, and HIV/STI risk reduction counselling.

Although the design of the trial can in principle be considered adequate, several methodological issues and concerns regarding study conduct were identified and subsequently addressed by the Applicant. This included submission of additional information regarding modifications to product adherence counselling which were implemented when the study was already ongoing, information on critical deviations requiring notification of the sponsor, and clarification that although final signatures were applied to the SAP after study results had been collected and after database lock, there was no analysis done prior to the final signatures on the SAP in accordance with the data management vendor's SOP on SAP development. Based on assessment of the provided information, it was concluded that the identified issues are considered resolved.

Efficacy data and additional analyses

The primary efficacy endpoint consisted of adherence to DVR-004 and Truvada as based on residual dapivirine levels in returned rings and TVF-DP concentrations in DBS, respectively. Efficacy of DVR-004 in prevention of the risk of HIV-1 infection was not investigated in the MTN-034 study. However, as from a clinical and biological perspective there is little reason to assume the pharmacokinetic profile and efficacy of DVR-004 will be different in adult women from 18 YOA and those 16-17 YOA when use of the product is similar, it is acceptable to base the EoI on (PK) extrapolation. Previous studies have however demonstrated that systemic dapivirine concentrations are very low following ring use, which hinders the opportunity of performing PopPK analyses as a means to extrapolate efficacy of DVR-004 from adults to adolescents 16-17 YOA. The measurement of residual dapivirine levels in used rings – as extensively discussed during the original MAA procedure - is unfortunately also not a very sensitive measure for adherence, as only a small proportion of the drug load is released during 28 days of ring use, even with full adherence. Furthermore, residual dapivirine levels provide no or very limited discriminative power to detect short periods of non-use. However, comparison of residual dapivirine levels in adolescent girls 16-17 YOA to adult women can be considered sufficiently suitable to provide an indication of (similar) dapivirine ring use between these two age groups, although it is acknowledged that adolescents are a particularly challenging population when it comes to adherence to study drugs. The proposed secondary endpoints such as product choice and acceptability, together with DVR-004 adherence data, can contribute to the totality of evidence that DVR-004 can be expected to be used similarly by 16-17 year old and adult women and can therefore also be considered similarly efficacious. The Applicant provided upon request a separate analysis of the adherence data to DVR-004 from the randomized crossover period of the participants 16 and 17 YOA in comparison to the adult participants. The available information confirms that the residual dapivirine levels in used rings were very similar between adult

women from 18 YOA and those 16-17 YOA. Hence, the efficacy of DVR-004 can also be expected to be similar in these age categories.

4.4.3. Conclusions on the clinical efficacy

In absence of efficacy data and feasibility issues in establishing efficacy in this population, a comparison between residual dapivirine levels in used rings of participants 16 and 17 YOA and adults was considered more relevant in the context of this application for extension of the indication.

The available information confirms that the residual dapivirine levels in used rings were very similar between adult women from 18 YOA and those 16-17 YOA. Hence, the efficacy of DVR-004 can also be expected to be similar in these age categories.

4.5. Clinical safety

Introduction

Dapivirine Vaginal Ring 25 mg (DVR-004) has been authorised for use in adults and demonstrated an acceptable safety profile with no major identified safety issues in this population of women from 18 YOA. Limited safety data existed for adolescent girls aged 15-17 YOA. Study MTN-034 is executed with the intention to generate safety data in this population, and has studied the safety in adolescent girls 16-17 YOA and those 18-21 YOA.

The primary safety endpoint was Grade 2 or higher AEs. For the primary safety analysis, AEs were classified into one of the two participant product use periods, based on the reported time of event onset. Due to the absence of a washout period between treatments (product use periods), events were classified into Period 1 if the reported onset date was between the date of randomization and the date 30 days after the end of first 6-month treatment period, i.e., the participant's Week 24 Visit (inclusive). If the participant missed this visit, the date 30 days after the close of the visit window was used. Again, due to the absence of washout period between product use periods, events were classified into Period 2 if the reported onset date was between the date of the participant's Week 24 Visit and the date 30 days after the end of second 6-month treatment period, i.e., the participant's Week 48 Visit. AEs that occurred within 30 days of Week 24 Visit were classified into both periods.

Patient exposure

The safety data generated in study MTN-034 comprised a total of 239 participants receiving DVR-004 (79 adolescent girls less than 18 YOA, 160 young adult women 18-21 YOA) of the 247 enrolled and randomized participants; for two participants no ring insertion dates were reported, and these participants were not incorporated into the safety analysis.

Adverse events

In this trial, all reported AEs that started after the investigational products were inserted/taken were considered as treatment-emergent adverse events (TEAEs). Only TEAEs are discussed below.

The vast majority of participants reported an AE during the 72-week trial: a total of 822 AEs in 207/239 (87%) participants during DVR-004 use periods and a total of 895 AEs in 226/242 (93%) during Truvada use periods.

The majority of participants experienced AEs of moderate (Grade 2) intensity, reported (by any reported AE) in 82% (197/239) and 80% (194/242) of participants during DVR-004 and Truvada use periods, respectively. Mild (Grade 1) AEs were reported (by any reported AE) in 46% (110/239) and 65% (158/242) of participants during DVR-004 and Truvada use periods, respectively. Severe (Grade 3) AEs were reported in 0.4% (1/239) and 4% (9/242) of participants during DVR-004 and Truvada use periods, respectively. One (1/239; 0.4%) participant experienced a life-threatening (Grade 4) AE during DVR-004 use periods, polytrauma due to motor vehicle accident/multiple injuries (Table 19).

Two AEs in two participants led to study product discontinuation during the trial (one of which was an HIV infection), both reported during the Truvada use period; no AE led to trial discontinuation (Table 19).

A total of 6 SAEs were reported during the trial: none were determined to be related to study product use and none led to study product discontinuation or trial discontinuation.

Table 5. Summary of Adverse Events by Study Product - ITT Population

	DVR-004 N = 239 n (%) m	**Truvada N = 242 n (%) m**
Any AE	207 (86.6) 822	226 (93.4) 895
By Severity		
Any AE Grade 1 (Mild)	110 (46.0) 231	158 (65.3) 384
Any AE Grade 2 (Moderate)	197 (82.4) 589	194 (80.2) 501
Any AE Grade 3 (Severe)	1 (0.4) 1	9 (3.7) 10
Any AE Grade 4 (Potentially life-threatening)	1 (0.4) 1	0
AE Criterion		
Any AE leading to study product discontinuation	0	2 (0.8) 2
Any AE leading to trial discontinuation	0	0
Any AE leading to hospitalization	1 (0.4) 1	5 (2.1) 5
Any SAE	1 (0.4) 1	5 (2.1) 5
SAE Criterion		
Any SAE related to study product	0	0
Any SAE leading to study product discontinuation	0	0
Any SAE leading to trial discontinuation	0	0

AE = Adverse Event; SAE = Serious Adverse Event

N = Total number of participants; n = Number of participants in each category (the percentage calculation is based on the total number of participants in the sections denoted by indent); m = Number of mentions in each category (i.e., total number of AEs in each category)

Source: Section 14 Table 14.3.1.2.2

The incidences of any AEs reported and occurring in more than two percent of participants overall during the 72-week trial by SOC and MedDRA preferred terms and by study product, are presented in Table 6.

The most commonly reported AEs during DVR-004 use periods, reported by > 10% of participants, were genitourinary chlamydia infection (31%), decreased creatinine renal clearance (30%), vaginal discharge (17%), urinary tract infection (15%), headache (15%), upper respiratory tract infection (13%), genitourinary tract gonococcal infection (12%) and vulvovaginitis trichomonal (11%) and vaginal odour (10%).

The most commonly reported AEs during Truvada use periods, reported by > 10% of participants, were decreased creatinine renal clearance (27%), genitourinary chlamydia infection (26%), nausea (23%), headache (21%), vomiting (15%), dizziness (18%), genitourinary tract gonococcal infection (15%), diarrhoea (13%) and abdominal pain (12%).

Table 6. Incidence of Adverse Events by System Organ Class and Preferred Term Reported in at Least 2% of Participants, by Study Product - ITT population

System Organ Class **Preferred Term**	**DVR-004** **N = 239** **n (%) m**	**Truvada** **N = 242** **n (%) m**	**Total** **N = 247** **n (%) m**
Any Adverse Event	207 (86.6) 822	226 (93.4) 895	239 (96.8) 1717
Infections and infestations	160 (66.9) 377	151 (62.4) 309	203 (82.2) 686
Genitourinary chlamydia infection	73 (30.5) 101	62 (25.6) 67	105 (42.5) 168
Genitourinary tract gonococcal infection	29 (12.1) 32	36 (14.9) 43	55 (22.3) 75
Urinary tract infection	36 (15.1) 44	24 (9.9) 26	51 (20.6) 70
Upper respiratory tract infection	32 (13.4) 37	20 (8.3) 23	45 (18.2) 60

Vulvovaginitis trichomonal	26 (10.9) 31	22 (9.1) 26	42 (17.0) 57
Vulvovaginal candidiasis	23 (9.6) 27	16 (6.6) 19	38 (15.4) 46
Bacterial vaginosis	19 (7.9) 20	14 (5.8) 14	30 (12.1) 34
Malaria	12 (5.0) 15	13 (5.4) 20	22 (8.9) 35
Gastroenteritis	11 (4.6) 11	10 (4.1) 11	21 (8.5) 22
Influenza	6 (2.5) 6	5 (2.1) 5	10 (4.0) 11
COVID-19	4 (1.7) 4	4 (1.7) 4	8 (3.2) 8
Subcutaneous abscess	3 (1.3) 4	5 (2.1) 6	8 (3.2) 10
Respiratory tract infection	1 (0.4) 1	6 (2.5) 6	7 (2.8) 7
Syphilis	5 (2.1) 6	3 (1.2) 3	7 (2.8) 9
Tonsillitis	5 (2.1) 5	2 (0.8) 2	7 (2.8) 7
Cervicitis	4 (1.7) 4	2 (0.8) 2	6 (2.4) 6
Investigations	**77 (32.2) 95**	**80 (33.1) 96**	**137 (55.5) 191**
Creatinine renal clearance decreased	71 (29.7) 74	66 (27.3) 69	126 (51.0) 143
Blood creatinine increased	11 (4.6) 11	10 (4.1) 12	21 (8.5) 23
Neutrophil count decreased	2 (0.8) 2	6 (2.5) 6	8 (3.2) 8
Blood pressure increased	4 (1.7) 4	3 (1.2) 3	6 (2.4) 7
Gastrointestinal disorders	**46 (19.2) 59**	**111 (45.9) 193**	**134 (54.3) 252**
Nausea	16 (6.7) 16	55 (22.7) 69	65 (26.3) 85
Abdominal pain	17 (7.1) 17	28 (11.6) 31	43 (17.4) 48
Vomiting	6 (2.5) 6	35 (14.5) 42	41 (16.6) 48
Diarrhea	7 (2.9) 7	31 (12.8) 37	36 (14.6) 44
Gastritis	6 (2.5) 6	3 (1.2) 3	9 (3.6) 9
Reproductive system and breast disorders	**87 (36.4) 144**	**47 (19.4) 70**	**112 (45.3) 214**
Vaginal discharge	40 (16.7) 46	21 (8.7) 25	53 (21.5) 71
Vaginal odour	23 (9.6) 24	5 (2.1) 5	26 (10.5) 29
Dysmenorrhoea	14 (5.9) 15	8 (3.3) 8	21 (8.5) 23
Vulvovaginal pruritus	12 (5.0) 13	7 (2.9) 7	19 (7.7) 20
Intermenstrual bleeding	9 (3.8) 12	1 (0.4) 1	10 (4.0) 13
Pelvic pain	3 (1.3) 3	6 (2.5) 6	9 (3.6) 9

Vulvovaginal discomfort	8 (3.3) 8	0	8 (3.2) 8
Vulval ulceration	4 (1.7) 4	3 (1.2) 3	6 (2.4) 7
Nervous system disorders	**47 (19.7) 64**	**80 (33.1) 113**	**108 (43.7) 177**
Headache	36 (15.1) 44	50 (20.7) 64	75 (30.4) 108
Dizziness	10 (4.2) 11	43 (17.8) 44	51 (20.6) 55
Tension headache	8 (3.3) 8	2 (0.8) 4	10 (4.0) 12
Skin and subcutaneous tissue disorders	**15 (6.3) 15**	**17 (7.0) 21**	**31 (12.6) 36**
Pruritus	2 (0.8) 2	3 (1.2) 3	5 (2.0) 5
Rash	1 (0.4) 1	4 (1.7) 4	5 (2.0) 5
General disorders and administration site conditions	**7 (2.9) 7**	**19 (7.9) 20**	**25 (10.1) 27**
Fatigue	2 (0.8) 2	12 (5.0) 13	13 (5.3) 15
Musculoskeletal and connective tissue disorders	**11 (4.6) 11**	**14 (5.8) 15**	**22 (8.9) 26**
Back pain	5 (2.1) 5	5 (2.1) 5	8 (3.2) 10
Injury, poisoning and procedural complications	**9 (3.8) 9**	**10 (4.1) 10**	**18 (7.3) 19**
Metabolism and nutrition disorders	8 (3.3) 9	12 (5.0) 15	18 (7.3) 24
Decreased appetite	7 (2.9) 8	9 (3.7) 11	14 (5.7) 19
Respiratory, thoracic and mediastinal disorders	**8 (3.3) 9**	**8 (3.3) 8**	**16 (6.5) 17**
Cough	6 (2.5) 6	1 (0.4) 1	7 (2.8) 7
Renal and urinary disorders	**8 (3.3) 8**	**7 (2.9) 8**	**14 (5.7) 16**
Dysuria	5 (2.1) 5	7 (2.9) 7	11 (4.5) 12
Blood and lymphatic system disorders	**5 (2.1) 5**	**7 (2.9) 7**	**10 (4.0) 12**
Anemia	3 (1.3) 3	3 (1.2) 3	5 (2.0) 6
Social circumstances	**2 (0.8) 2**	**3 (1.2) 3**	**5 (2.0) 5**
Victim of sexual abuse	2 (0.8) 2	3 (1.2) 3	5 (2.0) 5

N = Total number of participants; n = Number of participants in each category (the percentage calculation is based on the total number of participants in the sections denoted by indent); m = Number of mentions in each category

Source: Section 14, Table 14.3.1.3.2

Adverse events considered related to investigator product

Adverse events considered to be study product-related by the Investigator occurring in at least one participant in either treatment group are presented by SOC and preferred term in Table 7.

There were fewer AEs considered related to DVR-004 than AEs considered to be related to Truvada: Overall, 36 DVR-004-related AEs were reported in 32/239 (13%) participants and 333 Truvada-related AEs reported in 136/242 (56%) participants.

The most common AEs considered related to DVR-004 were reproductive system AEs (reported in 29/239 (12%) participants) and included vaginal odour (12/239; 5%), vulvovaginal discomfort (7/239; 3%) and intermenstrual bleeding (metorrhagia) (6/239; 3%).

The most common AEs considered related to Truvada were gastrointestinal AEs [reported in 96/242 (40%) participants], including nausea (61/242; 25%), vomiting (35/242; 15%), diarrhoea (26/242; 11%) and abdominal pain (25/242; 10%). Nervous system AEs were also common AEs related to

Truvada [reported in 76/242 (31%) participants] and included headache (45/242; 19%) and dizziness (43/272; 18%). Another common Truvada related AE, decreased creatinine renal clearance, was reported in 24/242 (10%) participants.

By worst severity, the majority of product-related AEs were reported as mild or moderate AEs. Participants with at worst a mild (Grade 1) product related AE were reported in 93/247 (38%) of participants who used Truvada and 23/239 (10%) participants who used DVR-004. Participants with at worst a moderate (Grade 2) product-related AE were reported in 43/242 (18%) of participants who used Truvada and 9/239 (4%) participants who used DVR-004. None of the related AEs were of Grade 3 or 4 severity.

Table 7. Incidence of Adverse Events Considered Treatment-Releated by the Investigator by System Organ Class and Preferred Term Reported in at Least One Participant, by Study Product - ITT population

System Organ Class **Preferred Term**	**DVR-004** **N = 239** **n (%) m**	**Truvada** **N = 242** **n (%) m**	**Total** **N = 247** **n (%) m**
Any Product-Related Adverse Event	**32 (13.4) 36**	**136 (56.2) 333**	**144 (58.3) 369**
Gastrointestinal disorders	**1 (0.4) 1**	**96 (39.7) 177**	**97 (39.3) 178**
Nausea	0	61 (25.2) 77	61 (24.7) 77
Vomiting	0	35 (14.5) 39	35 (14.2) 39
Diarrhoea	0	26 (10.7) 30	26 (10.5) 30
Abdominal pain	0	25 (10.3) 27	25 (10.1) 27
Abdominal discomfort	1 (0.4) 1	1 (0.4) 1	2 (0.8) 2
Abdominal pain upper	0	1 (0.4) 1	1 (0.4) 1
Dyspepsia	0	1 (0.4) 1	1 (0.4) 1
Frequent bowel movements	0	1 (0.4) 1	1 (0.4) 1
Nervous system disorders	**0**	**76 (31.4) 97**	**76 (30.8) 97**
Headache	0	45 (18.6) 51	45 (18.2) 51
Dizziness	0	43 (17.8) 45	43 (17.4) 45
Presyncope	0	1 (0.4) 1	1 (0.4) 1
Reproductive system and breast disorders	**29 (12.1) 33**	**0**	**29 (11.7) 33**
Vaginal odor	12 (5.0) 12	0	12 (4.9) 12
Vulvovaginal discomfort	7 (2.9) 7	0	7 (2.8) 7
Intermenstrual bleeding	6 (2.5) 8	0	6 (2.4) 8
Vaginal discharge	2 (0.8) 2	0	2 (0.8) 2
Dyspareunia	1 (0.4) 1	0	1 (0.4) 1
Pelvic discomfort	1 (0.4) 1	0	1 (0.4) 1
Vulvovaginal pain	1 (0.4) 1	0	1 (0.4) 1
Vulvovaginal pruritus	1 (0.4) 1	0	1 (0.4) 1
Investigations	**0**	**26 (10.7) 28**	**26 (10.5) 28**
Creatinine renal clearance decreased	0	24 (9.9) 25	24 (9.7) 25

Blood creatinine increased	0	3 (1.2) 3	3 (1.2) 3
General disorders and administration site conditions	**0**	**13 (5.4) 14**	**13 (5.3) 14**
Fatigue	0	10 (4.1) 11	10 (4.0) 11
Asthenia	0	2 (0.8) 2	2 (0.8) 2
Feeling hot	0	1 (0.4) 1	1 (0.4) 1
Metabolism and nutrition disorders	**0**	**8 (3.3) 9**	**8 (3.2) 9**
Decreased appetite	0	7 (2.9) 7	7 (2.8) 7
Abnormal loss of weight	0	1 (0.4) 1	1 (0.4) 1
Increased appetite	0	1 (0.4) 1	1 (0.4) 1
Skin and subcutaneous tissue disorders	**0**	**5 (2.1) 6**	**5 (2.0) 6**
Rash	0	3 (1.2) 3	3 (1.2) 3
Rash papular	0	2 (0.8) 2	2 (0.8) 2
Pruritus	0	1 (0.4) 1	1 (0.4) 1
Musculoskeletal and connective tissue disorders	**0**	**2 (0.8) 2**	**2 (0.8) 2**
Myalgia	0	2 (0.8) 2	2 (0.8) 2
Infections and infestations	**1 (0.4) 1**	**0**	**1 (0.4) 1**
Bacterial vaginosis	1 (0.4) 1	0	1 (0.4) 1
Injury, poisoning and procedural complications	**1 (0.4) 1**	**0**	**1 (0.4) 1**
Vulvovaginal injury	1 (0.4) 1	0	1 (0.4) 1

N = Total number of participants; n = Number of participants in each category (the percentage calculation is based on the total number of participants in the sections denoted by indent); m = Number of mentions in each category

Source: Section 14, Table 14.3.1.4.2

Assessor's comment

Overall, the reported TEAEs and ADRs are similar to what has been reported for DVR-004 and Truvada in adults in previous studies, and no new safety issues were identified in this population of 16-21 year old women.

Upon request the Applicant provided an analysis of TEAEs and study product related TEAEs of DVR-004 for participants 16-17 YOA as compared to participants 18-21 YOA. No clinically significant differences were observed in the number or severity of reported AEs between the two age groups. As such, the provided analysis of overall TEAEs and study product related TEAEs related to DVR-004 use in 16-17 year old participants and participants 18+ YOA separately did not give raise to concerns.

Serious adverse event/deaths/other significant events

Deaths and SAEs

There were no deaths reported during this trial. Six SAEs were reported in 6 participants during the trial: 3 SAEs occurred during the randomized Crossover Period, during the Truvada use periods. Three additional SAEs occurred in 3 participants during the Choice Period. Five SAEs reported in 5 participants during the Truvada use periods were all of Grade 3 severity and included acute appendicitis (2 participants), headache, anaemia due to menorrhagia/heavy menstrual bleeding and UTI. One SAE,

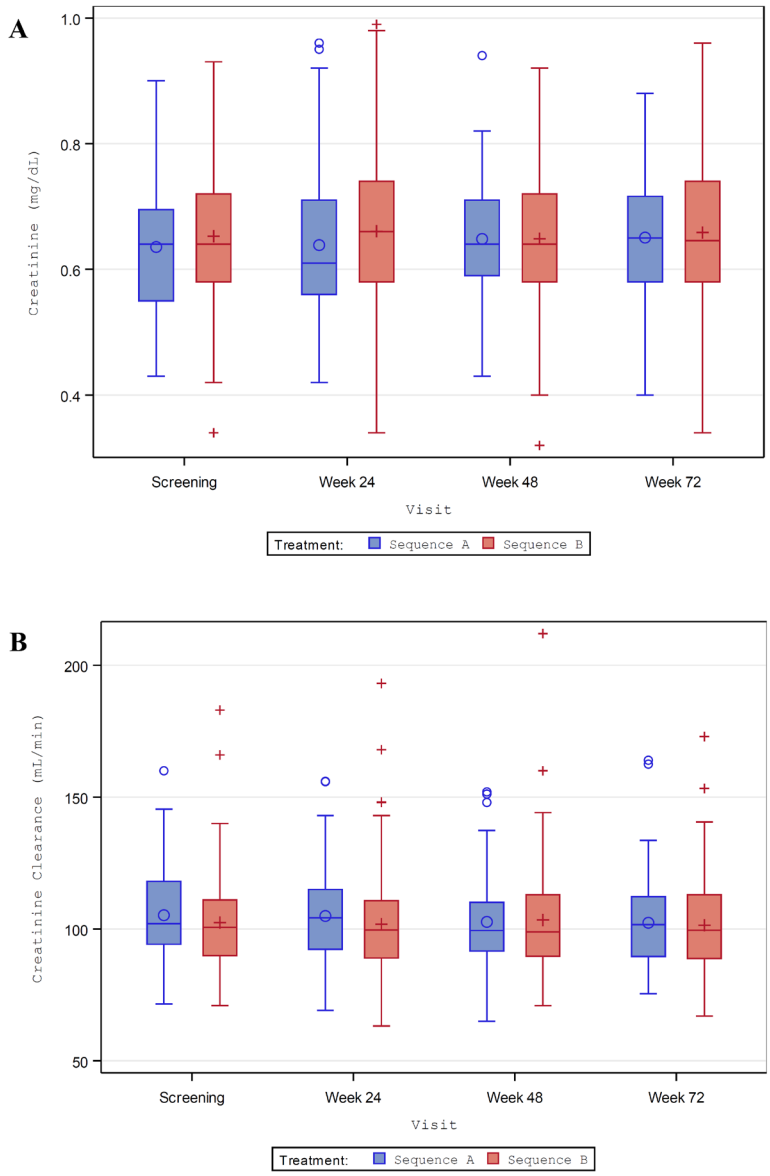
reported in one participant, a Grade 4 polytrauma due to motor vehicle accident/multiple injuries, was reported during the DVR-004 period. None of the SAEs were considered related to study product and no SAEs led to study product discontinuation and/or trial discontinuation.

Laboratory findings

The most common laboratory parameter AE was deceased creatinine renal clearance, reported in 126/247 (51%) participants, with majority (123/126) of participants experiencing it as Grade 2 AEs.

For each randomization sequence, median and IQR serum creatinine and creatinine clearance values at baseline and throughout the trial are visualised in Figure 9.

Figure 3. Boxplots of Serum Chemistry Results: Serum Creatinine and Creatinine Clearance by Visit - ITT Population



A Creatinine

B Creatinine clearance

Source: Section 14, Figure 14.3.2.2

Assessor's comment

In this graph, the blue boxplots (sequence A) correspond to DVR-004 use for the first 24 weeks, whereas the red boxplots (sequence B) correspond to Truvada use for the first 24 weeks. From week 24 until week 48 this is inversed with blue boxplots (sequence A) corresponding to Truvada use and the red boxplots (sequence B) corresponding to use of DVR-004. As compared to the data obtained during screening, overall no substantially different trends between serum creatinine and creatinine clearance levels are evident after use of DVR-004 or Truvada. The relatively high number of adverse events of creatinine clearance can likely be explained by the definition that was used for this adverse event: a 10% decrease from baseline, even if the measured value would be within normal physiological range, was defined as an adverse event of decreased creatinine clearance. No new safety signals regarding use of DVR-004 and a reduction in creatinine clearance are therefore evident from these results.

Safety in special populations

Pregnancies

A total of 5 pregnancies occurred during the trial, resulting in the birth of 5 babies:

• A participant randomized to Sequence A: Pregnancy positive test reported to RC on 22 May 2020 at the Week 12 Visit (using DVR-004 at the time). Full term live birth (greater than or equal to 37 weeks) via standard vaginal delivery of a male 3.2 kg infant.

• A participant randomized to Sequence A: Positive pregnancy test reported to RC on 05 October 2020 at the Week 52 Visit (at that point in time in the product choice period). Full term live birth via standard vaginal delivery of a male 3.5 kg infant.

• A participant randomized to Sequence A: Positive pregnancy test reported to RC on 15 November 2019 at the Week 16 Visit (using DVR-004 at the time). Full term live birth via standard vaginal delivery of a male 3.2 kg infant.

• A participant randomized to Sequence B) Positive pregnancy test reported to RC on 05 March 2020 at the Week 8 Visit (using Truvada at that time). Full term live birth via standard vaginal delivery of a male 3.9 kg infant.

• Participant randomized to Sequence B: Positive pregnancy test reported to RC on 27 November 2019 at the Week 4 Visit (using Truvada at that time). Premature birth via standard vaginal delivery of a female 2.9 kg infant.

No congenital abnormities were reported upon birth in any of the infants.

Discontinuation due to adverse events

Two AEs reported in 2 participants resulted in permanent discontinuation of study product during the trial: A Grade 2 nausea AE, considered as a product-related AE, was reported at the Week 56 Visit (Period 3) during the Truvada use period, and an acute HIV infection AE at the Week 56 Visit (Period 3) during use of Truvada.

Assessor's comment

Upon request the Applicant clarified that the reporting of "discontinuation due to HIV infection" was not in line with the SSP Safety Monitoring protocol and should not have been listed as such. Rather, for the

participant with symptomatic primary HIV infection, the term "seroconversion illness" should have been recorded on the AE Log CRF. This error also explains why the other 3 seroconverters were not included in the list of discontinuation due to adverse events, as they reported no symptoms related to primary HIV infection.

Post-marketing experience

No post-marketing data is available.

4.5.1. Discussion on clinical safety

The safety database provided from the MTN-034 study is comprised of 239 participants, and includes 79 adolescent women less than 18 YOA, which is considered modest. However, the size is considered sufficient for descriptive comparisons of safety with the known safety profile in adults.

Adverse events were reported in the vast majority of participants for both DVR-004 and Truvada use periods, which were predominantly mild-to moderate (grade 1 and 2) for both drug products. ADRs occurring during DVR-004 periods were similar to what has been observed in adults in previous studies and primarily consisted of AEs belonging to SOC 'Reproductive System and Breast Disorders', such as vaginal discharge, vaginal odour vulvovaginal discomfort and intermenstrual bleeding (metorrhagia).

A total of 6 SAEs occurred, of which 5 occurred during the Truvada use period and one occurred during use of DVR-004 (the latter concerning injuries due to a motor vehicle accident). None of the SAEs were considered related to study product use, and based on the narratives provided by the applicant this conclusion is agreed with. No deaths occurred during the study. Two AEs reported in 2 participants resulted in permanent discontinuation of study product during the trial, but not to trial discontinuation: a product related AE of grade 2 nausea at the Week 56 visit and an acute HIV infection at the Week 56 visit, both reported during the Truvada use period. The risk of resistance development is currently insufficiently addressed. Although it was stated in the MTN-034 study protocol that HIV-1 resistance tests will be performed for participants with a confirmed seroconversion, this has not yet been done. The Applicant clarified that no new data on the development of NNRTI (cross)resistance in women with unrecognised or acute HIV-1 infection are available from the ongoing studies and that further updates will be reported through annual PBRERs. As adherence is particularly challenging in adolescents, the risk of resistance development by use of DVR-004 in (young) women seroconverting and as a matter of fact being not immediately aware of their infections and hence exerting selective pressure, needs to be very carefully weighed in. Cross-resistance with other NNRTIs, used in antiretroviral therapies, has been found in vitro, potentially limiting women's treatment options. It was therefore concluded at the time of the original Art 58 opinion, that development of viral resistance to antiretroviral agents by use of DVR-004 should be closely followed post-marketing. The Applicant confirmed that the current risk minimisation measures addressing the importance of adherence will continue to be developed and implemented in close cooperation with the National Agencies in the region, and that community engagement programmes which can be an effective measure to promote adherence will continue to be supported. As these measures would also apply to adolescents, no specific action for this age category is currently required.

The most common laboratory parameter AE was decreased creatinine renal clearance. The relatively high number of adverse events of creatinine clearance can likely be explained by the definition that was used for this adverse event: a 10% decrease from baseline, even if the measured value would be within normal physiological range, was defined as an adverse event of decreased creatinine clearance. No new safety signals regarding use of DVR-004 and a reduction in creatinine clearance are therefore evident

from these results.

Although efforts were made to ensure no pregnancies occurred during the studies (inclusion criteria of contraceptive use and intention to use an effective contraceptive method for the duration of the study, as well as contraceptive counselling), a total of 5 pregnancies occurred resulting in 4 term and 1 pre-term infants with no congenital abnormalities.

Overall, no new safety issues were identified in the population of 16-21 year old women to what has been observed previously for adults. The comparison between participants 16-17 YOA and those of 18 and above did not identify concerns for this specific age category.

4.5.2. Conclusions on clinical safety

Overall, no new safety signals are detected in participants 16-17 YOA and the reported ADRs fall in line to what is known from the safety data in adults in previous studies. Dapivirine Vaginal Ring 25 mg displays an acceptable safety profile with very limited subjects discontinuing treatment and none showing related serious adverse events. With similar use, it can be expected that the safety of DVR-004 in adults will be similar in adolescents 16-17 YOA.

4.5.3. PSUR cycle

N/A

5. Risk management plan

The SOH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Rationale for submitting an updated RMP:

1) Updates are made to include additional safety and acceptability data for HIV-uninfected women 16 years and older from the MTN-034 trial in adolescent girls and young adult women (REACH - A Phase IIa crossover trial of the Dapivirine Vaginal Ring 25 mg (25 mg dapivirine) and oral PrEP (TDF/FTC) in an African healthy, HIV negative, sexually active adolescent and young adult female population 16 to 21 years of age). It is proposed that age indication for the Dapivirine Vaginal Ring 25 mg is for HIV-uninfected women 16 years and older. Exposure data of completed trials are also updated and epidemiological data also updated to reflect the new lock point of the RMP.

2) Milestone updates are made to reflect the MTN-034 clinical study report.

3) Milestone updates are made to reflect the MTN-042.

4) Editorial changes for clarity and most recent update to ongoing trials.

Summary of significant changes in this RMP:

Part I: Module Product(s) Overview – Indication(s) for the Art. 58 Opinion - update to reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 16 years and older.

Part II: Module SI Epidemiology of the indication(s) and target populations(s) – update to include women 16 years and older and editorial text and table updates made in this section.

Part II: Module SI Epidemiology of the indication(s) and target populations(s) – Transmission of HIV and risk factors – updated with adolescent girls and young women in sub-Saharan Africa information.

Part II: Module SIII Clinical Trial Exposure – updates made to text and in Table Part II: Modules SIII-1, SIII-2 and SIII-3. Data added from the MTN-034 trial.

Part II: Module SIV: Populations not studied in clinical trials: Part II: Module SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical trial Development Programs, Table Part II: Module SIV-1 - Updated timelines for MTN-042.

Part II: Module SV Post-authorisation Experience, SV.1.2 Exposure - Updated the information according to data lock point.

Part II: Module SVII.1.2 - Risks Considered Important for Inclusion in the List of Safety Concerns in the Risk Management Plan. Updated with MTN-034 (REACH) results.

Part II: Module SVII.2 - New Safety Concerns and Reclassification with a Submission of an Updated Risk Management Plan – Added information to remove missing information "Long-term use beyond 24 months of treatment" and "Use in sexually active female under 18 years of age" (given favourable results of MTN-034 (REACH)) from the list of safety concerns.

Part II: Module SVII3.2 - Presentation of the Missing Information: Updated timeline for MTN-042. Removed as missing information "Long-term use beyond 24-months of treatment" and "Use in sexually active females under 18 years of age".

Part II: Module SVIII Summary of the Safety Concerns, Table Part II: Module SVIII-1: Summary of Safety Concerns – Removed from missing information: "Long-term use beyond 24 months of treatment" and "Use in sexually-active females under 18 years of age".

PART III Pharmacovigilance Plan (Including Post-Authorisation Safety Studies) - Text updated to reflect the new recommended age and information at data lock point.

Part III.2: Additional Pharmacovigilance Activities - Removed long-term use beyond 24 months of treatment and use in sexually-active females under 18 years of age. Text updates to reflect information at the data lock point.

Part III.3: Summary Table of Additional Pharmacovigilance Activities, Table Part III-1: Ongoing and Planned Additional Pharmacovigilance Activities - Removed completed trials, namely IPM 032, MTN-025, IPM 007, MTN-015, MTN-043 and MTN-034. Editorial updates.

Part IV: Plans for post-authorisation efficacy studies - typographical error corrected. Editorial updates and text updated to reflect information at data lock point.

Part V: Risk Minimisation Measures (including Evaluation of Effectiveness of Risk Minimisation Activities) updated:

- Risk Minimisation Plan – Editorial updates.
- Section V.1: Table V.1, Description of Routine Risk Minimisation Measures by Safety Concern - Removed as missing information "Long-term use beyond 24 months of treatment" and "Use in sexually active female under 18 years of age".
- Section V.3 Summary of Risk Minimisation Measures: Table Part V-3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern - Milestone updates made regarding CSR availability for MTN-034 (REACH). Removed reference to IPM 007,

MTN-015, IPM 032, MTN-025. Updated timelines for MTN-042. Removed as missing information "Long-term use beyond 24 months of treatment" and "Use in sexually active female under 18 years of age"

Part VI: Summary of the Risk Management Plan, the following subsections were updated:

- Section I: The Medicine and What it is used for: age recommendation updated.
- Section II.A List of Important Risks and Missing Information - Removed as missing information "Long-term use beyond 24 months of treatment" and "Use in sexually active female under 18 years of age" including from Table II-1.
- Section II.B Summary of Important Risks, Table II-2: Summary of important risks and missing information - editorial updates made, including:
    - **Important potential risk: Development of non-nucleoside reverse transcriptase inhibitor resistance in women with unrecognized or acute HIV-1 infection -** Removed IPM 032, MTN-025, IPM 007 and MTN-015.
    - **Important missing information: Safety during pregnancy - R**emoved MTN-016 (EMBRACE). Editorial updates to MTN-042.
    - **Important missing information: Long-term use beyond 24 months of treatment -** Removed as missing information.
    - **Important missing information: Use in sexually active females under 18 years of age -** Removed as missing information
- Section II.C Post-authorisation Development Plan:
    - II.C.1 Studies Which Are Conditions of the Marketing Authorisation – Editorial updates
    - II.C.2 Other Studies in Post-authorisation Development Plan - Removed MTN-034 (REACH)

Annex 2: Tabulated Summary of Planned, Ongoing, and Completed PV Study Program - Updates made to Table Part VII-1, Planned and ongoing clinical safety trials/studies and editorial changes to Table Part VII-2, Completed Trials. Milestone updates made for MTN-034 (REACH).

Annex 3 Protocols for proposed, ongoing and completed studies in the Pharmacovigilance Plan: MTN-034 (REACH) protocol moved to completed studies section.

Annex 5: Updated brief description of the Implementation Study (IPM 055).

Annex 6: Details of proposed additional risk minimisation activities – HCP guide section 1: update to include lower age range for use.

Annex 7: Other supporting data – Updated numbering.

Annex 8: Summary of changes to the RMP over time, Table Part VII-1 Summary of Change to the Risk

Summary of the safety concerns

Table 8. Summary of the Safety Concerns (table from SOH RMP module SVIII)

Summary of safety concerns	
Important identified risks	• HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use
Important potential risks	• Development of NNRTI resistance in women with unrecognized or acute HIV-1 infection • Development of pelvic inflammatory disease
Missing information	• Safety during pregnancy

Summary of safety concerns	
	• Local drug-drug interaction with vaginally administered clindamycin and metronidazole

Assessor's comment:

The missing information: "Long-term use beyond 24 months of treatment" and "Use in sexually-active females under 18 years of age" were removed, which is accepted.

Conclusions on the safety specification

Having considered the data in the safety specification the PRAC assessor agrees that the safety concerns listed by the SOH are appropriate.

Pharmacovigilance plan

Clinical investigations have demonstrated that the Dapivirine Vaginal Ring 25 mg is well tolerated in HIV-1 negative, sexually-active women from 16 to 65 years of age. With a total of 5,835 women who have used the Dapivirine Vaginal Ring 25 mg in the clinical development program and in post-authorisation clinical trials at the data lock point of 23 January 2025, its safety profile is considered well understood.

As a result of the Applicant's assessment of the product safety profile, the proposed Pharmacovigilance Plan consists of routine PV activities, including the collection, assessment, and processing of individual case safety reports and ongoing safety surveillance and periodic signal detection, as well as additional pharmacovigilance activities to monitor and or better characterise the safety concerns.

Summary of planned additional PhV activities

Table 9. Ongoing and Planned Additional Pharmacovigilance Activities

Trial **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
	•	•		
	•	•		

Trial Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	•	•		
	•	•		
Safety During Pregnancy and Breastfeeding				
MTN-042 (DELIVER) Phase IIIa, randomized, open-label safety and pharmacokinetic trial of Dapivirine Vaginal Ring and oral TDF/FTC tablet use in pregnancy.	• Safety and pharmacokinetics of the Dapivirine Vaginal Ring and oral TDF/FTC tablet when used during pregnancy at different stages of gestation.	• Safety during pregnancy	Trial initiation was 09 January 2020 Database was locked on 23 August 2024	Final CSR expected Q3 2025
	•			
Safety in a Younger Female Population				
	•	•		
CSR = clinical study report; FTC = emtricitabine; MTN = Microbicide Trials Network; TDF = tenofovir disoproxil fumarate				

Assessor's comment:

Text updates were made in Part III of the RMP to reflect the new recommended age.

"Long-term use beyond 24 months of treatment" and "Use in sexually-active females under 18 years of age" were removed.

The completed trials, namely IPM 032, MTN-025, IPM 007, MTN-015, MTN-043 and MTN-034, were removed.

Overall conclusions on the PhV Plan

The PRAC assessor, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC assessor also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

A PAES has been imposed to address the current uncertainties in the efficacy in younger women. The Applicant has proposed an implementation study focusing on fostering adherence and persistence of use of the Dapivirine Vaginal Ring 25 mg in women 18-25 years old, as an alternative to the PAES. This study, apart from collecting information on product initiation and continuation, gathered information on

adherence challenges faced by young women who choose to use the Dapivirine Vaginal Ring 25 mg in a real-world setting. The study plans to enroll 500 women who will use the Dapivirine Vaginal Ring 25 mg over a 12-month period. Participants are stratified into two age groups, 18 to 21 years and > 21 to 25 years. The study started in Q3 2022 for a total duration of 30 months. A study report is expected to be available in Q3 2025.

Table 10. Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Trial **Status**	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due dates**
Implementation Study (PM 055) Observational study in healthy HIV-negative young women ages 18-25 years. (planned)	• Identify successful approaches to deliver the Ring to young women to increase continuation of use • Determine measures to increase adherence and prevention-effective use of the Ring in young women • Determine proportion and predicators of early non-use of the Ring by service delivery model and sub-population	• Lack of adherence leading to lower efficacy in younger women 18-25 years of age	Final protocol expected Q2 2022 Study initiation expected Q3 2022 Expected completion of study conduct Q4 2024	Final CSR Q3 2025

Risk minimisation measures

Table 11. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use	Routine risk communication: *Prescribing Information (Summary of Product Characteristics), Sections 4.2 and 4.4.* *Patient Information Leaflet, Sections 1, 2 and 3.* Additional risk minimisation measures: *Healthcare Professional Guide (country-specific)* *User Guide (country-specific)*	Routine pharmacovigilance beyond adverse event reporting and signal detection *Specific questionnaire for follow-up of "lack of efficacy" reports* Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Development of NNRTI resistance in women with unrecognized or acute HIV-1 infection	Routine risk communication: *Prescribing Information (Summary of Product Characteristics), Section 4.4.* *Patient Information Leaflet, Section 2.* Additional risk minimisation measures: *Healthcare Professional Guide (country-specific)* *User Guide (country-specific)*	Additional pharmacovigilance activities: None
Development of PID	Routine risk communication: *Prescribing Information (Summary of Product Characteristics), Section 4.4.* *Patient Information Leaflet, Section 2.* Additional risk minimisation measures: *Healthcare Professional Guide (country-specific)* *User Guide (country-specific)*	Additional pharmacovigilance activities None
Safety during pregnancy	Routine risk communication: *Prescribing Information (Summary of Product Characteristics), Section 4.6.* *Patient Information Leaflet, Section 2.* Additional risk minimisation measures: *Healthcare Professional Guide (country-specific)* *User Guide (country-specific)*	Additional pharmacovigilance activities: MTN-042 (DELIVER) *Phase IIIb, randomized, open-label safety and pharmacokinetic trial of Dapivirine Vaginal Ring and oral tenofovir disoproxil fumarate (TDF)/FTC tablet use in pregnancy.* *Trial initiation 09 January 2020.* *Database was locked 23 August 2024.* *Final CSR expected Q3 2025.*
Local drug-drug interaction with vaginally administered clindamycin and metronidazole	Routine risk communication: *Prescribing Information (Summary of Product Characteristics), Section 4.5.* *Patient Information Leaflet, Section 2.* *Additional risk minimisation measures:* *Healthcare Professional Guide (country-specific)* User Guide (country-specific)	Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
CSR = Clinical Study Report; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; MTN = Microbicide Trials Network; NNRTI = non-nucleoside reverse transcriptase inhibitor; TDF = tenofovir disoproxil fumarate		

Assessor´s comment:

The missing information "Long-term use beyond 24 months of treatment" and "Use in sexually active female under 18 years of age" were removed.

Milestone updates were made regarding CSR availability for MTN-034 (REACH) and the reference to IPM 007, MTN-015, IPM 032, MTN-025 were removed.

Conclusions on risk minimisation measures

The PRAC assessor, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

5.1. Overall conclusion on the RMP

☒ The changes to the RMP (version 1.6) are acceptable.

6. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated to extend the indication to include reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 16 years of age and older. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

6.1.1. User consultation

A justification for not performing a consultation with target patient groups on the package leaflet has been submitted by the SOH and has been found acceptable for the following reasons: The dossier is subject to evaluation of a medicinal product intended exclusively for markets outside the European Union. According to the Article 58 of Regulation (EC) No 726/2004, user consultation is not required.

7. Benefit-Risk Balance

7.1. Therapeutic Context

The following indication was claimed for Dapivirine Vaginal Ring 25 mg at the start of this procedure:

Reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 16 years and older in combination with safer sex practices when oral PrEP is not/cannot be used or is not available.

7.1.1. Disease or condition

HIV-1 can be transmitted from person to person through sex, contact with contaminated blood and needle or syringe sharing. With a wider range of better tolerable medicinal products that have become available in the past decade, in well-resourced countries HIV-1 infection is nowadays generally perceived as a chronic infection, not considered to relevantly shorten the life expectancy. However, the situation is different in Sub-Saharan Africa, where resource constraints limit the availability of newer antiretroviral therapies and partly even of any antiretroviral therapy. Also, appropriate medical care, allowing e.g. for HIV-diagnosis, for prevention of mother to child transmission, for regular monitoring of therapeutic success to enable rapid detection of failing antiretroviral therapies, may not be available. Hence, HIV-infection may still have deleterious consequences for the individual in these settings. In addition to medical consequences often also social harms and stigmatisation are experienced by those infected. Moreover, the risk of getting HIV infected increases with the prevalence in the population- this is particularly high in countries in Sub-Saharan Africa. Therefore, preventive measures can be considered to be particularly valuable in these settings. The risk of contracting HIV-1 infection can be reduced in various ways, including the use of male and female condoms, voluntary medical male circumcision, treatment as prevention, and pre-exposure prophylaxis (PrEP).

The intent of PrEP is to block the acquisition of HIV-1, by the use of antiretroviral drugs by HIV-uninfected people before the potential exposure to HIV-1.

7.1.2. Available therapies and unmet medical need

Despite progress against HIV, more than 2 million people still acquire HIV every year. Each person with HIV requires lifelong antiretroviral therapy (ART) to stay healthy and alive and to prevent further transmission. In 2016, 18 million people in the world were on ART. This figure equates to half of the 36.7 million people with HIV now eligible for ART following the new WHO Treat all recommendation.

PrEP: The World Health Organization (WHO) recommends that PrEP should be offered as an additional prevention choice to people at substantial risk of acquiring HIV infection. To date, oral tenofovir disoproxil (TDF) + emtricitabine (FTC) are approved to be used as PrEP for the prevention of HIV-1 infection. Daily oral PrEP with TDF alone or in combination with FTC has been shown to reduce the risk of acquisition of HIV-1 infection by $\geq$ 50% in several high-risk populations. While initial efficacy trial results in women at high risk of HIV-acquisition due to heterosexual intercourse did not show consistent results, pooled data from 6 randomised studies have shown a risk reduction of 57% (95% CI 0.34–0.94; P =0.03) for women. The effectiveness of PrEP among women in four trials that included both women and men was higher. For example, among women younger than 30 years in a trial that included both men and women, the effectiveness was 72% (95% CI: 29–92%, P =0.01) for TDF and 77% (95% CI: 25–90%, P =0.01) for FTC + TDF PrEP (Baeten et al., N Engl J Med. 2012 Aug 02;367(5):399-410). Recently, Apretude (cabotegravir prolonged-release injections) has been approved as PrEP in adults and adolescents weighing at least 35 kg who are at high risk of being infected. In a study involving over 3200 HIV-negative cisgender women which compared Apretude with TDF+FTC, 3 out of 1613 individuals taking Apretude tested positive for HIV-1 infection 1 year after treatment, versus 36 out of 1610 of those taking TDC+FTC (standard PrEP).

The following other options for prevention of HIV-1 infection are presently available:

• Condoms – if used consistently rates of protection of HIV-negative partners were as high as 80%. However, for different reasons condoms are often not used (e.g. due to perceived decrease in sexual enjoyment or cultural and gender-based norms) despite HIV prevention counselling and provision of male or female condoms.

• VMMC (Voluntary medical male circumcision) - Male circumcision was found to reduce the female-to-male sexual transmission of HIV by approximately 60% among men in sub-Saharan Africa.

• TasP (Treatment as prevention) - In HIV-discordant couples, the control of viral load through effective ARV therapy of HIV-infected individuals has been shown to reduce the transmission of HIV to their uninfected partners by 96% (study HPTN 052).

Challenges of these preventative measures include need for adherence (to regular use of condoms or to daily tablet regimen), need for male partner engagement, knowledge of HIV-status (TasP), side effects of drugs and risk of development of resistance to (subsequent) antiretroviral therapies in case of failure of prevention.

Survey-based studies of women in the US and Africa indicate that it would be helpful to have different options for PrEP, in such a way that women have a choice between different routes of medication administration and formulations that are suitable for their daily lives. As such, providing different options may enhance PrEP uptake and improve the public health approach to decreasing transmission.

Dapivirine Vaginal Ring 25 mg was developed as a female-initiated option to reduce the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-1 negative women. The ring is recommended by the applicant to be continuously worn into the vagina for a period of 28 days, after which it should be replaced with a new ring. Dapivirine Vaginal Ring 25 mg is intended for use by women as a complementary prevention approach to safer sex practices.

7.1.3. Main clinical studies

The main study results provided in support of the extension of the indication to adolescent girls 16-17 YOA is from study MTN-034; this is a phase 2a, open-label, multi-site, two-sequence crossover, randomised trial evaluating the safety of, and adherence to, Dapivirine Vaginal Ring 25 mg and Truvada (TDF+FTC) in an adolescent and young adult female population. The trial population included healthy HIV-uninfected adolescent girls and young women aged 16-21 years at enrolment, assigned in a 1:1 ratio to either sequence A (24 weeks of Dapivirine Vaginal Ring 25 mg followed by 24 weeks of Truvada) or sequence B (24 weeks of Truvada followed by 24 weeks of Dapivirine Vaginal Ring 25 mg). A total of 247 participants were enrolled, of which 124 to sequence A and 123 to sequence B. The total duration of the study was approximately 76 weeks; the 48 weeks randomised crossover period was followed-up by a 24 weeks 'choice period' in which participants were free to use Dapivirine Vaginal Ring 25 mg, Truvada, or neither study product for the duration of this period.

7.2. Favourable effects

Adherence, acceptability and product choice has been established in adolescent girls 16-17 YOA and young adult women 18-21 YOA. Based on pooled results from all trial visits during the randomised crossover period, the majority of participant-visits had residual dapivirine levels in returned rings indicating high use (45%) or some use (51%). During the choice period, for all trial visits 39% participant-visits indicated high use, and 54% participant-visits indicated some use.

Overall, most participants found use of Dapivirine Vaginal Ring 25 mg acceptable: the majority liked (liked or very much liked) the product during the randomised Crossover Period for both randomisation sequences. For Dapivirine Vaginal Ring 25 mg, the proportion of participants that liked or very much liked the product were > 80% for the week 12, 24, and 48 week visits for both sequence groups.

At the start of the Choice Period (i.e., at the Week 48 Visit), 227 participants reported their product preference: 150 (66%) participants preferred Dapivirine Vaginal Ring 25 mg, 67 (30%) preferred

Truvada, 7 (3%) participants preferred either product equally and 3 (1%) participants preferred neither product or didn't provide a response. Six months later, at the end of Period 3 (i.e., at the Week 72 Visit), 223 participants reported their choice/preference again. Preferences were relatively similar to those at Week 48: 133 (60%) of participants preferred Dapivirine Vaginal Ring 25 mg, and 68 (31%) preferred Truvada.

7.3. Uncertainties and limitations about favourable effects

The efficacy of Dapivirine Vaginal Ring 25 mg in the prevention of the risk of HIV-1 infection has been established in adults. Conventionally, efficacy will be inferred to the paediatric population based on popPK and/or modelling and simulation analyses. Previous studies have however demonstrated that systemic dapivirine concentrations are very low following ring use, which hinders the opportunity of performing popPK analyses as a means to extrapolate efficacy of Dapivirine Vaginal Ring 25 mg from adults to adolescents 16-17 YOA. Consequently, it would have been a more conventional approach to establish efficacy of Dapivirine Vaginal Ring 25 mg in this adolescent population. This is however infeasible. From a clinical and biological perspective, there is little reason to assume any differences will exist between the pharmacokinetic profile and efficacy of Dapivirine Vaginal Ring 25 mg in this population as compared to adults when product use is similar. It is acknowledged that measurement of residual dapivirine levels in used rings – as extensively discussed during the original MAA procedure – is not a very sensitive measure for adherence. Regardless, comparison of residual dapivirine levels in adolescent women 16-17 YOA to adult women can be considered sufficiently suitable to provide an indication of (similar) dapivirine ring use between these two age groups, despite the knowledge that adolescents are a particularly challenging population when it comes to the adherence to study drugs.

7.4. Unfavourable effects

The safety profile of Dapivirine Vaginal Ring 25 mg in the population of 16-21 year old women appeared similar to what has been established for adults in previous studies, and no new safety issues were identified in the MTN-034 study. ADRs occurring during Dapivirine Vaginal Ring 25 mg periods primarily consisted of AEs belonging to SOC 'Reproductive System and Breast Disorders', such as vaginal discharge, vaginal odour vulvovaginal discomfort and intermenstrual bleeding (metorrhagia), which can be expected based on the nature of the study product. TEAEs were generally mild to moderate and no discontinuations related to Dapivirine Vaginal Ring 25 mg use were reported.

7.5. Uncertainties and limitations about unfavourable effects

The safety dataset provided for adolescent women 16-17 YOA is modest (79 participants), howeverthe comparison between participants 16-17 YOA and those of 18 and above did not identify concerns for this specific age category.

7.6. Effects Table

Table 12. Effects Table for Dapivirine Vaginal Ring 25 mg based on CSR MTN-034

Short description	Unit	Dapivirine Vaginal Ring 25 mg	Truvada	Uncertainties / Strength of evidence
Favourable Effects				
	N	1337	1306	
Adherence to study	n (%)			**Primary endpoint.**

Short description	Unit	Dapivirine Vaginal Ring 25 mg	Truvada	Uncertainties / Strength of evidence
product during the randomised crossover period, for overall participant-visits as defined per category:				The measurement of residual dapivirine levels in returned rings has been demonstrated to be an insensitive measure of adherence
• Low/no use		46 (3%)	17 (1%)	
• Some use		688 (51%)	535 (41%)	
• High use		603 (45%)	754 (58%)	
Unfavourable Effects				
	N	239	242	
Vaginal odour	Incidence n (%)	12 (5%)	0 (0%)	
Vulvovaginal discomfort		7 (2.9%)	0 (0%)	
Metorrhagia		6 (2.5%)	0 (0%)	

Abbreviations:

Notes:

7.7. Benefit-risk assessment and discussion

7.7.1. Importance of favourable and unfavourable effects

For the extension of the indication of an antiretroviral agent for (the protection against) HIV infection to a paediatric population, an extrapolation approach would be acceptable, as it is assumed that the PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient. As such, the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be inferred. The parameters that would be applied to conclude on similarity should be based on available data from the entire development programme, including PK and efficacy data in adults. See also Guideline on the clinical development of medicinal products for the treatment of HIV infections (EMEA/CPMP/EWP/633/02 Rev. 3).

For Dapivirine Vaginal Ring 25 mg, systemic dapivirine concentrations are very low following ring use, which hinders the opportunity of performing PopPK analyses as a means to extrapolate efficacy of Dapivirine Vaginal Ring 25 mg from adults to adolescents 16-17 YOA. The measurement of residual dapivirine levels in used rings – as extensively discussed during the original MAA procedure - is unfortunately also not a very sensitive measure for adherence. However, comparison of residual dapivirine levels in adolescent women 16--17 YOA to adult women can be considered sufficiently suitable to provide an indication of (similar) dapivirine ring use between these two age groups. This analysis confirmed that the residual dapivirine levels in used rings were very similar between adult women from 18 YOA and those 16-17 YOA. Hence, the efficacy of Dapivirine Vaginal Ring 25 mg can also be expected to be similar in these age categories.

As adherence is particularly challenging in adolescents, the risk of resistance development by use of Dapivirine Vaginal Ring 25 mg in (young) women seroconverting and as a matter of fact being not immediately aware of their infections and hence exerting selective pressure, needs to be very carefully weighed in. Cross-resistance with other NNRTIs, used in antiretroviral therapies, has been found in vitro, potentially limiting women's treatment options. It was therefore concluded at the time of the original Art 58 opinion, that development of viral resistance to antiretroviral agents by use of Dapivirine Vaginal Ring 25 mg should be closely followed post-marketing. Further updates will be reported in the annual PSURs.

7.7.2. Balance of benefits and risks

Currently, only tenofovir disoproxil (TDF) + emtricitabine (FTC) and Apretude are approved to be used as PrEP for the prevention of HIV-1 infection for young women 16 YOA and older in sub-Saharan Africa. Accessibility of these drug products can however be limited, and there is a clear need for additional PrEP options.

Dapivirine Vaginal Ring 25 mg was developed as a female-initiated option to reduce the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-1 negative women and is currently approved for adult women.

As from a clinical and biological perspective there is little reason to assume the pharmacokinetic profile and efficacy of Dapivirine Vaginal Ring 25 mg will be different in adult women from 18 YOA and those 16-17 YOA when use of the product is similar, the EoI can be assessed based on analysis of the residual dapivirine levels in used rings (which is the best proxy we can get for product use) to Dapivirine Vaginal Ring 25 mg from the randomised crossover period of the participants 16 and 17 YOA in comparison to the adult participants. These data confirm that the residual dapivirine levels in used rings were very similar between adult women from 18 YOA and those 16-17 YOA. Hence, the efficacy of Dapivirine Vaginal Ring 25 mg can also be expected to be similar in these age categories. Also, no new safety signals were detected in participants 16-17 YOA and the reported ADRs fall in line to what is known from the safety data in adults in previous studies.

7.8. Conclusions

The overall benefit-risk of Dapivirine Vaginal Ring 25 mg in adolescent girls 16-17 years of age is positive.

Annex 1: Request for Supplementary Information

Other concerns

Clinical efficacy aspects

1. The Applicant is requested to provide an analysis of DVR-004 use for adolescents 16-17 YOA and the adults 18+ YOA included in the study separately. The following data must be included:

    a. Residual dapivirine levels in used rings in 16-17 year old participants and participants 18+ YOA, provided as data per all participant-visits overall, as well as per visit;

    b. A separate analysis for product choice, preference and acceptability for the participants 16-17 YOA as well as for the adults who used DVR-004.

    c. An analysis of overall TEAEs and study product related TEAEs related to DVR-004 use in 16-17 year old participants and participants 18+ YOA separately.

2. The Applicant should elaborate if and when a database lock has occurred for study MTN-034.

3. The Applicant should provide a justification as to why the SAP was changed after all study results were likely to have been collected

4. The Applicant should specify when and which changes to adherence counselling or information provided during these sessions were implemented when the study was ongoing. The applicant should then also provide the adherence data of all participant-visits including the number of enrolled participants prior to implementation of this amendment, and the adherence data of all participant-visits including number of enrolled participants after implementation of these amendments.

5. Ten deviations required notification of the sponsor, DAIDS, as a critical event. Please specify what these deviations entailed.

6. A substantial number of screened participants were ultimately not enrolled in the study. The Applicant is requested to provide information regarding the reasons for screen failure.

7. The Applicant is requested to clarify the numbers presented for the characteristics 'currently attending school' and 'ever attended school'. A total of 247 participants were enrolled, yet for the category 'Ever attended school', for sequence A 71 participants are reported as being 97.3% of the total and for sequence B this concerns 82 participants as being 100%. This is not understood.

Clinical safety aspects

8. It is stated in the protocol of MTN-34 that resistance tests will have been performed for the participants who seroconverted. The Applicant should clarify if resistance tests have been performed for the 4 participants who seroconverted and provide the results of these tests.

9. The Applicant is requested to provide any updates regarding (cross)resistance development to dapivirine, either from new study data or post-marketing experience, if available.

10. The portrayed number of participants for Truvada (N=242) and DVR-004 (N=239) are not entirely understood, as the Applicant stated that a total of 239 participants have been included in the safety analysis but 242 participants are reported in the table for Truvada. The Applicant is requested to clarify on which data these numbers are based, how many participants have been included in the safety analysis set and how many of these are incorporated into the safety analysis for DVR-004 and Truvada.

11. Any collected safety data of the 6 participants who discontinued study product use early should be provided in the safety analysis. The Applicant is requested to elaborate on the decision of excluding these participants from the safety analysis entirely and provide the reason for discontinuation for these participants. Finally, if safety data is available for these participants, these should be incorporated into the new safety analysis for 16-17 year old participants and adults.

12. All participants who seroconverted would have to discontinue study product use. However, only 1 out of the 4 participants who seroconverted have been reported as 'AE leading to study discontinuation'. The Applicant is requested to clarify why the remaining 3 seroconverted participants were not included as having an 'AE leading to study discontinuation', and should also clearly specify which participants and which data sets are included in the safety analysis.

13. Given the known challenges with adherence in adolescents, the Applicant should consider and discuss if additional risk minimisation measures specific to use in adolescents may be warranted.

RMP

14. The RMP should be updated to be in line with the responses to the clinical efficacy and clinical safety aspects in section 5.

15. The missing information "Long-term use beyond 24 months of treatment" should be removed from the Summary of Safety Concerns.

16. The missing information "Use in sexually-active females under 18 years of age" should be removed from the Summary of Safety Concerns.

17. Based on the dates of the final CSR/addendum to the final CSR, the following studies are completed: The studies IPM032, MTN-025, IPM 007, MTN-015, MTN-043 and MTN-034 should be removed from the PhV plan.

Annex 2: Rapporteur assessment report of the SOH responses to the Request for Supplementary Information

Other concerns

Clinical efficacy aspects

Question 1. The Applicant is requested to provide an analysis of DVR-004 use for adolescents 16-17 YOA and the adults 18+ YOA included in the study separately. The following data must be included:

- ***a) Residual dapivirine levels in used rings in 16-17 year old participants and participants 18+ YOA, provided as data per all participant-visits overall, as well as per visit;***
- ***b) A separate analysis for product choice, preference and acceptability for the participants 16-17 YOA as well as for the adults who used DVR-004.***
- ***c) An analysis of overall TEAEs and study product related TEAEs related to DVR-004 use in 16-17 year old participants and participants 18+ YOA separately.***

Summary of SOH answer

@a. Residual dapivirine levels in used rings in 16-17 year old participants and participants 18+ YOA, provided as data per all participant-visits overall, as well as per visit;

Please find the requested residual dapivirine level data in the tables below.

The geometric mean of the dapivirine residual levels across all the participant visits was 21.16 mg in the 16-17 years of age group and 21.09 mg for the age group 18 to 21 years. Comparing the treatment sequences between the age groups, there is no difference in the geometric means with 20.95 mg and 21.35 mg for the 16-17 year old participants and 21.26 mg and 20.94 mg for the 18 to 21 year old

participants in Sequence A and Sequence B, respectively.

Dapivirine Residual Levels for All Participant-Visits

Sequence	Age 16-17 YOA	Age 18-21 YOA	Total N = 239
	N m Dapivirine levels (mg): Geometric mean C.V. Mean; S.D. Median; Min, Max	N m Dapivirine levels (mg): Geometric mean C.V. Mean; S.D. Median; Min, Max	N m Dapivirine levels (mg): Geometric mean C.V. Mean; S.D. Median; Min, Max
Sequence A	41 327 20.95 6.976 21.00; 1.465 20.90; 18.0-26.0	83 785 20.94 7.122 21.00; 1.495 20.90; 9.0-25.2	124 1112 20.94 7.076 21.00; 1.486 20.90; 9.0-26.0
Sequence B	44 370 21.35 7.121 21.40; 1.524 21.20; 16.3-27.2	79 710 21.26 7.153 21.32; 1.525 21.10; 9.0-25.9	123 1080 21.29 7.141 21.35; 1.524 21.10; 9.0-27.2
Overall	85 697 21.16 7.115 21.21; 1.509 21.00; 16.3-27.2	162 1495 21.09 7.175 21.15; 1.517 21.10; 9.0-25.9	147 2192 21.11 7.155 21.17; 1.515 21.00; 9.0-27.2
Abbreviations: C.V. = Coefficient of Variation; Max = Maximum; Min = Minimum; m = Number of dapivirine residual levels; N =Number of enrolled participants; YOA = Year of Age; S.D. = Standard Deviation Sequence A: DVR-004 for 24 weeks (study product use Period 1) Sequence B: DVR-004 for 24 weeks (study product use Period 2)			

The residual dapivirine levels per participant visits are shown in the table below. The geometric mean of the residual dapivirine levels was similar in the two age groups at visits within each 24-week treatment period. Among participants 16-17 years old, values ranged from 20.36 (Week 4) to a maximum of 21.48 mg (Week 48), while for those 18 to 21 years, values ranged from 20.36 (Week 4) to a maximum of

21.44 mg (Week 48).

Residual Dapivirine Levels per Participant Visits

Sequence	Follow-up Visit	Age 16-17 YOA	Age 18-21 YOA	Total
		M Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max	M Geometric mean C.V. Mean; S.D. Median; Min, Max
Sequence A (N = 124)	Week 4	40 20.36 6.324 20.40; 1.290 20.10; 18.2-24.1	81 20.36 5.035 20.39; 1.026 20.30; 18.0-23.5	121 20.36 5.468 20.39; 1.115 20.30; 18.0-24.1
	Week 8	36 20.68 7.481 20.74; 1.551 20.65; 18.0-24.4	79 20.65 5.057 20.67; 1.045 20.70; 18.4-23.8	115 20.66 5.894 20.69; 1.220 20.70; 18.0-24.4
	Week 12	36 20.48 6.590 20.52; 1.352 20.40; 18.2-23.7	75 20.66 5.356 20.69; 1.108 20.60; 18.5-23.7	111 20.60 5.763 20.64; 1.189 20.60; 18.2-23.7
	Week 16	34 20.73 6.632 20.77; 1.377 20.85; 18.7-24.5	80 20.70 8.943 20.81; 1.861 20.80; 9.0-25.0	114 20.71 8.294 20.80; 1.725 20.80; 9.0-25.0
	Week 20	35 20.90 6.056 20.94; 1.268 21.00; 18.5-23.9	80 20.94 7.119 20.99; 1.494 20.80; 18.0-24.9	115 20.93 6.789 20.97; 1.424 20.8; 18.0-24.9
	Week 24	36 20.99 6.402 21.03; 1.346 20.60; 19.2-24.1	78 20.79 9.419 20.91; 1.970 21.15; 9.0-24.3	114 20.85 8.550 20.95; 1.791 20.92; 9.0-24.3
Sequence B (N = 115)	Week 28	33 20.61 5.975 20.65; 1.234 20.60; 18.7-24.2	74 20.96 6.083 21.00; 1.277 20.80; 18.8-24.1	107 20.85 6.071 20.89; 1.268 20.70; 18.7-24.2
	Week 32	34 21.18 7.414 21.23; 1.574 20.85; 19.0-24.6	74 21.23 6.903 21.28; 1.469 21.10; 18.6-24.9	108 21.21 7.033 21.26; 1.496 21.05; 18.6-24.9
	Week 36	37 21.37 7.491 21.42; 1.605	72 21.13 6.715 21.18; 1.422	109 21.21 6.978 21.26; 1.484

Sequence	Follow-up Visit	Age 16-17 YOA	Age 18-21 YOA	Total
		M Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max	M Geometric mean C.V. Mean; S.D. Median; Min, Max
		21.4; 19.1-26.5	21.00; 18.9-25.5	21.10; 18.9-26.5
	Week 40	38 21.44 5.849 21.48; 1.256 21.35; 19.3-24.2	70 21.3 7.854 21.36; 1.678 21.05; 18.1-25.5	108 21.35 7.184 21.40; 1.538 21.20; 18.1-25.5
	Week 44	38 21.42 6.812 21.47; 1.462 21.40; 18.8-24.1	72 21.31 6.644 21.35; 1.419 21.05; 19.2-25.1	110 21.35 6.677 21.39; 1.428 21.10; 18.8-25.1
	Week 48	37 21.48 6.995 21.53; 1.506 21.40; 18.8-26.2	73 21.44 6.933 21.49; 1.490 21.20; 19.1-25.3	110 21.45 6.922 21.50; 1.488 21.30; 18.8-26.2
CHOICE PERIOD[1] (Initially DVR-004, N=155)	Week 52	49 21.18 8.304 21.25; 1.765 20.90; 16.3-26.0	100 21.11 7.059 21.16; 1.494 20.90; 18.4-25.9	149 21.13 7.468 21.19; 1.582 20.90; 16.3-26.0
	Week 56	45 21.48 6.765 21.53; 1.456 21.30; 19.3-27.2	101 21.25 6.392 21.29; 1.361 21.20; 18.6-24.7	146 21.32 6.508 21.36; 1.390 21.20; 18.6-27.2
	Week 60	43 21.47 6.300 21.52; 1.355 21.30; 19.1-24.3	102 21.36 6.203 21.40; 1.327 21.25; 19.0-24.7	145 21.39 6.215 21.43; 1.332 21.30; 19.0-24.7
	Week 64	42 21.54 7.124 21.60; 1.539 21.40; 18.8-24.6	97 21.31 9.075 21.42; 1.944 21.30; 9.0-25.2	139 21.38 8.509 21.47; 1.827 21.30; 9.0-25.2
	Week 68	42 21.58 7.157 21.63; 1.548 21.40: 18.8-25.2	95 21.41 7.092 21.46; 1.522 21.30; 18.7-25.5	137 21.46 7.095 21.51; 1.526 21.40; 18.7-25.5
	Week 72	42 21.65 7.806 21.71; 1.695 21.50; 19.2-25.5	92 21.54 6.735 21.59; 1.454 21.40; 18.5-24.9	134 21.57 7.066 21.63; 1.528 21.45; 18.5-25.5

Abbreviations: C.V. = Coefficient of variation; Max = Maximum; Min = Minimum; m = Number of returned rings by age group; M = Total number of returned rings; YOA = Year of Age; S.D. = Standard Deviation

Sequence A (N=124): DVR-004 for 24 weeks (study product use Period 1); N=41 for 16-17 YOA; N=83 for 18+ YOA
Sequence B (N=123): DVR-004 for 24 weeks (study product use Period 2) ; N=44 for 16-17 YOA; N=79 for 18+ YOA

[1] The CHOICE period is only added in the table for completeness.

These results suggest that adherence measured by residual dapivirine levels was comparable between the

adolescent women 16-17 years old, and the adult women 18 to 21 years old, per visit and overall during the crossover period.

@b. A separate analysis for product choice, preference and acceptability for the participants 16-17 YOA as well as for the adults who used DVR-004.

DVR-004 Product Choice

Overall, most participants (59%) selected the DVR-004 as their preferred option for the CHOICE period. There were no notable differences between the two age groups: 57% of 16-17 year olds and 60% of the 18-21 year olds chose DVR-004 at week 48. Approximately 13% of participants in both age groups switched between the two products.

Product Choice by Age Group

Product Selected during CHOICE Period	Age Groups		All Ages
	Age 16-17 YOA N (%)	Age 18-21 YOA N (%)	Total N (%)
Neither	0 (0.0%)	2 (1.3%)	2 (0.9%)
Ring	43 (57.4%)	94 (60.3%)	137 (59.3%)
Switching	10 (13.3%)	20 (12.8%)	30 (13.0%)
Tablets	22 (29.3%)	40 (25.6%)	62 (26.8%)
TOTAL	75 (100%)	156 (100%)	231 (100%)

Abbreviations: % = Percentage; Ring = Dapivirine Vaginal Ring-004; N = Number of participants completing the questionnaire; Switching = No of participants changing their product during the CHOICE period; Tablets = Truvada, YOA = Year of Age

Overall, the preferred option for HIV prevention among participants comparing both age groups within the designated product use periods was very similar. In the younger age group however, it seems the Sequence influenced the choice, since in Sequence B where the ring was used immediately prior to product selection for the CHOICE period, approximately 15% more participants in the 16-17 age group chose to continue with the ring compared to Sequence A. No differences were observed between the age

groups in the proportion of participants who switched between the two products.

Product Selected for the Choice Period by Age Group by Assigned Treatment Group

Product Selected	Age Groups		All Ages
	Age 16-17 YOA N (%)	Age 18-21 YOA N (%)	Total N (%)
Sequence A			
Neither	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ring	18 (48.7%)	48 (59.3%)	66 (55.9%)
Switching	4 (10.8%)	13 (16.0%)	17 (14.4%)
Tablets	15 (40.5%)	20 (24.7%)	35 (29.7%)
TOTAL	**37 (100%)**	**81 (100%)**	**118 (100%)**
Sequence B			
Neither	0 (0.0%)	2 (2.7%)	2 (1.8%)
Ring	25 (65.8%)	46 (61.3%)	71 (62.8%)
Switching	6 (15.8%)	7 (9.3%)	13 (11.5%)
Tablets	7 (18.4%)	26 (26.7%)	27 (23.9%)
TOTAL	**38 (100%)**	**75 (100%)**	**113 (100%)**

Abbreviations: % = Percentage; Ring = Dapivirine Vaginal Ring-004; N = Number of participants; Switching = No of participants changing their product during the CHOICE period; Tablets = Truvada, YOA = Year of Age

Sequence A: DVR-004 for 24 weeks (DVR-004 use Period 1)
Sequence B: DVR-004 for 24 weeks (DVR-004 study product use Period 2)

DVR-004 Preference

At week 48, after using the DVR-004 first (Sequence A), 57% of the 16 to 17 year olds preferred the DVR-004 over Truvada which is an increase from 32% based on expected preference information collected at enrolment. In the 18 to 21 years age group, 67% preferred the DVR-004 at 48 weeks from 46% at enrolment. Six months later at the end of the Choice period (week 72), 49% of the younger age group and 62% of the adult women preferred the DVR-004.

For participants in Sequence B, the younger women 16-17 years old, preferred the DVR-004 from 32% at enrolment to 76% at the start of the choice period, and 37% to 64% respectively in the age group 18 to 21 years. Six months later the preference for the DVR-004 was 59% in 16- to 17-year-old participants

and 62% in the adult women 18 to 21 years.

Product Preference by Age Group and Treatment Sequence

Treatment Sequence	Visit	ACASI[1] Question - *Would you prefer the ring or tablets for HIV prevention?*		
		Age 16-17 YOA	**Age 18-21 YOA**	**Total N=247**
Sequence A	Enrolment	**N=41** Ring 13 (32%) Tablets 19 (46%) Equal 9 (22%) Missing 0	**N= 83** Ring 38 (46%) Tablets 24 (29%) Equal 20 (24%) Missing 1 (1%)	**N=124** Ring 51 (41%) Tablets 43 (35%) Equal 29 (23%) Missing 1 (1%)
	Week 48	37 Ring 21 (57%) Tablets 14 (38%) Equal 2 (5%) Missing 0	79 Ring 53 (67%) Tablets 23 (29%) Equal 3 (4%) Missing 0	116 Ring 74 (64%) Tablets 37 (32%) Equal 5 (4%) Missing 0
	Week 72	35	80	115

Treatment Sequence	Visit	ACASI[1] Question - *Would you prefer the ring or tablets for HIV prevention?*		
		Age 16-17 YOA	**Age 18-21 YOA**	**Total N=247**
		Ring 17 (49%) Tablets 16 (45%) Equal 2 (6%) Missing 0	Ring 50 (62%) Tablets 19 (24%) Equal 11 (14%) Missing 0	Ring 67 (58%) Tablets 35 (31%) Equal 13 (11%) Missing 0
Sequence B	Enrolment	**N=44** Ring 14 (32%) Tablets 22 (50%) Equal 6 (14%) Neither 2 (4%) Missing 0	**N=79** Ring 29 (37%) Tablets 35 (44%) Equal 12 (15%) Neither 2 (3%) Missing 1 (1%)	**N=123** Ring 43 (35%) Tablets 57 (46%) Equal 18 (15%) Neither 4 (3%) Missing 1 (1%)
	Week 48	37 Ring 28 (76%) Tablets 8 (23%) Equal 0 Neither 0 Missing 1 (1%)	74 Ring 48 (64%) Tablets 22 (30%) Equal 2 (3%) Neither 2 (3%) Missing 0	111 Ring 76 (68%) Tablets 30 (27%) Equal 2 (2%) Neither 2 (2%) Missing (1%)
	Week 72	37 Ring 22 (59%) Tablets 13 (35%) Equal 1 (3%) Neither 1 (3%) Missing 0	71 Ring 44 (62%) Tablets 20 (28%) Equal 4 (6%) Neither 3 (4%) Missing 0	108 Ring 66 (62%) Tablets 33 (31%) Equal 5 (5%) Neither 4 (4%) Missing 0

Abbreviations: % = Percentage; ACASI = Audio Computer-Assisted Self-Interview; Ring = Dapivirine vaginal ring-004; N = Number of participants completing the questionnaire; Tablets = Truvada, YOA = Year of Age

[1] The ACASI questionnaire outcome was included since it was completed at Day 0/enrolment, Week 48 and Week 72, whereas a CRF questionnaire was completed only at Week 72. No significant differences were observed at Week 72, namely 68% 16-17 YOA and 58% of 18-21 YOA preferred the ring.

Sequence A: DVR-004 for 24 weeks (study product use Period 1); Enrolment at CHOICE period after 48 weeks.
Sequence B: DVR-004 for 24 weeks (study product use Period 2); Enrolment at CHOICE period after 48 weeks.
CHOICE Period: Participants selected between DVR-004 and Truvada for final 24 weeks (Period 3).

DVR-004 Acceptability

The acceptability of the DVR-004 remained stable over time and comparable in both age groups. Among participants 16 to 17 years old, acceptability ranged from 89% after 3 months of use to 85% after 6 months of use. For the adult women 18-21 years old, the range was 92% to 89% over the 6 months.

DVR-004 Product Acceptability as Reported via ACASI Over Time

DVR-004 Period of Use[1]	Age 16-17 YOA N=79	Age 18-21 YOA N=160	Total N=139
ACASI Questionnaire[4]	DVR-004 (Like/Did not Like[2, 3])	DVR-004 (Like/Did not Like[2, 3])	DVR-004 (Like/Did not Like[2, 3])
12 weeks	N=73 Like 65 (89%)	N=143 Like 131 (92%)	N=216 Like 196 (91%)

	Did not Like 8 (11%)	Did not Like 12 (8%)	Did not Like 20 (9%)
24 weeks	72 Like 61 (85%) Did not Like 11 (15%)	150 Like 134 (89%) Did not Like 16 (11%)	222 Like 195 (88%) Did not Like 27 (12%)

Abbreviations: % = Percentage; ACASI = Audio Computer-Assisted Self-Interview; DVR-004 = Dapivirine vaginal ring-004; N = Number of participants completing the questionnaire; YOA = Year of Age

[1] Participants in Sequence A and B.
[2] 'Like' includes response of "like" and 'like very much'.
[3] 'Did not like' includes responses of 'dislike very much', 'dislike' and 'neither like nor dislike'.
[4] The ACASI questionnaire outcome was included since it was completed after 12 weeks and 24 week, whereas a CRF questionnaire was completed only after 24 weeks. No significant differences were observed at Month 6, namely 93% 16-17 YOA and 88% of 18-21 YOA liked the ring.

Sequence A: DVR-004 for 24 weeks (study product use Period 1)
Sequence B: DVR-004 for 24 weeks (study product use Period 2)

Similarly, DVR-004 acceptability remained stable over time and comparable in both age groups across the two study sequences. For Sequence A participants, acceptability ranged from 97% to 94% over 6 months in the 16 to 17 years of age groups and 93% to 96% in the 18 to 21 year old participants. For sequence B participants, a slightly lower acceptability was observed, ranging from 83% to 76% over the same timeframe amongst younger participants and 87% to 81% in the older age groups.

DVR-004 Product Acceptability as Reported via ACASI Per Sequence Over Time

Sequence	Visit	Age 16-17 YOA N=79	Age 18-21 YOA N=160	Total N=139
Acceptability as Reported via ACASI over Time		DVR-004 (Like[1]/Did not like[2])	DVR-004 (Like[1]/Did not like[2])	DVR-004 (Like[1]/Did not like[2])
Sequence A	Week 12	N=37 Like 36 (97%) Did not Like 1 (3%)	N=74 Like 69 (93%) Did not Like 5 (7%)	N=111 Like 105 (95%) Did not Like 6 (5%)
	Week 24	N=35 Like 33 (94%) Did not Like 2 (6%)	N=75 Like 72 (96%) Did not Like 3 (4%)	N=110 Like 105 (95%) Did not Like 5 (5%)
Sequence B	Week 36	N=35 Like 29 (83%) Did not Like 6 (17%)	N=68 Like 61 (88%) Did not Like 7 (12%)	N=103 Like 90 (87%) Did not Like 13 (13%)
	Week 48	N=37 Like 28 (76%) Did not Like 9 (24%)	N=74 Like 62 (84%) Did not Like 12 (16%)	N=111 Like 90 (81%) Did not Like 21 (19%)

Abbreviations: % = Percentage; ACASI = Audio Computer-Assisted Self-Interview; DVR-004 = Dapivirine vaginal ring-004; N = Number of participants completing the questionnaire; YOA = Year of Age

[1] "Like" includes 'like" and "like very much'.
[2] 'Did not like' includes responses of 'dislike very much', 'dislike' and 'neither like nor dislike'.

Sequence A: DVR-004 for 24 weeks (study product use Period 1)
Sequence B: DVR-004 for 24 weeks (study product use Period 2)

Overall, no notable differences were observed between the two age groups with regards to product choice, preference and acceptability. These data complement the comparative adherence data in the two age groups as shown above. In totality, the data provide some assurance of an expected similar use in younger women compared to adult women suggesting that a similar efficacy can be expected.

c. An analysis of overall TEAEs and study product related TEAEs related to DVR-004 use in 16-

17 year old participants and participants 18+ YOA separately.

During the 72 weeks of the study (Sequence A, Sequence B, and the CHOICE period), 231 participants reported 1105 adverse events (AEs) occurring after using the DVR-004; 372 (33.7%) AEs occurred in 77 (33%) participants in 16-17 year age group and 733 (66.3%) AEs occurred in 154 (64%) participants in the 18 to 21 year old group. Please note that the AE numbers presented here are higher than the presentation of AEs over 72 weeks during DVR usage in the CSR. The database provided to the Applicant by the data analysis vendor (which generated the CSR) did not include an explicit variable indicating which treatment (DVR-004 or Truvada) an AE occurred. The count of participants and adverse events experiencing AEs during DVR-004 usage presented in the table below include AEs that occurred during or after DVR-004 usage, whereas the counts in the CSR include only AEs occurring during DVR-004 usage.

Thirty-six events were assessed as related to the DVR-004 and were reported by 33 participants – 13 AEs in 12 participants 16-17 years old and 23 AEs in 20 participants 18 to 21 years old. None of the 16-17 year old participants had more than one DVR-related AE. No clinically significant differences were observed in the number or severity of reported AEs between the two age groups.

No study product-related SAEs were reported. One SAE was reported while the participant was using the DVR-004, namely "polytrauma due to a motor vehicle accident" which occurred in the 18-21 year group. It was assessed as Grade 4 and unrelated to the product.

None of the AEs led to DVR-004 discontinuation or study withdrawal (see response to Question 12 for further discussion).

Overall Reported Adverse Events

Reported AEs during DVR-004 usage	Age 16-17 YOA (N=79)		Age 18-21 YOA (N=160)		Total (N=239)	
	N %	M %	N %	M %	N %	m
Any AE over 72 weeks (Sequence A + B and CHOICE)	77 33%	372 33.7%	154 64%	733 66.3%	231 96.7%	1105
Any AE related to DVR-004	12 15%	13 36%	20 13%	23 64%	33 13.8%	36
Any SAE	0 0%	0 0%	1 0.6%	1 100%	1 0.4%	1
Abbreviations: % = Percentage; AE = Adverse Event; m = Number of adverse events; N = Number of participants; TEAE = Treatment-Emergent Adverse Event; YOA = Year of Age Definitions: AE = Any untoward medical occurrence in a participant administered an investigational product (IP) and which does not necessarily have a causal relationship with the IP.						

DVR-004 Related Adverse Events

Any AE related to DVR-004		Age 16-17 YOA (N=79)		Age 18-21 YOA (N=160)		Total (N=239)	
System Organ Class (SOC)	Preferred Term	N %	m	N %	m	N %	m

Total related TEAEs		12 15.2%	13	20 12.5%	23	32 13.4%	36
Gastrointestinal disorders	Abdominal discomfort	1	1	0	0	1 0.4%	1
Subtotal		1 1.3%	1	0 0%	0	1 0.4%	1
Infections and infestations	Bacterial vaginosis	0	0	1	1	1 0.4%	1
Subtotal		0 0%	0	1 1.3%	1	1 0.4%	1
Injury, poisoning and procedural complications	Vulvovaginal injury	0	0	1	1	1 0.4%	1
Subtotal		0 0%	0	1 1.3%	1	1 0.4%	1
Reproductive system and breast disorders	Dyspareunia	1	1	0	0	1 0.4%	1
	Intermenstrual bleeding	4	5	2	3	6 2.5%	8
	Pelvic discomfort	1	1	0	0	1 0.4%	1
	Vaginal discharge	1	1	1	1	2 0.8%	1
	Vaginal odour	2	2	10	10	12 5.0%	12
	Vulvovaginal discomfort	1	1	6	6	7 2.9%	7
	Vulvovaginal pain	0	0	1	1	1 0.4%	1
	Vulvovaginal pruritus	1	1	0	0	1 0.4%	1
Total		**11 14%**	**12**	**18 11%**	**21**	**29 12.1%**	**33**
Abbreviations: % = Percentage; AE = Adverse Event; m = Number of adverse events; N = Number of participants; PT = Preferred Term; SOC = System Organ Class; TEAE = Treatment-Emergent Adverse Event; YOA = Year of Age							

DVR-004 Related Adverse Events by Severity

Description	Severity Grade	Age 16-17 YOA (N=79)		Age 18-21 YOA (N=160)		Total (N=239)	
Any Adverse Event	Severity Grade	N %	m	N %	M	N %	M
	Total	12 15.2%	13	20 12.5%	23	32 13%	36
	1	9	10	14	17	23	27
	2	3	3	6	6	9	9
System Organ Class (SOC)	Total	11 (13.9%)	12	18 (11.2%)	21	29 (12.1%)	33
Reproductive system and breast disorders	1	8	9	13	16	21	25
	2	3	3	5	5	8	8

Dyspareunia	1	1	1	0	0	1	1
Intermenstrual bleeding	1	3	4	1	2	4	6
	2	1	1	1	1	2	2
Pelvic discomfort	1	1	1	0	0	1	1
Vaginal discharge	1	1	1	1	1	2	2
Vaginal odour	1	1	1	9	9	10	10
	2	1	1	1	1	2	2
Vulvovaginal discomfort	1	0	0	3	3	3	3
	2	1	1	3	3	4	4
Vulvovaginal pain	1	0	0	1	1	1	1
Vulvovaginal pruritus	1	1	1	0	0	1	1
Abbreviations: % = Percentage; m = Number of adverse events; N = Number of participants; PT = Preferred Term; SOC = System Organ Class; YOA = Year of Age							

Rapporteur Assessment

The SOH provided the requested information. The available information confirms that the residual dapivirine levels in used rings is very similar between adult women from 18 YOA and those 16-17 YOA. Hence, the efficacy of DVR-004 can also be expected to be similar in these age categories.

Also for product choice, preference and acceptability of the product there was no notable difference between the 16-17 YOA and young adult women 18-21 YOA. A majority of women in both age categories chose DVR-004 at week 48 as their preferred PrEP method. At the end of the Choice period, the preference for DRV-004 was slightly declined. This was somewhat more notable in the younger women. Acceptability remained relatively stable and high over time, and comparable in both age groups across the two study sequences. The SOH conclusion that 'the data provide some assurance of an expected similar use in younger women compared to adult women suggesting that a similar efficacy can be expected', is agreed with.

The provided analysis of overall TEAEs and study product related TEAEs related to DVR-004 use in 16-17 year old participants and participants 18+ YOA separately also did not give raise to concerns. No clinically significant differences were observed in the number or severity of reported AEs between the two age groups.

Overall, the additional analyses provide sufficient reassurance that DRV-004 will be similarly efficacious and has a comparable safety profile in women 16-17 YOA and adult women.

Issue resolved.

Question 2. The Applicant should elaborate if and when a database lock has occurred for study MTN-034.

Summary of SOH answer

Database lock occurred on 2 March 2022. All relevant SOPs were followed and close-out memos are

available upon request.

Rapporteur Assessment

The SOH provided the requested information.

Issue resolved.

Question 3. The Applicant should provide a justification as to why the SAP was changed after all study results were likely to have been collected.

Summary of SOH answer

The development of the SAP was led by the data management vendor (Scharp) according to their internal SOPs. The data analyses were conducted by a separate data analysis vendor (TECRO). The development of the SAP was initiated by the data management vendor during the conduct of the study. It is acknowledged that final signatures were applied to the SAP after study results had been collected and after database lock. However, there was no analysis done prior to the final signatures on the SAP in accordance with the data management vendor's SOP on SAP development. The following is a timeline of the relevant activities:

1) Database lock: 2 March 2022

2) SAP approval:

- The draft SAP was sent for review by the sponsor (NIAID/DAIDS) on 1 March 2022.
- Comments from NIAID/DAIDS were received on 15 March 2022. Comments incorporated into the SAP based on NIAID/DAIDS feedback include:
    - Enhancing sample size description
    - Addition of section to describe handling of missing data
    - Changing from the mixed effects model for evaluating safety outcomes to a generalized estimating equation (GEE) model, consistent with the trial protocol
    - Addition of details on GEE model to be used for evaluation of adherence, including a justification for the change from protocol
- There were no changes to the SAP between 1 March 2022 and the final sign-off other than the ones listed above as requested by NIAID/DAIDS
- SAP was finalized and signed on 26 April 2022

3) Data analysis was initiated on 7 July 2022 at the data analysis vendor.

Between 26 April when the SAP was finalized and 7 July when data analysis began, no changes were made to the database or the SAP. During this period, contractual arrangements were made to transfer the dataset from the data management vendor to the data analysis vendor so that analyses could be

initiated. At no time before or after database lock did NIAID/DAIDS have access to the database.

Rapporteur Assessment

The SOH clarified that although final signatures were applied to the SAP after study results had been collected and after database lock, there was no analysis done prior to the final signatures on the SAP in accordance with the data management vendor's SOP on SAP development.

Issue resolved.

Question 4. The Applicant should specify when and which changes to adherence counselling or information provided during these sessions were implemented when the study was ongoing. The applicant should then also provide the adherence data of all participant-visits including the number of enrolled participants prior to implementation of this amendment, and the adherence data of all participant-visits including number of enrolled participants after implementation of these amendments.

Summary of SOH answer

The initial schedule in the protocol was to provide drug level feedback to each participant twice during each period of use or a total of six times; four times during the crossover period (twice in Period 1, twice in Period 2) and twice during the Choice period. The drug level feedback provided was based on participants' adherence data for the previous month.

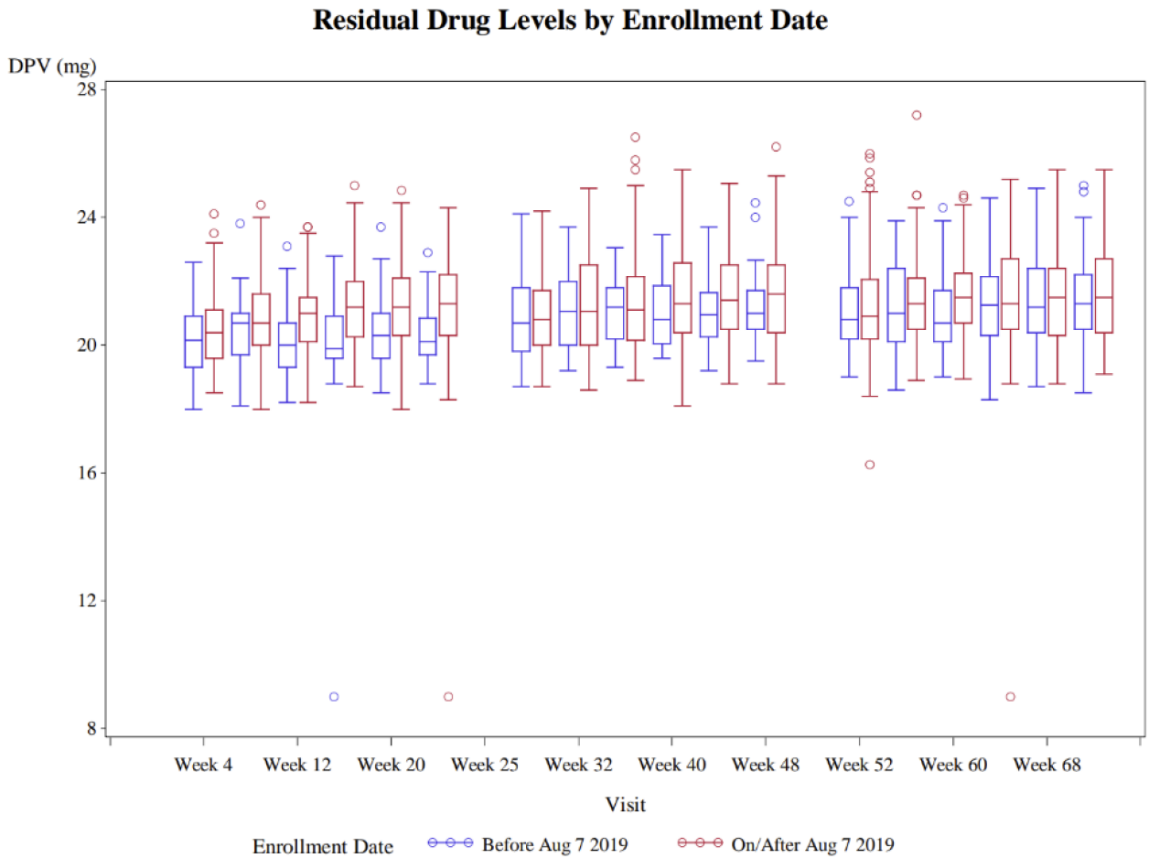
Once the trial started, it became clear that ensuring samples could be processed and drug-level counselling data made available at the specific pre-specified timepoints was going to be logistically challenging; delays were occurring at different points in the process of shipping samples to the labs, analysing the samples, and receiving data back at the sites. Therefore, to avoid multiple protocol deviations for drug-level counselling occurring at timepoints other than those specified in the protocol, NIAID/DAIDS issued a clarification memo on 26 July 2019 to allow for drug level counselling to be done at visits beyond those specified in the protocol, whenever results were available. The information provided at these visits did not change. The memo was implemented at all sites on August 7, 2019. The sites were not required to get IRB/IEC approval to implement the memo. NIAID/DAIDS had intended to incorporate the change outlined in the memo into the next protocol amendment, however, no amendments to the protocol were made.

The drug-level feedback process document (provided in Annex 1) outlines the procedures for providing drug level feedback. Step 7 states that "in the event results are not available, the visit should proceed as originally scheduled and the participant should be counseled that she would be contacted when this information is available (either as part of an interim visit or at the next scheduled study visit)."

Seventy-six participants had been enrolled prior to the implementation of the memo and 171 were enrolled after implementation. Of the 76 enrolled prior to the memo, 42 of these did not have drug-level counselling visits prior to the implementation of the memo (either because they were not scheduled for such visits or because drug-level data were not available).

With respect to DVR-004 use and residual dapivirine drug level data, 38 participants were enrolled prior to the implementation of the memo and 83 were enrolled after implementation. Of the 38 participants, 13 of these did not have drug-level counselling visits prior to the implementation of the memo. The drug-level adherence data for participants using DVR-004 are presented below in the figure and table for the cohorts of participants enrolled before and after the memo was implemented. The data do not suggest

differences in adherence between these cohorts.



Residual Dapivirine Levels per Participant Visits, Before and After Memo Implementation

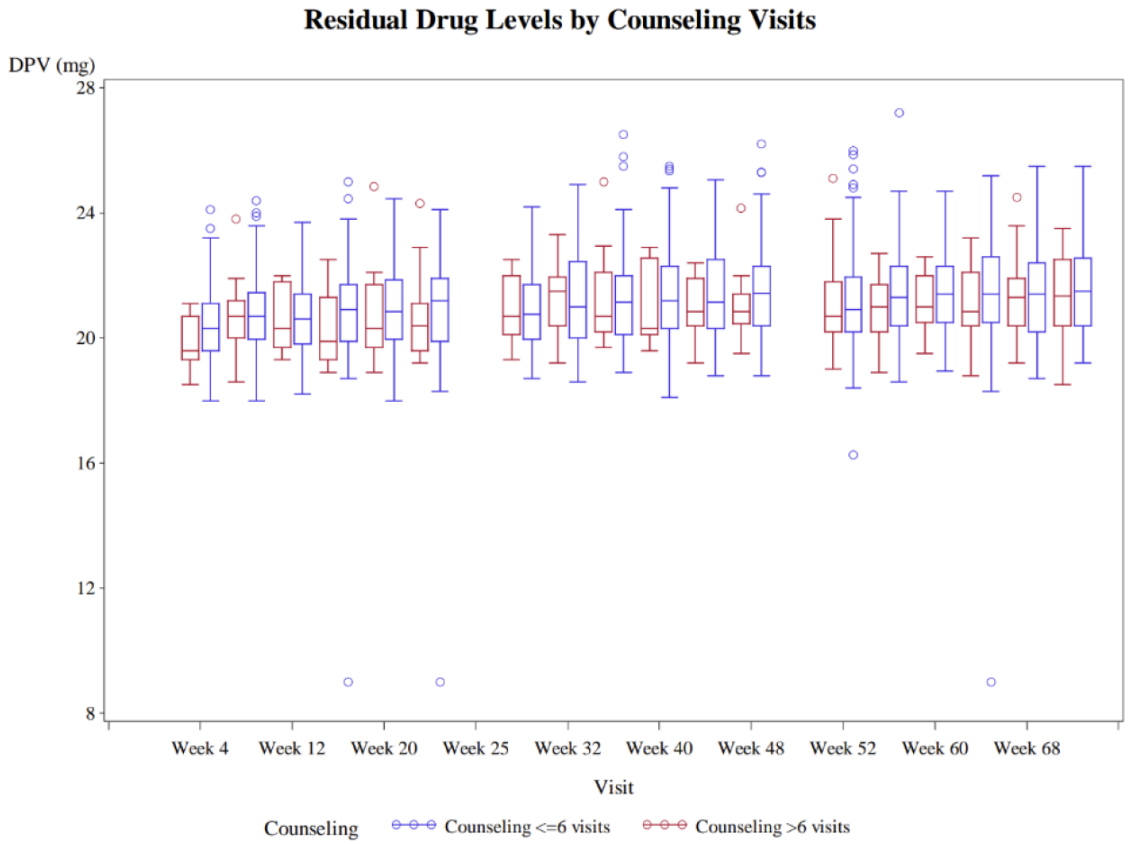
Follow-up Visit	Enrollment Before Aug 7 2019 m Geometric mean C.V. Mean; S.D. Median; Min, Max	Enrollment On/After Aug 7 2019 m Geometric mean C.V. Mean; S.D. Median; Min, Max	Total M Geometric mean C.V. Mean; S.D. Median; Min, Max
Week 4	38 20.48 5.440 20.14; 1.096 20.15; 18.0-22.6	83 20.48 5.420 20.5; 1.111 20.40; 18.5-24.1	121 20.36 5.468 20.39; 1.115 20.30; 18.0-24.1
Week 8	37 20.35 5.816 20.38; 1.185 20.70; 18.1-23.8	78 20.81 5.832 20.84; 1.216 20.70; 18.0-24.4	115 20.66 5.894 20.69; 1.220 20.70; 18.0-24.4
Week 12	37 20.11 5.508 20.14; 1.109 20.00; 18.2-23.1	74 20.85 5.356 20.89; 1.156 21.00; 18.2-23.7	111 20.60 5.763 20.64; 1.189 20.60; 18.2-23.7

Follow-up Visit	Enrollment Before Aug 7 2019	Enrollment On/After Aug 7 2019	Total
	m Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max	M Geometric mean C.V. Mean; S.D. Median; Min, Max
Week 16	38 19.76 10.198 19.91; 2.030 19.90; 9.0-22.8	76 21.20 6.399 21.24; 1.359 21.20; 18.7-25.0	114 20.71 8.294 20.80; 1.725 20.80; 9.0-25.0
Week 20	37 20.33 5.652 20.36; 1.151 20.30; 18.5-23.7	78 21.21 6.841 21.26; 1.455 21.20; 18.0-24.9	115 20.93 6.789 20.97; 1.424 20.8; 18.0-24.9
Week 24	36 20.34 5.026 20.37; 1.024 20.10; 18.8-22.9	78 21.09 9.429 21.22; 2.001 21.30; 9.0-24.3	114 20.85 8.550 20.95; 1.791 20.92; 9.0-24.3
Week 28	34 20.79 6.071 20.82; 1.264 20.70; 18.7-24.1	73 20.88 6.108 20.92; 1.278 20.80; 18.7-24.2	107 20.85 6.071 20.89; 1.268 20.70; 18.7-24.2
Week 32	34 21.01 5.484 21.04; 1.154 21.05; 19.2-23.7	74 21.31 7.610 21.36; 1.626 21.05; 18.6-24.9	108 21.21 7.033 21.26; 1.496 21.05; 18.6-24.9
Week 36	33 21.05 5.179 21.08; 1.092 21.20; 19.3-23.1	76 21.28 7.614 21.34; 1.625 21.10; 18.9-26.5	109 21.21 6.978 21.26; 1.484 21.10; 18.9-26.5
Week 40	32 20.94 5.291 20.96; 1.109 20.80; 19.6-23.5	76 21.53 7.678 21.59; 1.657 21.30; 18.1-25.5	108 21.35 7.184 21.40; 1.538 21.20; 18.1-25.5
Week 44	32 20.97 5.425 21.00; 1.139 20.95; 19.2-23.7	72 21.51 6.994 21.56; 1.508 21.40; 18.8-25.1	110 21.35 6.677 21.39; 1.428 21.10; 18.8-25.1
Week 48	33 21.12 5.224 21.15; 1.105 21.00; 19.5-24.5	77 21.60 7.427 21.65; 1.608 21.60; 18.8-26.2	110 21.45 6.922 21.50; 1.488 21.30; 18.8-26.2
Week 52	45 20.94 6.045 20.97; 1.268 20.80; 19.0-24.5	104 21.22 7.977 21.28 1.698 20.90; 16.3-26.0	149 21.13 7.468 21.19; 1.582 20.90; 16.3-26.0
Week 56	46	100	146

Follow-up Visit	Enrollment Before Aug 7 2019	Enrollment On/After Aug 7 2019	Total
	m Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max	M Geometric mean C.V. Mean; S.D. Median; Min, Max
	21.12 6.276 21.16; 1.328 21.00; 18.6-23.9	21.41 6.595 21.45; 1.415 21.30; 18.9-27.2	21.32 6.508 21.36; 1.390 21.20; 18.6-27.2
Week 60	45 21.02 6.120 21.06; 1.289 20.70; 19.0-24.3	100 21.56 6.126 21.60; 1.323 21.50; 19.0-24.7	145 21.39 6.215 21.43; 1.332 21.30; 19.0-24.7
Week 64	44 21.27 7.150 21.32; 1.524 21.25; 18.3-24.6	95 21.43 9.074 21.55; 1.955 21.30; 9.0-25.2	139 21.38 8.509 21.47; 1.827 21.30; 9.0-25.2
Week 68	43 21.42 7.012 21.47; 1.505 21.20: 18.7-24.9	94 21.48 7.167 21.50; 1.544 21.50; 18.8-25.5	137 21.46 7.095 21.51; 1.526 21.40; 18.7-25.5
Week 72	41 21.40 6.634 21.45; 1.423 21.30; 18.5-25.0	93 21.65 7.249 21.70; 1.573 21.50; 19.1-25.5	134 21.57 7.066 21.63; 1.528 21.45; 18.5-25.5
Abbreviations: C.V. = Coefficient of variation; Max = Maximum; Min = Minimum; N =Number of returned rings; YOA = Year of Age; S.D. = Standard Deviation			

Only 27 participants received drug-level feedback more than six times. These instances of drug-level feedback occurred during all three periods of the trial, in participants using both regimens, and at all sites. The Applicant reviewed the 27 cases and could find no pattern in terms of the extra counselling received by these 27 participants or in their drug-level adherence data compared to the cohort of participants who received only the six specified drug level counselling sessions (see figure and table

below presenting the data for the participants using DVR-004).



Residual Dapivirine Levels per Participant Visits, for Cohorts with >6 or ≤6 Drug-level Counselling Visits

Follow-up Visit	Drug-level Counselling Visits >6	Drug-level Counselling Visits ≤6	Total
	m Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max
Week 4	11 19.82 4.189 19.84; 0.831 19.60; 18.5-21.1	110 20.42 5.515 20.45; 1.128 20.30; 18.0-24.1	121 20.36 5.468 20.39; 1.115 20.30; 18.0-24.1
Week 8	11 20.78 6.255 20.82; 1.302 20.70; 18.6-23.8	104 20.65 5.883 20.68; 1.217 20.70; 18.0-24.4	115 20.66 5.894 20.69; 1.220 20.70; 18.0-24.4
Week 12	10 20.63 5.508 20.65; 1.049 20.30; 19.3-22.0	101 20.60 5.849 20.64; 1.207 20.60; 18.2-23.7	111 20.60 5.763 20.64; 1.189 20.60; 18.2-23.7
Week 16	9 20.34	105 20.74	114 20.71

Follow-up Visit	Drug-level Counselling Visits >6	Drug-level Counselling Visits ≤6	Total
	m Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max
	6.723 20.38; 1.370 19.90; 18.9-22.5	8.413 20.83; 1.753 20.90; 9.0-25.0	8.294 20.80; 1.725 20.80; 9.0-25.0
Week 20	11 20.80 7.981 20.85; 1.664 20.30; 18.9-24.9	104 20.94 6.693 20.99; 1.405 20.85; 18.0-24.5	115 20.93 6.789 20.97; 1.424 20.8; 18.0-24.9
Week 24	11 20.66 7.664 20.71; 1.587 20.40; 19.2-24.3	103 20.88 8.662 20.98; 1.817 21.20; 9.0-24.1	114 20.85 8.550 20.95; 1.791 20.92; 9.0-24.3
Week 28	15 20.91 4.837 20.93; 1.013 20.70; 19.3-22.5	92 20.84 6.272 20.88; 1.310 20.75; 18.7-24.2	107 20.85 6.071 20.89; 1.268 20.70; 18.7-24.2
Week 32	16 21.29 5.338 21.32; 1.138 21.05; 19.2-23.3	92 21.20 7.313 21.25; 1.554 21.00; 18.6-24.9	108 21.21 7.033 21.26; 1.496 21.05; 18.6-24.9
Week 36	15 21.19 6.660 21.24; 1.414 20.70; 19.7-25.0	94 21.22 7.061 21.27; 1.502 21.15; 18.9-26.5	109 21.21 6.978 21.26; 1.484 21.10; 18.9-26.5
Week 40	15 20.88 5.774 20.92; 1.208 20.30; 19.6-22.9	93 21.43 7.335 21.48; 1.576 21.20; 18.1-25.5	108 21.35 7.184 21.40; 1.538 21.20; 18.1-25.5
Week 44	16 21.03 4.638 21.05; 0.976 20.85; 19.2-22.4	94 21.40 6.936 21.45; 1.488 21.15; 18.8-25.1	110 21.35 6.677 21.39; 1.428 21.10; 18.8-25.1
Week 48	16 20.96 5.453 20.99; 1.145 20.85; 19.5-24.2	94 21.54 7.074 21.59; 1.527 21.43; 18.8-26.2	110 21.45 6.922 21.50; 1.488 21.30; 18.8-26.2
Week 52	27 20.96 6.724 21.01; 1.413 20.70; 19.0-25.1	122 21.17 7.632 21.23 1.620 20.90; 16.3-26.0	149 21.13 7.468 21.19; 1.582 20.90; 16.3-26.0
Week 56	27 20.99 4.931	119 21.39 6.765	146 21.32 6.508

Follow-up Visit	Drug-level Counselling Visits >6	Drug-level Counselling Visits ≤6	Total
	m Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max	m Geometric mean C.V. Mean; S.D. Median; Min, Max
	21.01; 1.036 21.00; 18.9-22.7	21.44; 1.451 21.30; 18.6-27.2	21.36; 1.390 21.20; 18.6-27.2
Week 60	27 21.11 4.275 21.13; 0.903 21.00; 19.5-22.6	118 21.46 6.536 21.51; 1.406 21.40; 19.0-24.7	145 21.39 6.215 21.43; 1.332 21.30; 19.0-24.7
Week 64	26 21.06 5.402 21.08; 1.139 20.85; 18.8-23.2	113 21.46 9.017 21.56; 1.945 21.40; 9.0-25.2	139 21.38 8.509 21.47; 1.827 21.30; 9.0-25.2
Week 68	27 21.30 5.550 21.33; 1.184 21.30: 19.2-24.5	110 21.50 7.425 21.56; 1.601 21.40; 18.7-25.5	137 21.46 7.095 21.51; 1.526 21.40; 18.7-25.5
Week 72	26 21.34 6.388 21.38; 1.366 21.35; 18.5-23.5	108 21.63 7.216 21.68; 1.565 21.50; 19.2-25.5	134 21.57 7.066 21.63; 1.528 21.45; 18.5-25.5
Abbreviations: C.V. = Coefficient of variation; Max = Maximum; Min = Minimum; N =Number of returned rings; YOA = Year of Age; S.D. = Standard Deviation			

Rapporteur Assessment

The SOH provided additional information on the modifications to product adherence counselling which were implemented when the study was already ongoing, as requested.

The reason for the introduced changes – being the logistical challenges in processing drug level samples on time in order to meet the specific pre-specified timepoints to be able to give feedback to participants – is understood. It would indeed have resulted in multiple protocol deviations for drug-level counselling occurring at timepoints other than those specified in the protocol if no action would have been taken. The provided analyses of the adherence data pre- and post-implementation of the memo that allowed for drug level counselling to be done at visits beyond those specified in the protocol, whenever results were available, does not suggest that the updated strategy for adherence counselling resulted in clinically relevant changes in adherence of participants.

Issue resolved.

Question 5. Ten deviations required notification of the sponsor, DAIDS, as a critical event. Please specify what these deviations entailed.

Summary of SOH answer

Five of the 10 deviations were related to participant adherence (one participant did not have her ring intact upon arrival, and four did not return their oral tablets). Five deviations were procedural protocol deviations (PDs) namely: completion of ACASI for the wrong IP, IP delivered at home, two dry blood

sample (DBS) were prepared in error and one vaccination was not administered on time. Two deviations occurred during the DVR-004 treatment periods, as summarised in the table below. None of the PDs compromised participant safety or impacted the overall data integrity. Appropriate corrective and/or preventive actions were successfully implemented to address the deviations and prevent similar deviations during the trial. Please find attached a protocol deviation summary.

Summary of the Ten Deviations

Non Compliance by Research Center or Participant	Deviation Description	Deviation Category
Research Center	ACASI VISIT 6/13/20 TABLET incorrectly completed and not ACASI VISIT 6/13/20 RING (N=1)	Protocol Non-Compliance
	IP home delivered – Truvada (N=1)	Protocol Non-Compliance
	DBS in error collected, was not required (N=2)	Protocol Non-Compliance
	Second dose of Hepatitis B and HPV vaccines in error not given at Visit 4.0, but later at Interim Visit (N=1)	Protocol Non-Compliance
Participant	IP lost – Truvada (N=1)	IP Non-Adherence
	IP not returned – Truvada (N=3)	IP Non-Adherence
	IP not intact or returned – Ring (N=1)	IP Non-Adherence
Abbreviation: ACASI = Audio Computer-Assisted Self-Interview, IP = Investigational Product (ring or tablets); N = Number of Deviations		

Rapporteur Assessment

The SOH clarified the 10 deviations, as requested. Five were related to protocol non-compliance, namely: completion of ACASI for the wrong IP, IP delivered at home, two dry blood sample (DBS) were prepared in error and one vaccination was not administered on time. It is agreed that these deviations are not expected to have had an impact on the overall conclusions of the study. The remaining 5 deviations were related to IP being either not returned, lost or not intact. Also these deviations are not expected to have had an impact on the overall conclusions of the study.

Issue resolved.

Question 6. A substantial number of screened participants were ultimately not enrolled in the study. The Applicant is requested to provide information regarding the reasons for screen failure.

Summary of SOH answer

Of the 396 participants screened, 149 (38%) were not enrolled. The most common reasons for non-enrollment were ineligibility (58%), driven primarily by unwillingness to comply with all study procedural requirements (26%); unwillingness to use effective contraception (15%); and non-negative (15%) or positive HIV test results (14%) upon screening. Incomplete screening accounted for 38% of non-enrollment. Please find a screen-out summary by site for MTN-034 with the complete screening data in Annex 2 of the response document.

Rapporteur Assessment

The SOH was requested to provide information on reasons for screen failure to exclude the possibility that bias was introduced during the selection of screened participants. The most common reasons for non-enrollment were related to unwillingness to comply with (parts of) study procedures and HIV test results. It is not expected that this would have resulted in significant bias making the enrolled population not representative for the claimed population.

Issue resolved.

Question 7. The Applicant is requested to clarify the numbers presented for the characteristics 'currently attending school' and 'ever attended school'. A total of 247 participants were enrolled, yet for the category 'Ever attended school', for sequence A 71 participants are reported as being 97.3% of the total and for sequence B this concerns 82 participants as being 100%. This is not understood.

Summary of SOH answer

The question about "ever attending" school was only asked to participants who were not currently attending school. Therefore, the denominator for the "ever attended" school question differs from the total denominator in each sequence.

- Of the total 124 participants in Sequence A, 51 participants were currently in school and 73 participants were not currently enrolled in school. Of the 73 participants who were not currently enrolled in school, 71 (97.3%) had ever attended school.
- Of the total 123 participants in Sequence B, 41 participants were currently in school and 82 participants were not currently enrolled in school. Of the 82 participants who were not currently enrolled in school, 82 participants (100%) had ever attended school.

Rapporteur Assessment

The SOH clarified the numbers presented for the characteristics 'currently attending school' and 'ever attended school'. The misunderstanding was due to the denominator for the "ever attended" school question which differed from the total denominator in each sequence.

Issue resolved.

Clinical safety aspects

Question 8. It is stated in the protocol of MTN-34 that resistance tests will have been performed for the participants who seroconverted. The Applicant should clarify if resistance tests have been performed for the 4 participants who seroconverted and provide the results of these tests.

Summary of SOH answer

The resistance testing on samples from these 4 participants have not been done. The Applicant is exploring having this testing performed by an outside laboratory.

Rapporteur Assessment

The SOH clarified that resistance testing has unfortunately not (yet) been done for the 4 participants who seroconverted. Although it is understood that there may be challenges in performing these tests, the SOH is urged to do their utmost best to perform resistance testing, as this will provide important information.

Issue not further pursued.

Question 9. The Applicant is requested to provide any updates regarding (cross)resistance development to dapivirine, either from new study data or post-marketing experience, if available.

Summary of SOH answer

No new data on the development of NNRTI (cross)resistance in women with unrecognised or acute HIV-1 infection are available from the ongoing studies, from post-marketing experience, or in the literature. The latest comprehensive review of the published literature had a search end date of 31 March 2025.
As noted in the response to question #8, resistance testing on samples from the two seroconverters in the DVR-004 group in MTN-034 has not yet been done. The Applicant will report any updates in the annual PBRER.

Rapporteur Assessment

No new information is currently available. Further updates will be reported through annual PBRERs.

Issue resolved.

Question 10. The portrayed number of participants for Truvada (N=242) and DVR-004 (N=239) are not entirely understood, as the Applicant stated that a total of 239 participants have been included in the safety analysis but 242 participants are reported in the table for Truvada. The Applicant is requested to clarify on which data these numbers are based, how many participants have been included in the safety analysis set and how many of these are incorporated into the safety analysis for DVR-004 and Truvada.

Summary of SOH answer

In the MTN-034 CSR, the safety data set included all participants (N=247). The safety analyses included only participants to whom either Truvada (N=242) or DVR-004 (N=239) was dispensed. Please refer to Table 14.1.1.1.1 for the number of participants to whom each study drug was dispensed.

In Module 2.7.4, subsection 1.3.4.3, the statement that N=239 were included in safety and exposure calculations refers specifically to the safety and exposure calculations for DVR-004 only, not Truvada or overall. A total of N=241 were assigned to DVR-004 in MTN-034 (N=124 in Period 1 and N=117 in Period 2). However, 2 participants in Period 2 were never dispensed DVR-004 and thus had no exposure (see

also response below).

Rapporteur Assessment

The SOH clarified that the statement that 'N=239 were included in safety and exposure calculations' refers specifically to the safety and exposure calculations for DVR-004 only, not Truvada or overall. The numbers included in the safety analysis set are herewith understood.

Issue resolved.

Question 11. Any collected safety data of the 6 participants who discontinued study product use early should be provided in the safety analysis. The Applicant is requested to elaborate on the decision of excluding these participants from the safety analysis entirely and provide the reason for discontinuation for these participants. Finally, if safety data is available for these participants, these should be incorporated into the new safety analysis for 16-17 year old participants and adults.

Summary of SOH answer

The Applicant confirms that all participants to whom the DVR-004 was dispensed were considered in the safety analysis, including those who discontinued early. See above, a total of N=241 were assigned to DVR-004 in MTN-034 (N=124 in Period 1 and N=117 in Period 2). However, 2 participants in Period 2 were never dispensed DVR-004 and thus had no exposure. Therefore, the safety analysis was based on N=239 (2 fewer than the total assigned to DVR-004). The six participants who discontinued early were included in all safety analyses.

Rapporteur Assessment

The SOH confirms that the six participants who discontinued early were included in all safety analyses. This was not clear from the wording in the dossier, but is as would have been expected.

Issue resolved.

Question 12. All participants who seroconverted would have to discontinue study product use. However, only 1 out of the 4 participants who seroconverted have been reported as 'AE leading to study discontinuation'. The Applicant is requested to clarify why the remaining 3 seroconverted participants were not included as having an 'AE leading to study discontinuation', and should also clearly specify which participants and which data sets are included in the safety analysis.

Summary of SOH answer

All MTN-034 participants who seroconverted (N=2 on DVR-004 and N=2 on Truvada) permanently discontinued study product use. However, participants who seroconverted and discontinued study product use were able to remain in the trial if they chose to do so. Seroconversion was one of the study outcomes of MTN-034 and was therefore not defined as an adverse event per protocol.

However, if a participant seroconverted and developed one or more signs or symptoms of acute HIV-infection, this participant would be reported to have had a single AE using the term "seroconversion illness." Clinical site staff were instructed accordingly in section 8.3.9 from MTN-034 SSP Safety Monitoring for the relevant protocol (below).

One of the four seroconverters in MTN-034 had signs or symptoms of acute HIV-infection upon seroconversion and was reported to have had an AE leading to study product discontinuation (but not study discontinuation). This AE was reported in the eCRF as "discontinuation due to HIV infection" rather

than "seroconversion illness" which the Applicant acknowledges is a discrepancy from the SSP Safety Monitoring protocol. The other three seroconverters did not have signs or symptoms of acute HIV-infection and thus permanently discontinued study product use without being assigned an AE leading to study product discontinuation.

"8.3.9 Reporting HIV Infection Illness

HIV acquisition (seroconversion) is one of the study endpoints, thus is not considered an AE for data collection or reporting purposes. "HIV infection" should not be reported as an AE or written anywhere on an AE Log CRF. Final determination of HIV status will instead be captured on the HIV Confirmatory Results CRF.

However, primary HIV infection is often symptomatic, and a constellation of symptoms may best be summarized as primary HIV infection illness. In this case, as in other cases when symptoms are best expressed as a unifying diagnosis, it is important to use that summary diagnosis. Thus, if a participant seroconverts and develops one or more signs or symptoms of acute HIV- infection, it is appropriate to report these sign(s)/symptom(s) as a single AE using ONLY the term "seroconversion illness" for the AE Term on the AE Log CRF. Use the comments section of the AE Log CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis) and to note the alternative aetiology as due to "acute HIV". To avoid generating a clinical query, please ensure that the term "acute" is included when describing the required alternative aetiology in the Comments section.

Complete the other items on the AE Log CRF per the general form instructions. The onset date should be completed using the date on which the participant first reported experiencing the first sign/symptom of acute HIV-infection. If there is more than one HIV-related sign/symptom, record the highest severity grade. A seroconversion illness AE is considered 'resolved' when all of the associated signs/symptoms have resolved or returned to baseline per participant report, and medications for the symptoms are no longer indicated. Mark any medications indicated and taken for the associated symptoms, if applicable.

If one or more signs/symptoms, reported on separate AE Log entries, are later attributed to acute HIV infection, update the AE term for the earliest reported sign/symptom AE to the "seroconversion illness" diagnosis and list any other signs or symptoms in the comments section of this AE Log CRF. Inactivate the applicable AE Log line within Medidata Rave."

The safety data set included all 247 participants of the study. See also the responses to questions #10

and #11 for further clarification on the safety data set and analyses.

Rapporteur Assessment

The SOH clarified that the reporting of "discontinuation due to HIV infection" was not in line with the SSP Safety Monitoring protocol and should not have been listed as such. Rather, for the participant with symptomatic primary HIV infection, the term "seroconversion illness" should have been recorded on the AE Log CRF. This error also explains why the other 3 seroconverters were not included in the list of discontinuation due to adverse events, as they reported no symptoms related to primary HIV infection.

With this explanation, it is clarified why the other 3 participants who seroconverted were not included as having an 'AE leading to study discontinuation'. The SOH also confirmed which participants and which data sets are included in the safety analysis, as requested.

Issue resolved.

Question 13. Given the known challenges with adherence in adolescents, the Applicant should consider and discuss if additional risk minimisation measures specific to use in adolescents may be warranted.

Summary of SOH answer

Challenges of adherence in adolescents are acknowledged. In order to explore potential risk minimisation measures specific for adolescents, the Applicant reviewed current guidelines for HIV treatment and prevention and government programmes in the region but was not able to identify specific adolescent focused guidance to promote better adherence. The current risk minimisation measures addressing the importance of adherence when using the DVR-004 are the Healthcare Professional Guide (HCP), User Guide, the Patient Information Leaflet (PIL) as well as educational programmes. These materials and programmes will continue to be developed and implemented in close cooperation with the National Agencies in the region. The Applicant is committed to discuss potential specific adolescent focused messaging with these Agencies but is currently not in the position to commit to specific changes or additions to the material or programmes. The Applicant would like to emphasize that community engagement programmes which can be an effective measure to promote adherence will continue to be supported.

Rapporteur Assessment

The response of the SOH - stating that the current risk minimisation measures addressing the importance of adherence will continue to be developed and implemented in close cooperation with the National Agencies in the region, and that community engagement programmes which can be an effective measure to promote adherence will continue to be supported – is very much appreciated and supported. It is agreed that the current efforts would also be sufficient for adolescent women 16-17 YOA and that no specific action for this age category is currently required.

Issue resolved.

RMP

Question 14. The RMP should be updated to be in line with the responses to the clinical efficacy and clinical safety aspects in section 5.

Summary of SOH answer:

See revised RMP included in the submission.

PRAC Rapporteur Assessment:

The RMP was updated as requested.

Issue resolved.

Question 15. The missing information "Long-term use beyond 24 months of treatment" should be removed from the Summary of Safety Concerns.

Summary of SOH answer:

See revised RMP included in the submission.

PRAC Rapporteur Assessment:

"Long-term use beyond 24 months of treatment" was removed from the Summary of Safety Concerns. The RMP was updated as requested.

Issue resolved.

Question 16. The missing information "Use in sexually-active females under 18 years of age" should be removed from the Summary of Safety Concerns.

Summary of SOH answer:

See revised RMP included in the submission.

PRAC Rapporteur Assessment:

"Use in sexually-active females under 18 years of age" was removed from the Summary of Safety Concerns. The RMP was updated as requested.

Issue resolved.

Question 17. Based on the dates of the final CSR/addendum to the final CSR, the following studies are completed: The studies IPM032, MTN-025, IPM 007, MTN-015, MTN-043 and MTN-

034 should be removed from the PhV plan.

Summary of SOH answer:

See revised RMP included in the submission.

PRAC Rapporteur Assessment:

The studies IPM032, MTN-025, IPM 007, MTN-015, MTN-043 and MTN-034 were removed from the PhV plan. The RMP was updated as requested.

Issue resolved.