IPM BELGIUM

AN AFFILIATE OF THE POPULATION COUNCIL

A. EUROPEAN UNION RISK MANAGEMENT PLAN FOR THE DAPIVIRINE VAGINAL RING

Risk management Plan (RMP) version to be assessed as part of this application:

Data lock point for this RMP	23 January 2025	Version number	2.0
Date of final sign off	1 July 2025		

Rationale for submitting an updated RMP: 1) Updates 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 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 is for HIV-uninfected women 16 years and older. Exposure data of completed trials are also updated and epidemiological data are also updated to reflect the new lock point of the RMP. 2) Milestone updates are made to reflect the MTN-034 clinical study report (CSR). 3) Milestone updates are made to reflect the MTN-042. 4) Editorial changes for clarity and most recent update to ongoing trials. The significant changes are reflected in the following modules/sections:

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 Tables of 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 favorable 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

Other RMP versions under evaluation:

RMP Version number: None

Submitted on: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP:

Version number: 1.4

Approved with procedure: EMEA/H/W/002168/II/0025/G

Date of approval: 18 July 2024

IPM BELGIUM

AN AFFILIATE OF THE POPULATION COUNCIL

Deputy European Union (EU) Pharmacovigilance (PV) contact person name: Ana Rafaela Araújo

Deputy EU PV contact person signature: _____

EU PV contact person oversight declaration: The content of this RMP has been reviewed and approved by the scientific opinion applicant's EU PV contact person.

IPM SA NPC Head of PV and Medical Safety (MS): [redacted]

IPM SA NPC Head of PV and MS signature: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
APR	Antiretroviral Pregnancy Registry
ARV	Antiretroviral
ART	Antiretroviral therapy
AUC	Area under the concentration-time curve
BLQ	Below level of quantification
BV	Bacterial vaginosis
CAB LA	Cabotegravir long acting (injection)
CD4	Cluster of differentiation 4
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
CYP	Cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DREAM	Dapivirine Ring Extended Access and Monitoring
DVR	Dapivirine Vaginal Ring
DPV	Dapivirine
EFV	Efavirenz
ETV	Etravirine
EU	European Union
FC	Fold change
FTC	Emtricitabine
GA	Gestational age
HCP	Healthcare professional
HIV-1/2	Human immunodeficiency virus type 1 or 2
HIVdb	Human immunodeficiency virus database
HOPE	HIV Open-label Prevention Extension
HPV	Human papilloma virus
HSV	Herpes simplex virus
IC_{99}	99% inhibitory concentration
IPM	International Partnership for Microbicides

Abbreviation	Definition
IUD	Intrauterine device
Ki	Inhibitory constant
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	Modified intent-to-treat
MTN	Microbicide Trials Network
NGS	Next generation sequencing
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOAEL	No observed adverse effect level
NVP	Nevirapine
OLE	Open label extension
PAES	Post-Authorisation Efficacy Study
PBRER	Periodic Benefit Risk Evaluation Report
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PID	Pelvic inflammatory disease
PIL	Patient Information Leaflet
PrEP	Pre-exposure prophylaxis
PROM	Preterm premature rupture of membranes
PV	Pharmacovigilance
REACH	Reversing the Epidemic in Africa with Choices in HIV Prevention
RAM	Resistance-associated mutation
RMP	Risk Management Plan
RNA	Ribonucleic acid
RPV	Rilpivirine
RT	Reverse transcriptase
SAE	Serious adverse event
SA NPC	South Africa Non-Proft Company
SmPC	Summary of Product Characteristics
SOC	System Organ Class (MedDRA)
STI	Sexually transmitted infection
TasP	Treatment as prevention
TBD	To be determined
TEAE	Treatment-emergent adverse event
TDF	Tenofovir disoproxil fumarate

1.8.2 Risk Management Plan

Abbreviation	Definition
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UC	Unlimited Company
US	United States
UTI	Urinary tract infection
VMMC	Voluntary medical male circumcision
VR	Vaginal ring
VTE	Venous thromboembolic events
VVC	Vulvovaginal candidiasis
WHO	World Health Organization

Part I PRODUCT(S) OVERVIEW

Table Part I-1: Product Overview

Active substance(s) (International non-proprietary name or common name):	Dapivirine
Pharmacotherapeutic group(s) (Anatomical therapeutic chemical Code):	G01AX17
Name of Scientific Opinion Holder or Applicant:	International Partnership for Microbicides (IPM) Belgium (IPM Belgium) Association Internationale sans but Lucratif
Medicinal products to which this Risk Management Plan (RMP) refers:	Dapivirine Vaginal Ring
Invented name(s) in the European Economic Area:	Not applicable
Scientific Opinion procedure:	Committee for Medicinal Products for Human Use (CHMP) Opinion under Art. 58 of Regulation 726/2004
Brief description of the product:	Small molecule
	Dapivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Non-nucleoside reverse transcriptase inhibitors bind to the human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) enzyme, thereby preventing viral replication.
Hyperlink to the Product Information:	Dapivirine Vaginal Ring SmPC
Indication(s) for the Art. 58 Opinion:	Current (if applicable): 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 pre-exposure prophylaxis (PrEP) is not/cannot be used or is not available.
Dosage for the Art. 58 Opinion:	Current (if applicable): One Dapivirine Vaginal Ring is inserted into the vagina and kept in until replaced each month with a new ring. To maintain efficacy, a new Dapivirine Vaginal Ring should be inserted immediately after the previous ring is removed. If the Dapivirine Vaginal Ring is accidentally expelled or removed, the woman should rinse the ring in clean water and immediately re-insert it, if this occurred in a clean environment. If this occurs in an unhygienic environment a new ring should be inserted immediately.
Pharmaceutical form(s) and strengths:	Current (if applicable): Vaginal delivery system. The Dapivirine Vaginal Ring is a flexible, off-white vaginal ring with an outer diameter of 56 mm and a cross-sectional diameter of 7.7 mm.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Not applicable

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

The Dapivirine Vaginal Ring is indicated for reducing the risk of HIV-1 infection via vaginal intercourse in sexually-active, HIV-uninfected women 16 years and older in combination with safer sex practices.

Incidence of HIV infection:

Eastern and Southern Africa is the region most strongly affected by the human immunodeficiency virus (HIV) epidemic. HIV infection incidence rates per 1000 population in 2022 (modelled estimates: percent [estimated range] among adults 15 to 49 years of age is 1.7 [1.24 – 2.27]. In comparison, the global average HIV incidence rate is 0.28 [0.21 – 0.37]. The HIV infection incidence rates, as well as the number of new HIV infections in the African countries in which marketing of the Dapivirine Vaginal Ring-004 is approved or under review, are listed below (Table Part II: Module SI-1). Of the 1,200,000 [900,000 – 1,600,000] adults 15 years and older who became newly infected with HIV in 2022 globally, approximately 440,000 (37%) are living in Eastern and Southern Africa[1]. Due to the increased availability of antiretroviral therapy (ART), the number of new HIV infections is slowly declining in many sub-Saharan African countries.

The extent of HIV epidemic among women and its potential impact on children is highlighted by the number of pregnant women needing ARVs for the prevention of vertical transmission of HIV infection.

Table Part II: Module SI-1: HIV Infection Incidence Rates and Number of New HIV Infections in Relevant Countries in 2022

Country	**Incidence rate**[a]		
	Adults overall (15 to 49 years of age)	***Adults number of new infections overall (≥ 15 years of age)***	***Pregnant women needing ARVs to prevent vertical transmission***
Botswana	3.32 [2.65 – 4.12]	41,000 [33,000 – 52,000]	9,800 [7,300 – 11,000]
South Africa	5.21 [3.58 – 7.28]	150,000 [110,000 – 210,000]	260,000 [170,000 – 350,000]
Zimbabwe	1.68 [1.17 – 2.32]	13,000 [9,200 – 18,000]	52,000 [40,000 – 60,000]
Zambia	3.25 [2.79 – 3.74]	29,000 [25,000 – 33,000]	51,000 [43,000 – 55,000]
Uganda	2.19 [1.77 – 2.86]	46,000 [36,000 – 62,000]	85,000 [73,000 – 93,000]
Malawi	1.30 [1.00 – 1.72]	13,000 [9,900 – 17,000]	36,000 [29,000 – 40,000]
Kenya	0.68 [0.38 – 1.13]	18,000 [10,000 – 30,000]	52,000 [44,000 – 61,000]
Tanzania	0.88 [0.68 – 1.15]	26,000 [20,000 – 35,000]	74,000 [61,000 – 84,000]
Rwanda	0.38 [0.27 – 0.53]	2,700 [2,000 – 3,800]	6,700 [5,500 – 7,700]

HIV = human immunodeficiency virus
ARV = Antiretroviral therapy
[a] HIV incidence rates per 1000 population (only available for adult population but not for women only).
Data shown as number [estimated range].
Source: aidsinfo.unaids.org, “Incidence rates among adults (15-49)” and “Number of new HIV infections” on national level[1].

Prevalence of HIV infection:

HIV prevalence is very high in Eastern and Southern Africa compared to the average global prevalence rate per 100 individuals of 0.7 [0.6 – 0.8] among adults 15 to 49 years of age. HIV prevalence rates vary across the relevant countries, with the highest rate in South Africa (Table Part II: Module SI-2).

Globally, there were 39,000,000 [33,000,000 – 45,700,000] adults and children living with HIV in 2022, with approximately 20,730,000 (53.2%) living in Eastern and Southern Africa[1].

Among people living with HIV globally, 20,000,000 [16,900,000 – 23,400,000] are women 15 years of age and older, with approximately 12,700,000 (64.0%) living in Eastern and Southern Africa. HIV prevalence is rising, because more people are living longer as a result of the availability of ART. Adolescents and young women 15 to 24 years of age, especially those between 15 and 19 years of age being particularly at high risk[2]. The number of people living with HIV in relevant countries is listed below (Table Part II: Module SI-2).

Table Part II: Module SI-2: HIV Prevalence Rates (Per 100 Individuals) in Relevant Countries in 2019

Country	**Prevalence rate**[a]		**Number of people living with HIV**	
	Adults overall (15 to 49 years of age)	***Young women (15 to 24 years of age)***	***Adults overall (≥ 15 years of age)***	***Females (≥ 15 years of age)***
Botswana	16.4 [13.7 – 17.9]	5.3 [2.7 – 7.5]	340,000 [310,000 – 360,000]	210,000 [190,000 – 220,000]
South Africa	17.8 [11.9 – 23.2]	8.7 [3.5 – 13.8]	7,400,000 [5,200,000 – 9,400,000]	4,800,000 [3,400,000 – 6,100,000]
Zimbabwe	11.0 [9.8 – 12.0]	4.4 [2.9 – 5.6]	1,200,000 [1,100,000 – 1,300,000]	750,000 [690,000 – 820,000]
Zambia	10.8 [10.4 – 11.1]	4.5 [2.2 – 5.8]	1,300,000 [1,300,000 – 1,400,000]	840,000 [800,000 – 900,000]
Malawi	7.1 [6.5 – 7.4]	2.2 [1.4 – 2.7]	950,000 [900,000 – 1,000,000]	590,000 [560,000 – 630,000]
Uganda	5.1 [4.9 – 5.3]	2.5 [1.4 – 3.2]	1,400,000 [1,300,000 – 1,500,000]	860,000 [800,000 – 960,000]
Kenya	3.7 [3.3 – 4.1]	1.7 [1.3 – 2.2]	1,300,000 [1,200,000 – 1,500,000]	860,000 [770,000 – 1,000,000]
Tanzania	4.3 [4.0 – 4.5]	1.7 [0.9 – 2.2]	1,600,000 [1,500,000 – 1,800,000]	1,100,000 [990,000 – 1,200,000]
Rwanda	2.3 [2.1 – 2.5]	0.9 [0.7 – 1.1]	230,000 [210,000 – 250,000]	140,000 [130,000 – 160,000]

HIV = human immunodeficiency virus

[a]HIV prevalence rates reflect the number of cases per 100 individuals at risk per year.

Data shown as number [estimated range].

Source: aidsinfo.unaids.org, “HIV prevalence” and “Number of people living with HIV” on national level[1].

Demographics of the population in the proposed indication and risk factors for the disease:

Demographics

In 2023, the population of sub-Saharan Africa was estimated to be 1.197 billion[2,3]. The proportion of the population between 15 and 64 years of age is estimated to be 55%, and the region has a high proportion of the population in the less than 15 years of age group, with 42% compared to 25% globally. Accordingly, the population at highest risk for

HIV infection will be further increasing in the future. Fertility rates in sub-Saharan Africa are among the highest in the world, with 4.6 children per woman, compared to the global average of 2.2 children per woman. Accordingly, the number of people living in sub-Saharan Africa is expected to dramatically increase in the future, with a projected population of 2.128 billion people in 2050.

Transmission of HIV and risk factors

Transmission of HIV occurs through contact with bodily fluids such as blood, semen, pre-ejaculate, vaginal fluid, and breast milk from infected individuals. The primary modes of HIV transmission are unprotected vaginal and anal sex, contaminated blood transfusion, contaminated hypodermic needles, and mother-to-child transmission during pregnancy, delivery, or breastfeeding[4,5].

In sub-Saharan Africa, heterosexual vaginal intercourse remains the major mode of HIV transmission, with women bearing the greatest impact of the epidemic. Unprotected vaginal intercourse inherently places women at greater physiological risk of HIV infection than men. This is because the vagina has a large mucosal surface area, which increases exposure to pathogens and infectious fluids. Additionally, women are more likely to experience tissue injury during heterosexual vaginal intercourse than men.

Other biological risk factors that influence the risk of female HIV infection include sexually transmitted infections (STIs), increased levels of oestrogen and/or progesterone (e.g., during pregnancy, or through use of hormone-based contraceptives), and cervical ectopy[6]. Some studies indicate that the risk of HIV infection may be increased during pregnancy, potentially because of hormone-associated physiological changes[7-10].

In addition to female physiology, numerous cultural and socioeconomic factors increase women's vulnerability to HIV infection[6]. The dominant patriarchal culture of sub-Saharan Africa exacerbates female exposure to HIV by limiting women's freedom in sexual decision making. Women are often forced to accept polygamous relationships, sexual subordination, and physical and emotional abuse. In some African cultures, young girls are encouraged, or forced, to marry older men who are more likely to be HIV infected than younger men. Additionally, HIV stigma and discrimination can discourage women from seeking advice on HIV prevention. Other factors that increase the risk of HIV in women living in low-income countries include high rates of transactional sex and/or female sex work, alcohol abuse (which may influence sexual decision-making), and financial dependence on men. Urbanization has also facilitated the spread of HIV in sub-Saharan Africa; this may be due to fewer restrictions on sexual behaviour, or social issues that foster high risk behavior[6].

A large proportion of new HIV infections occur among young women and adolescent girls. As of 2024, adolescent girls and young women in sub-Saharan Africa remain disproportionately affected by HIV. Approximately 77% of all new HIV infections among adolescent girls and young women aged 15-24 years globally occur in sub-Saharan Africa. Despite some progress in reducing new infections over the years, this still translates to roughly 4,000 new infections per week, with about 3,100 of those occurring in this region[91]. The issues faced by young women and adolescent girls – gender-based violence including sexual abuse, lack of access to education and health services, as well as social protection – determine their ability to protect themselves from HIV[2]. A review of more than 45 studies across sub-Saharan Africa revealed that relationships between young women and older male partners, and low rates of condom use were common. In South Africa, in some settings, up to 45% of adolescent girls report that their first sexual experience was forced. Additionally, young women who experienced intimate partner violence were 50% more likely to have acquired HIV than women who had not experienced violence[2].

Current options for prevention of HIV infection:

Currently, there is no effective vaccine to prevent HIV infection. Recommended options by the World Health Organization (WHO) to reduce the risk of heterosexual transmission of HIV include male and female condoms, voluntary medical male circumcision (VMMC), antiretroviral (ARV) treatment as prevention (TasP), oral pre-exposure prophylaxis (PrEP), and to a limited extent in sub-Saharan Africa, the long acting cabotegravir injection [11,12]. Since each of these existing prevention options has limitations, it is recommended to follow a tailored

approach that suits the individual's needs when deciding on the most appropriate option(s) to reduce the risk of HIV infection:

Condoms and safer sex practices

In serodiscordant couples, the relative risk reduction for the HIV-negative partner to become infected was 80% in couples who were consistently using male or female condoms, compared to those who did not[13,14]. Although highly effective, condoms often are not used consistently due to multiple factors, including a perceived decrease in sexual enjoyment, cultural and gender-based norms, the desire to conceive a child, and allergic reactions. The lack of adherence to safer sex practices in sub-Saharan Africa is evident in the high infection rates observed in the placebo arm of several clinical trials, where condoms were provided together with HIV prevention counselling[15-17]. A major limitation of condom use is the requirement for partner participation or consent since, many women in sub-Saharan Africa have limited options to negotiate the use of condoms during sexual encounters[6].

Voluntary medical male circumcision

Male circumcision was found to reduce female to male sexual transmission of HIV by approximately 60% among men in sub-Saharan Africa[18-21]. While VMMC contributes to the reduction of transmission of HIV to women at a population level, it does not directly protect women and depends on the male partners to take preventive action.

Treatment as prevention

In HIV discordant couples, the control of viral load through effective ART of HIV infected individuals has been shown to dramatically reduce the transmission of HIV to their uninfected partners[22]. Limitations of TasP, as a prevention option for uninfected women, include knowledge of the serostatus of male partners and dependence on the male partner to initiate and maintain HIV-suppressive treatment.

Oral pre-exposure prophylaxis

Daily oral PrEP with tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (FTC) has been shown to reduce the risk of HIV type 1 (HIV-1) infection by ≥ 50% in several high-risk populations, including men who have sex with men, heterosexual serodiscordant couples, and injection-drug users, among persons with high adherence to the treatment regimen[23-26]. Two studies with oral PrEP in women in sub-Saharan Africa have not demonstrated risk reduction for HIV-1 infection. However, adherence as measured by plasma levels of study drugs was low in these trials[17,27]. Further limitations of oral PrEP include potential systemic side effects (and required laboratory monitoring) and/or development of resistance to TDF and/or FTC in individuals who seroconvert while receiving PrEP[28,29].

Cabotegravir long acting (CAB LA) injection, although it is not yet widely available in sub-Saharan Africa, CAB LA efficacy and safety have been established in the general population. However, some clinical and implementation issues remain. Women in sub-Saharan Africa are at high risk for HIV acquisition during pregnancy and breastfeeding (up to three times higher risk compared to non-pregnant women), however safety for CAB LA injectable PrEP has not yet been established during pregnancy or breastfeeding. There is also a need to better understand and characterize breakthrough HIV infections amongst CAB LA users and the potential for selection of drug resistance mutations due to residual plasma pharmacological concentrations which may persist for up to a median time of 67 weeks in women after a single injection. Additionally, there are potential implementation challenges, most notably, the need for trained healthcare professionals to administer the product and more frequent visits anticipated than with oral PrEP or the Dapivirine Vaginal Ring-004[30].

Diagnosis of HIV infection and treatment:

Human immunodeficiency virus testing and counselling have been promoted by national campaigns in many countries in sub-Saharan Africa and resulted in increasing numbers of people who have been tested and treated for HIV. In 2022 86% [73-98%] of people living with HIV were aware of their HIV positive status[4].

Currently, there is no cure for HIV infection or acquired immunodeficiency syndrome (AIDS). Although ART is able to suppress viral load and greatly improve patients' lives, complete eradication of HIV is not possible due to the existence of a stable latent proviral reservoir in memory cluster of differentiation (CD4)+ T-cells. Access to ART in sub-Saharan Africa has improved greatly over recent years, with 82% of people living with HIV in the WHO African region receiving ART in 2022[4]. Accordingly, viral replication was not suppressed in more than half of people living with HIV in Africa, mainly due to gaps in knowledge of HIV status and limited accessibility of ART, increasing the risk of death of HIV infected people and further transmission of HIV.

Since HIV infection rates remain very high in sub-Saharan Africa, there is an urgent need for additional options that enable women to reduce their risk of HIV infection.

Natural history of the indicated condition in the population, including mortality and morbidity:

Course of HIV infection and morbidity

Human immunodeficiency virus-infected individuals develop AIDS over time, which is characterised by a progressive failure of the immune system. Symptoms include life-threatening opportunist infections such as tuberculosis and certain types of tumours, which rarely affect individuals with intact immune systems[4].

Initial infection with HIV may be accompanied with influenza-like illness and is followed by a prolonged period with no symptoms called clinical latency. However, the longer the infection progresses, the more it interferes with the immune system, until symptoms of AIDS appear[4,32]. The average time between HIV infection and development of AIDS, without treatment, is usually between 5 and 10 years[33]. Following progression to AIDS, patients typically survive 3 years without treatment, or less in cases of opportunistic infection[32].

While ART does not cure HIV infection, it can slow the progression of the disease and may lead to a near-normal life expectancy. According to currently accepted guidelines, ART is initiated as soon as HIV seroconversion is identified, and all people diagnosed with HIV infection, regardless of WHO clinical stage and CD4+ T-cell counts should receive ART[4,11].

Mortality

Globally, in 2022 there were 630,000 [480,000 – 880,000] AIDS-related deaths; of which 400,000 [300,000 – 570,000] occurred in adults 15-49 years. In Eastern and Southern Africa AIDS-related deaths in adults 15-49 years of age accounted for 160,000 [130,000 – 250,000] of these cases[14].

The number of AIDS-related deaths in relevant sub-Saharan African countries is listed below (Table Part II: Module SI-3). Due to the availability of ART, the number of adults dying of AIDS-related illnesses is declining globally and in sub-Saharan Africa.

Table Part II: Module SI-3: Number of AIDS-related Deaths in Relevant Countries in 2022

Country	Adults (> 15 years of age)
Botswana	3,700 [3,100 – 4,300]
South Africa	42,000 [30,000 – 86,000]
Kenya	16,000 [13,000 – 24,000]
Tanzania	19,000 [16,000 – 23,000]
Zimbabwe	18,000 [14,000 – 21,000]
Malawi	10,000 [8,800 – 13,000]
Uganda	14,000 [11,000 – 20,000]
Zambia	17,000 [14,000 – 20,000]
Rwanda	2,500 [2,100 – 3,100]
AIDS = acquired immunodeficiency syndrome Data shown as number [estimated range]. No recent data for only female adults. Source: aidsinfo.unaids.org, "AIDS-related deaths" on national level[1]	

Important co-morbidities and co-medications:

Sexually transmitted infections (other than HIV)

According to World Bank estimates, STIs, excluding HIV, are the second most common cause of healthy life years lost by women in the 15 to 44 years age group in Africa and account for approximately 17% of the total burden of disease[34].

Sexually transmitted infections increase susceptibility to HIV by causing disruption of the genital epithelium, by increasing the number of HIV target cells and by immune activation in the genital mucosa. As the route of transmission is the same, women who are at risk for STIs (both curable and incurable), including those with repeated STI diagnoses, are at higher risk of acquiring HIV[6].

The four most common curable STIs in 2008 in the WHO African Region were the bacterial STIs *Chlamydia trachomatis, Neisseria gonorrhoeae, Treponema pallidum subspecies pallidum* (syphilis), and *Trichomonas vaginalis*; incidence rates are listed below (Table Part II: Module SI-4). These STIs not only cause acute conditions such as cervicitis, urethritis, and genital ulceration, but also lead to severe complications and long-term sequelae, including pelvic inflammatory disease (PID), ectopic pregnancy, infertility, chronic pelvic pain, and neurological and cardiovascular disease in adults, neonatal death, premature delivery, blindness, or severe disability in infants, and increased risk of HIV acquisition and transmission. Beyond medical issues, STIs also frequently result in stigma, stereotyping, vulnerability, and shame, and have been associated with gender-based violence[35].

Table Part II: Module SI-4: Incidence Rates and Prevalence of Curable Sexually Transmitted Infections in the World Health Organization African Region in 2008

Sexually transmitted infection	Incidence (per 1,000)		Prevalence (%)	
	Females	***Males***	***Females***	***Males***
Chlamydia trachomatis	2.23	2.09	2.6	2.1
Neisseria gonorrhoeae	4.97	6.03	3.5	3.9
Syphilis	0.85	0.94	2.3	2.0

Sexually transmitted infection	**Incidence (per 1,000)**		**Prevalence (%)**	
	Females	***Males***	***Females***	***Males***
Trichomonas vaginalis	14.6	16.48	29.2	2.0
Source: Global incidence and prevalence of selected curable sexually transmitted infections, 2008[36].				

Viral STIs such as herpes simplex virus (HSV) and genital human papillomavirus (HPV) are persistent and incurable.

Herpes simplex virus type 2 (HSV-2) is one of the most prevalent viral STIs globally with rates as high as 78% in African women. There are several reports suggesting that HSV-2 is a biological co-factor for HIV acquisition. It is suggested that HSV-2 infection may contribute to > 50% of new HIV infections among women in sub-Saharan Africa[6]. Although antiviral medications can treat HSV-2 symptoms, current medication regimens do not prevent HIV acquisition. Thus, the only way to reduce the excess risk of HIV infection related to HSV-2 is through primary prevention of HSV-2 infection[37].

Human papillomavirus-infection can become persistent and cause cervical dysplasia, which may progress to cervical cancer. Based on systematic reviews and meta-analyses, the prevalence of HPV among women in South Africa with normal cytology, low-grade cervical lesions, high-grade cervical lesions, or cervical cancer was estimated to be 3.2%, 21.1%, 33.7%, and 64.2%, respectively[38]. Cervical cancer is the most common cause of cancer mortality among African women, and its frequency and progression are increased with HIV infection[34].

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

Repeat dose toxicity

No local or systemic toxicity was observed when dapivirine was administered vaginally as a gel to rats at concentrations of up to 5 mg/mL for 3 months, or to rabbits at concentrations up to 20 mg/mL for 2 weeks, at concentrations up to 5 mg/mL for 3 months, and concentrations up to 2 mg/mL for 9 months (Module 2.4, Section 4).

In studies conducted in rats via the oral route, effects such as increased weight and hypertrophy were observed in the liver, thyroid, and pituitary, but these were considered to be adaptive rather than toxicological changes (Module 2.4, Section 5). The no observable adverse effect level (NOAEL) was considered to be 20 mg/kg/day. The maximum concentration (C_{max}) at the NOAEL was 0.39 µg/mL and the area under the concentration-time curve (AUC_{0-24}) was 4.80 µg·h/mL, which were more than 840 and 570 times, respectively, the corresponding values (0.462 ng/mL and 8.379 ng·h/mL) in women using the Dapivirine Vaginal Ring-004, which is the vaginal ring formulation used in the Phase III trials and is the product that is intended to be marketed.

In dogs, hepatotoxicity and prolongation of the QT interval of the electrocardiogram was evident at ≥ 30 mg/kg/day, and an increase in the incidence and severity of adrenal cortical fatty changes (vacuolation) was observed at ≥ 40 mg/kg/day (Module 2.4, Section 5). The NOAEL in the dog was also 20 mg/kg/day, at which the C_{max} was 1.21 µg/mL and the AUC_{0-24} was 12.98 µg·h/mL, which is more than 2600 and 1500 times, respectively, the corresponding values in women using the Dapivirine Vaginal Ring-004.

Relevance to human usage:

Due to the large safety margins achieved, the oral studies in rats and dogs provide a robust assessment of systemic effects of dapivirine, and none of the findings are considered to represent safety concerns for women using the Dapivirine Vaginal Ring-004. The lack of notable findings following vaginal administration further support the use of dapivirine as a microbicide.

Genotoxicity and carcinogenicity

Dapivirine was shown to be non-genotoxic (Module 2.4, Section 4.4), and no treatment-related neoplastic or non-neoplastic findings were seen in a 2-year intravaginal carcinogenicity study in rats at dapivirine concentrations up to 5 mg/mL (Module 2.4, Section 4.5), resulting in systemic exposures more than 310 and 240 times, respectively, the maximum mean C_{max} and AUC_{0-24} in women using the Dapivirine Vaginal Ring-004.

Antigenicity

Dapivirine showed no evidence of delayed contact sensitization in the guinea pig (Module 2.4, Section 4.8.6).

Developmental and reproductive toxicity

In a rat oral fertility study, increased post-implantation loss, decreased body weight and weight gain pre-mating and during the post-coitum period, and decreased fertility and conception were seen at 80 and 320 mg/kg (Module 2.4, Section 4.6). No effects were seen at 20 mg/kg, at an exposure more than 1000-fold higher than that resulting from maximum human vaginal exposure (based on C_{max} and AUC_{0-24}).

There were no findings in embryofoetal development studies in rats and rabbits following vaginal administration of dapivirine at nominal concentrations up to 3.3 mg/mL dapivirine, at systemic exposures in excess of those in women using the Dapivirine Vaginal Ring-004 (Module 2.4, Section 4.6).

In oral embryofoetal development studies, embryofoetal toxicity, such as increased post-implantation loss, decreased foetal body weight, increased cardiac and skeletal malformations/anomalies, and reduction in skeletal

ossification was seen at maternally toxic doses in rats (≥ 80 mg/kg), but not in rabbits (Module 2.4, Section 4.6). No effects were seen in oral studies in rats at 20 mg/kg, at which systemic exposure was more than 1,000-fold higher than that resulting from maximum human vaginal exposure (based on C_{max} and AUC_{0-24}).

In a rat oral pre- and postnatal development study, effects on offspring body weight were associated with maternal reductions in body weight gain and food consumption (Module 2.4, Section 4.6). No effects were seen at 20 mg/kg, at an exposure more than 1,000-fold higher than that resulting from maximum human vaginal exposure (based on C_{max} and AUC_{0-24}).

Relevance to human usage:

It was concluded that the animal studies did not indicate any direct or indirect harmful effects with respect to reproductive toxicity that are relevant to use of Dapivirine Vaginal Ring-004, due to the absence of findings in intravaginal studies and the large safety margins established in oral studies.

In summary, no relevant safety concerns have been identified from nonclinical studies.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

The non-nucleoside reverse transcriptase inhibitor (NNRTI), dapivirine, is a diaminopyrimidine derivative, inhibiting HIV-1 reverse transcriptase (RT) activity by allosteric binding, thereby preventing viral replication in all HIV-1 strains/subtypes. It was initially developed as an oral formulation by Janssen Sciences Ireland Unlimited Company (UC), and the clinical development program included eleven Phase I/II trials. Following discontinuation of the oral formulation, the International Partnership for Microbicides (IPM) entered into a licensing agreement with Janssen Sciences Ireland UC, which allowed the development of formulations for local administration, including the Dapivirine Vaginal Ring-004, dapivirine vaginal gel, and vaginal film formulations.

The Risk Management Plan (RMP) covers the Dapivirine Vaginal Ring-004 formulation, which is the final ring formulation with optimized delivery properties. The Dapivirine Vaginal Ring-004 has been used in Phase I, II, and III trials, and is the product intended to be marketed. The initial ring formulations (Ring-001, Ring-002, and Ring-003) have only been used in Phase I trials and are not included in this RMP. Throughout this document where text only refers to the Dapivirine Vaginal Ring, this refers to the formulation intended to be marketed, namely the Dapivirine Vaginal Ring-004.

The Dapivirine Vaginal Ring-004 is a platinum-catalysed, cured silicone matrix vaginal ring containing 25 mg dapivirine, which provides sustained release of approximately 4 mg dapivirine over a 1-month period when used continuously. Inhibition of HIV-1 infection of cervical explant models in vitro (HIV-1_{BaL} 99% inhibitory concentration [IC_{99}] 3.3 ng/mL, equivalent to 3.3 ng/g of vaginal fluid) is considered to be a relevant model for the reduction of the risk of HIV-1 infection via the genital route, even when considering the limitations of correlating antiviral activity in vitro and the risk reduction in HIV-1 infection by a vaginal microbicide in vivo. Therefore, dapivirine vaginal fluid concentrations well in excess of 3.3 ng/g were targeted in vivo. (Module 2.5, Section 3).

At the data lock point of 23 January 2025, a total of twelve Phase I/II trials, two pivotal Phase III trials and three Phase IIIb trials with the Dapivirine Vaginal Ring-004 in HIV negative-, healthy, adult women and adolescents were completed and are included in the overall exposure analysis. At the time of the overall exposure analysis, a total of 6,368 women had been exposed to the Dapivirine Vaginal Ring-004, including 5,835 women in completed clinical trials, (IPM 013, IPM 015, IPM 024, IPM 028, IPM 032, IPM 034, IPM 035, IPM 036, MTN-023/IPM 030, MTN-024/IPM 031, MTN-025, MTN-029/IPM 039, MTN-036/IPM047 and MTN-043), which included 2,619 women in the two pivotal Phase III trials (IPM 027 and MTN-020).

Results from Phase I pharmacokinetic trials demonstrated very limited systemic exposure to dapivirine associated with high dapivirine vaginal fluid concentrations (Module 2.5, Section 4). Dapivirine vaginal fluid concentrations well in excess of the in vitro IC_{99} for dapivirine activity against HIV-1 in cervical tissue were achieved within 24 hours of ring insertion, with maximum concentrations reached within 14 days post insertion. Concentrations then declined gradually but remained well above the IC_{99} for the entire 1 month (28-days) of proposed use of Dapivirine Vaginal Ring-004. Results of the two large Phase III trials demonstrated that the Dapivirine Vaginal Ring-004 was safe and well tolerated in HIV-negative, sexually-active women in sub-Saharan Africa (Module 2.5, Section 6), and use of the Dapivirine Vaginal Ring-004 in the IPM 027 trial resulted in an overall risk reduction of HIV-1 infection of approximately 35% (Module 2.5, Section 4).

Tabular summaries of duration of exposure (Table Part II: Module SIII-1), participant's age (Table Part II: Module SIII-2), and ethnicity (Table Part II: Module SIII-3), are provided below.

Table Part II: Module SIII-1: Duration of Exposure

Duration of exposure	Women n (%)	Person-years[a]
< 1 month	136 (2.3%)	7.26
≥ 1 to < 3 months	608 (10.4%)	127.08
≥ 3 to < 6 months	412 (7.1%)	153.15
≥ 6 to < 12 months	1,872 (32.1%)	1,658.64
≥ 12 to < 18 months	1,175 (20.1%)	1,440.33
≥ 18 to < 24 months	926 (15.9%)	1,761.81
≥ 24 to < 30 months	544 (9.3%)	1,179.97
≥ 30 months	141 (2.4%)	354.46
≥ 12 months	2,786 (47.7%)	4,736.56
≥ 24 months	685 (11.7%)	1,534.41
Missing duration	21 (0.4%)	-
Total	**5,835 (100.0%)**	**6,682.7**

n = number of women
[a] Time of product hold in the MTN-020 trial was not included in the calculation of person-years.
Note: This table includes all participants who were exposed to the Dapivirine Vaginal Ring-004 (any duration) in completed trials at the data lock point of 23 January 2025.
Source: Data on file

Table Part II: Module SIII-2: Age Group

Age group	Women n (%)	Person-years[a]
≥15 to <18 years	152 (2.6%)	84.21
≥18 to <45 years	5,523 (94.7%)	6,501.47
≥ 45 years	160 (2.7%)	97.00
Total	**5,835 (100.0%)**	**6,682.7**

n = number of women
[a] Time of product hold in the MTN-020 trial was not included in the calculation of person-years.
Note: This table includes all participants who were exposed to the Dapivirine Vaginal Ring-004 (any duration) in completed trials at the data lock point of 23 January 2025.
Source: Data on file

Table Part II: Module SIII-3: Ethnic Origin

Ethnic origin	Women n (%)	Person-years[a]
Black	5306 (90.93%)	6398.98
Caucasian	286 (4.92%)	54.63
Coloured (mixed race)	11 (0.19%)	10.92
Asian	25 (0.43%)	32.14
Multiple	10 (0.17%)	3.43
Other	185 (3.17%)	180
Unknown	11 (0.19%)	2.60
Total	**5,835 (100.0%)**	**6,682.7**

n = number of women
[a] Time of product hold in the MTN-020 trial was not included in the calculation of person-years.
Note: This table includes all participants who were exposed to the Dapivirine Vaginal Ring-004 (any duration) in completed trials at the data lock point of 23 January 2025.
Source: Data on file

Of note, there were relevant differences in ethnicity over the clinical development program. Clinical pharmacokinetic and safety trials (Phase I) and the Phase II trials in special populations (postmenopausal women, adolescent girls and lactating women) have been conducted in Belgium and the United States (US), enrolling mainly Caucasian women. The Phase I/II trials, IPM 015 and MTN-034 (adolescent girls and young women), as well as the two Phase III trials, IPM 027 and MTN-020, and the open-label extension trials IPM 032 and MTN-025 have been conducted in sub-Saharan African countries, enrolling mainly Black women.

Additionally, the open-label extension Phase IIIb trials (IPM 032 and MTN-025) have enrolled 2,309 HIV-negative participants who had participated in trials IPM 027 and MTN-020 and who elected to use the Dapivirine Vaginal Ring-004 in the Phase IIIb trials, collected additional safety data, and assessed the acceptability of and adherence to the Dapivirine Vaginal Ring-004 use. Additionally, both clinical trials assessed the incidence of HIV-1 seroconversion. An additional Phase IIIb trial, MTN-043, enrolled 148 breastfeeding mothers and their infant pairs.

Two long-term observational cohort studies (IPM 007 and MTN-015) enrolled women who were HIV-1 infected in the trials IPM 027 and IPM 032, or trials MTN-020 and MTN-025, respectively. These trials assessed the potential impact of exposure to dapivirine at the time of HIV-1 infection on disease progression and the participants' response to ART.

In addition to trials with the Dapivirine Vaginal Ring-004, 38 women used the prototype ring formulations (Ring-001, Ring-002, Ring-003) in three clinical trials, and 491 women have been exposed to vaginal gels in eight clinical trials. Moreover, more than 200 participants were exposed to oral dapivirine at doses ranging from 50 to 1,000 mg daily during 11 Phase I/II trials. The maximum tolerated oral dose was established as 300 mg twice daily for multiple doses (14 days) (Module 2.7.4, Section 1.2.1.2).

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Trials within the Development Program

Currently pregnant, last pregnancy within 3 months prior to screening or intends to become pregnant during trial participation

Reason for exclusion:

Standard safety precaution in clinical trials to avoid any potential teratogenic effects of dapivirine.

Is it considered to be included as missing information?

Yes

Currently breastfeeding

Reason for exclusion:

Standard safety precaution in clinical trials to avoid any potential effects of dapivirine on child development.

Is it considered to be included as missing information?

Yes

History of anaphylaxis or severe allergy, or sensitivity/allergy to latex or silicone elastomer

Reason for exclusion:

Standard safety precaution in clinical trials to avoid any potential allergy or sensitivity effects of dapivirine or its components.

Is it considered to be included as missing information?

No

Rationale:

Known sensitivity or allergy is a contraindication for use of the Dapivirine Vaginal Ring-004 to avoid potential hypersensitivity reactions to the active ingredient or any of the excipients.

Diagnosed with urinary tract infection, unless treated and symptoms are resolved prior to enrolment

Reason for exclusion:

To rule out any confounding effects of urinary tract infections (UTIs) on safety variables, ie, genitourinary signs or symptoms.

Is it considered to be included as missing information?

No

Rationale:

Although excluded in clinical trials at enrolment, UTIs occurred during the trials and participants could be adequately managed using available treatment guidelines. During the Phase III trials, UTI was reported in 15.3% (402/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 16.7% (329/1,968) of participants in the placebo ring group (ISS Phase III, Table 14.4.1.3). In the Dapivirine Vaginal Ring-004 group, there were no permanent discontinuations of the investigational product due to UTIs (ISS Phase III, Table 14.4.1.38) and only

one participant required temporary discontinuation of the investigational product due to an UTI (ISS Phase III, Table 14.4.1.37). No permanent or temporary discontinuations of the investigational product due to UTIs occurred in the placebo ring group.

Diagnosed with pelvic inflammatory disease, unless treated and symptoms are resolved prior to enrolment

Reason for exclusion:

To rule out any confounding effects of PID on safety and efficacy variables, ie, any associated genital tract signs or symptoms and to limit any associated increased risk for HIV-1 infection.

Is it considered to be included as missing information?

No

Rationale:

In the Phase III trials, PID was reported in 1.8% (48/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 2.7% (54/1,968) of participants in the placebo ring group (ISS Phase III, Table 14.4.1.3), and these participants could be adequately managed using available treatment guidelines. There were no permanent discontinuations of the investigational product due to PID. Temporary discontinuation of the investigational product was only required in 0.1% (3/2,619) of participants and 0.3% (5/1,968) of participants with PID in the Dapivirine Vaginal Ring-004 and placebo ring groups, respectively (ISS Phase III, Table 14.4.1.36).

Diagnosed with a sexually transmitted infection requiring treatment per current World Health Organization guidelines, unless treated and symptoms are resolved prior to enrolment

Reason for exclusion:

To rule out any confounding effects of STIs on safety and efficacy variables, ie, local adverse reactions or increased risk for HIV-1 infection.

Is it considered to be included as missing information?

No

Rationale:

While STIs requiring treatment were an exclusion criterion at enrolment, STIs occurred frequently during the Phase III trials, and participants could be adequately managed using available treatment guidelines. Chlamydia urogenital events were reported in 27.0% (708/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 24.6% (484/1,968) of participants in the placebo ring group, gonococcal urogenital events in 15.7% (410/2,619) of participants and 13.4% (264/1,968) of participants, and trichomonal urogenital events in 14.5% (380/2,619) of participants and 13.5% (265/1,968) of participants, in the Dapivirine Vaginal Ring-004 and placebo ring groups, respectively (Module 2.7.4, Section 8.1.1.10).

There were no permanent discontinuations of investigational product due to STIs. In the vast majority of these participants, no temporary discontinuation of the investigational product was necessary in the presence of STIs. Temporary discontinuation of investigational product due to STIs occurred in a small proportion of participants (ISS Phase III, Table 14.4.1.36). Temporary discontinuation due to chlamydia infection was reported in 0.3% (7/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 0.3% (6/1,968) of participants in the placebo ring group. Temporary discontinuation due to gonococcal infection was reported in 0.3% (8/2,619) of participants and 0.3% (5/1,968) of participants in the Dapivirine Vaginal Ring-004 and placebo ring groups, respectively. Temporary discontinuation due to trichomonal infection was reported in < 0.1% (1/2,619) of participants and 0.1% (1/1,968) of participants in the Dapivirine Vaginal Ring-004 and placebo ring groups, respectively.

Diagnosed with reproductive tract infection other than sexually transmitted infections requiring treatment per current World Health Organization guidelines, unless treated and symptoms are resolved prior to enrolment

Reason for exclusion:

To rule out any confounding effects of reproductive tract infection on safety and efficacy variables, ie, local adverse reactions or increased risk for HIV-1 infection.

Is it considered to be included as missing information?

No

Rationale:

While an exclusion criterion at enrolment in the Phase III trials, reproductive tract infections other than STIs and requiring treatment occurred frequently, and participants could be adequately managed using available treatment guidelines. Gynaecological infection was reported in 11.5% (300/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 6.4% (125/1,968) of participants in the placebo ring group, bacterial vaginosis (BV) in 10.1% (264/2,619) of participants and 9.8% (192/1,968) of participants, and vulvovaginitis in 8.6% (225/2,619) of participants and 8.9% (176/1,968) of participants, in the Dapivirine Vaginal Ring-004 and placebo ring groups, respectively (Module 2.7.4, Section 8.1.1.10).

There were no permanent discontinuations of investigational product due to these reproductive tract infections. Temporary discontinuation of the investigational product due to reproductive tract infections other than STIs was necessary in ≤ 0.1% of participants. There was < 0.1% (1/2,619) of participants in the Dapivirine Vaginal Ring-004 group with BV, and < 0.1% (1/2,619) of participants and 0.1% (1/1,968) of participants in the Dapivirine Vaginal Ring-004 and placebo ring groups, respectively, with vulvovaginitis who required temporary discontinuation of the investigational product (ISS Phase III, Table 14.4.1.36).

Clinically apparent Grade 2 or higher pelvic examination finding at baseline

Reason for exclusion:

To rule out any confounding effects of an abnormal pelvic examination finding on safety and efficacy variables, i.e., local adverse reactions or increased risk for HIV-1 infection.

Is it considered to be included as missing information?

No

Rationale:

Although abnormal pelvic examination findings were excluded at baseline in the Phase III trials, post enrolment abnormal pelvic examination/speculum findings of any severity were reported in 56.2% (1,435/2,552) of participants in the Dapivirine Vaginal Ring-004 group and 58.4% (1,111/1,901) of participants in the placebo ring group (Module 2.7.4, Section 8.4.3).

Additionally, overall in the Phase III trials, treatment-emergent adverse events (TEAEs) of any severity in the System Organ Class (SOC) Reproductive system and breast disorders were reported in 63.6% (1,665/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 68.3% (1,344/1,968) of participants in the placebo ring group. The majority of these TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Treatment-emergent adverse events that were Grade 3 (severe) or higher in severity were reported in 0.7% (18/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 0.6% (12/1,968) of participants in the placebo ring group (ISS Phase III, Table 14.4.1.7).

In the Phase III trials, no participants had permanent discontinuation of the investigational product due to a TEAE in the SOC Reproductive system and breast disorders that was considered by the Investigator to be related to investigational product use (IPM 027 CSR and MTN-020 CSR).

Additionally, in the Phase III trials, few participants required temporary discontinuation of the investigational product for any event in the SOC Reproductive system and breast disorders. Overall, less than 1% of participants in either group in both Phase III trials (5/1,306 and 11/1,313 participants in the Dapivirine Vaginal Ring-004 group in IPM 027 and MTN-020 respectively; 1/652 and 7/1,316 participants in the placebo ring group in IPM 027 and MTN-020, respectively) required temporary discontinuation of the investigational product due to TEAEs in the SOC Reproductive system and breast disorders. When considering specific reported adverse event terms, the highest proportion of participants in either group of any adverse event term which led to temporary discontinuation of investigational product, was 0.2%. These adverse event terms included: vulvovaginal erythema, cervix erythema, adnexa uteri pain, vaginal erosion, and genital ulceration (ISS Phase III, Table 14.4.1.36).

With the low proportion of participants in whom temporary product discontinuations was deemed necessary despite a high incidence of TEAEs in the SOC Reproductive system and breast disorders, and the fact that these conditions could easily be managed with available treatment guidelines despite continued use the Dapivirine Vaginal Ring-004 in the majority of participants, these data indicate that the Dapivirine Vaginal Ring-004 was well tolerated.

Vaginal candidiasis at baseline

Reason for exclusion:

To rule out any confounding effects of vaginal candidiasis on safety and efficacy variables, i.e., any associated genital tract signs or symptoms and to limit any associated increased risk for HIV-1 infection.

Is it considered to be included as missing information?

No

Rationale:

Vulvovaginal candidiasis (VVC) occurred commonly during the Phase III trials and was reported in 12.3% (321/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 10.6% (209/1,968) of participants in the placebo ring group (Module 2.7.4, Section 8.1.1.10). There were no permanent or temporary discontinuations due to VVC in the Dapivirine Vaginal Ring-004 group, and only 0.1% (1/1,968) of participants required temporary discontinuation of the investigational product due to VVC in the placebo ring group (ISS Phase III, Table 14.4.1.36).

Two drug-drug-interaction trials (IPM 028 CSR and IPM 036 CSR) have shown that concurrent use of vaginally administered miconazole or clotrimazole, medicinal products for treatment of vaginal candidiasis, were well tolerated.

Gynaecologic or genital procedure (e.g., tubal ligation, dilation and curettage, and piercing) 90 days or less prior to enrolment

Reason for exclusion:

To rule out any confounding effects of gynaecological or genital procedures on safety and efficacy variables, i.e., genital signs and symptoms as a result of the procedure and to limit any potential increased risk for HIV-1 infection as a result of a recent procedure.

Is it considered to be included as missing information?

No

Rationale:

When gynaecologic or genital procedures were necessary during the Phase III trials, a potential interruption of the use of the investigational product and subsequent continuation was based on the Investigator's assessment. Generally, a pelvic examination was required to ensure that healing had occurred following the procedure prior to re-inserting the ring. This approach likely reflects the post marketing setting and indicates that women requiring gynaecologic or genital procedures should be able to be adequately managed according to local treatment guidelines and recommendations.

HIV post-exposure prophylaxis within 6 months prior to enrolment

Reason for exclusion:

To ensure women included in the trial are HIV-negative and to avoid confounding effects on efficacy outcomes.

Is it considered to be included as missing information?

No

Rationale:

The Dapivirine Vaginal Ring is contraindicated in women with HIV-1 positive status. Since HIV post-exposure prophylaxis (PEP) is taken following suspected exposure to HIV to reduce the risk of infection, HIV-1 status is unclear until the treatment course is completed, and successful prevention of HIV-1 infection is confirmed by diagnostic testing at least one month post potential exposure. Once HIV-1 negative status is confirmed, women who have used PEP will be eligible for using the Dapivirine Vaginal Ring.

Any significant uncontrolled serious chronic or progressive disease, or alterations in laboratory parameters (aspartate aminotransferase, alanine transaminase Grade 1 (mild) or higher, or creatinine, haemoglobin, platelet count or PAP smear result Grade 2 [moderate] or higher), including blood dyscrasias

Reason for exclusion:

To rule out pre-existing health issues that could confound safety data interpretation in an essentially healthy trial population.

Is it considered to be included as missing information?

No

Rationale:

Dapivirine Vaginal Ring-004 delivers dapivirine locally in the vagina, with very low systemic exposure and with observed dapivirine plasma concentrations not exceeding 2 ng/mL (Module 2.5, Section 4.3). Accordingly, hepatic impairment is not expected to affect dapivirine exposure. Given the low systemic exposures, drug-drug interactions with systemically administered drugs metabolized by the liver are considered unlikely. Similarly, based on low systemic exposure of dapivirine, and the fact that oral dapivirine was shown to undergo negligible renal clearance, renal impairment is not expected to affect dapivirine exposure. Furthermore, no adverse effects attributed to use of dapivirine in terms of any impairment in liver function (e.g., changes in transaminases) and haematological parameters (e.g., haemoglobin levels, white blood cell counts, platelet counts) were observed during clinical trials with vaginally administered dapivirine.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Adverse drug reactions (ADRs) were identified based on the pooled analysis of the large Phase III trials, as well as a Phase I/II trial and included 4867 participants (2,759 Dapivirine Vaginal Ring-004, 2,108 placebo ring).

The safety profile of the Dapivirine Vaginal Ring-004 is based on data from the pooled Phase III trials, including a total of 4,587 participants (2,619 Dapivirine Vaginal Ring-004, 1,968 placebo ring) from sub-Saharan African countries (Malawi, South Africa, Uganda, Zimbabwe). The safety population allowed for the detection of rare adverse reactions; however, the sample size is not sufficient to detect adverse reactions with lower frequency, i.e., very rare adverse reactions.

The IPM 027 trial had a planned duration of 24 months, and the MTN-020 trial had a minimum duration of 12 months. While limited data is available from MTN-020 with exposures of up to 36 months, currently no prolonged exposure data beyond 36 months is available at data cut-off, and there is no information on ADRs with a long latency period.

Nevertheless, data indicating there is no systemic accumulation of dapivirine during continued use of the Dapivirine Vaginal Ring-004 is available. During the Phase III trials, the women participating in these trials visited the research centre every 4 weeks for insertion of a new vaginal ring, and dapivirine plasma concentrations were measured. Results show that dapivirine plasma concentrations were similar at visits throughout the duration of the trial.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table Part II: Module SIV-1:Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. Aggregate pregnancy outcome data from adult women, 18 years and older, enrolled in the Phase I/II trial IPM 015, Phase III trials IPM 027 and MTN-020, and Phase IIIb trials IPM 032 and MTN-025 showed that adverse pregnancy outcomes (spontaneous abortion, stillbirth, or ectopic pregnancy) were generally similar across treatment groups. In total, 240 pregnancies were reported for 233 (233/5303; 4.4%) participants in the Dapivirine Vaginal Ring-004 group and 122 pregnancies were reported for 115 (115/2127; 5.4%) participants in the placebo ring group, (Module 2.7.4, Section 12.4.1). The clinical study report (CSR) of the MTN-042 trial in pregnant women is expected in Q3 2025. This trial will generate important data on the safety of Dapivirine Vaginal Ring-004 use in pregnant women and their infants. IPM has approached the APR Steering Committee and Advisors for inclusion of the Dapivirine Vaginal Ring-004 in the list of marketed drugs currently monitored in the registry, however the decision to participate in the APR will be deferred until the final results of the MTN-042 trial are available. Currently available data, although limited, do not suggest an increased risk of adverse outcomes associated with use of the Dapivirine Vaginal Ring-004 in the periconception period.

Type of special population	Exposure
Breastfeeding women	Not included in the clinical development program. A Phase I clinical trial was conducted in 16 lactating but not breastfeeding women 18 years of age and older (MTN-029/IPM 039 CSR). Participants used the Dapivirine Vaginal Ring-004 for approximately 14 days. Low concentrations of dapivirine (C_{max} < 1.5 ng/mL) in breast milk were identified, which decreased rapidly (approximately 64%) within 48 hours following removal of the ring from the vagina. Infant exposure to dapivirine did not occur in this trial. The estimated potential daily levels of infant exposure to dapivirine were low (approximately 75 ng/kg/day) compared to the maximum tolerated dose after multiple oral doses in adults of 300 mg dapivirine twice daily for 14 days (equivalent to 12 mg/kg/day for a 50 kg female). The estimated daily dapivirine intake by an 8 kg breastfed infant was calculated at approximately 594 ng/day based on the daily consumption of 150 mL/kg/day breast milk and a mean dapivirine intake of 74.32 ng/kg/day. Infant exposure to dapivirine is therefore expected to be below 1 µg/day. The MTN-043 trial in a population of breastfeeding women and their infant pairs was completed in Q4 2023. Pharmacokinetic results confirmed the findings from the MTN-029/IPM 039 trial with dapivirine breast milk concentrations being approximately 80% higher than dapivirine plasma concentrations. Dapivirine plasma concentration in infants was quantifiable in the minority of infants (15%) at any visit, and when quantifiable, concentrations were low. The Dapivirine Vaginal Ring-004 was well tolerated with no product discontinuations due to AEs and no product related AEs were reported in the infants.
Postmenopausal women	A Phase IIa clinical trial was conducted in postmenopausal women 45 to 65 years of age, using the ring for one month (inserted every 4 weeks) over a period of 12 weeks (MTN-024/IPM 031 CSR). A total of 96 women were enrolled, of whom 72 were assigned to the Dapivirine Vaginal Ring-004 group and 24 to the placebo ring group. Compared to the clinical pharmacokinetic trials with mostly premenopausal women (18 to 45 years of age), the mean dapivirine vaginal fluid concentrations in the postmenopausal trial appeared to be somewhat higher, with 64.3, 78.5, and 72.1 µg/g at Weeks 4, 8, and 12, respectively, compared to mean values observed in the clinical pharmacokinetic trials (20 to 36 µg/g) (Module 2.7.2, Section 3.1.1). However, median dapivirine concentrations tended to be lower than the mean concentrations, at 33.7, 45.2 and 40.6 µg/g, at Weeks 4, 8, and 12, respectively. No differences in dapivirine plasma concentrations were observed. The covariate analysis performed in the population pharmacokinetic analysis also did not show a clinically relevant effect of age on dapivirine pharmacokinetics. The population of the trial (MTN-024/IPM 031 CSR) is considered to be representative of the elderly population. The Dapivirine Vaginal Ring-004 was well tolerated in this population with the array and severity of adverse events expected for the enrolled population.
Women with renal impairment	Not included in the clinical development program. Based on low systemic exposure of dapivirine, and the fact that oral dapivirine was shown to undergo negligible renal clearance, renal impairment is not expected to affect dapivirine exposure.
Women with hepatic impairment	Not included in the clinical development program. Based on the low systemic exposure following vaginal administration of dapivirine, hepatic impairment is not expected to have a clinically relevant effect on dapivirine exposure levels.

Type of special population	Exposure
Women with other co-morbidities	Not included in the clinical development program. Due to the low systemic exposure, effects of morbidities on the pharmacokinetics and safety of the Dapivirine Vaginal Ring, or interactions with concomitant medications, are considered unlikely.
Population with relevant different ethnic origin	The Phase I/II trial IPM 015 (IPM 015 CSR) and both Phase III trials (IPM 027 CSR and MTN-020 CSR) were conducted in countries in sub-Saharan Africa where the Dapivirine Vaginal Ring is intended to be marketed. Therefore, the relevant ethnicities are represented in the clinical development program. There were differences in ethnicities across the clinical development program. Predominantly Caucasian women were enrolled in the smaller Phase I/II trials, where sampling was more frequent. In contrast, predominantly Black women were included in the Phase III trials where pharmacokinetic sampling was sparse. Therefore, race was not evaluated as a covariate in the population pharmacokinetic model. However, data suggest that dapivirine concentrations in vaginal fluid and plasma are within the same range in Caucasian and Black women. The overall median dapivirine vaginal fluid concentration prior to ring removal after 28 days of ring use was 13.2 µg/g in one of the Phase III trials (IPM 027), compared to 20 to 36 µg/g in the Phase I clinical pharmacokinetic trials. Median dapivirine plasma concentrations prior to ring removal were 264 pg/mL (IPM 027) and 199 pg/mL (MTN-020) in the Phase III trials, compared to mean values of 218 to 329 pg/mL observed in the Phase I clinical pharmacology trials (Module 2.7.2). The safety profile of the Dapivirine Vaginal Ring-004 was similar between the Phase I trials in a predominantly Caucasian population and the Phase II/III trials in a predominantly Black population.
APR = Antiretroviral Pregnancy Registry; CSR = Clinical Study Report	

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation Exposure

The Dapivirine Vaginal Ring is not currently being marketed for general use in any country. It is being made available in implementation studies.

SV.1.1 Method Used to Calculate Exposure

Enrolment numbers in implementation studies.

SV.1.2 Exposure

Approximately 1,877 women have accepted the Dapivirine Vaginal Ring as their initial preferred PrEP method. No data are currently available on how long these participants have used the Dapivirine Vaginal Ring.

PART II: MODULE SVI ADDITIONAL EUROPEAN UNION REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

There is no potential for misuse for illegal purposes.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial Risk Management Plan Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the Risk Management Plan

Adverse drug reactions

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse drug reactions are listed in Module 1.3.1, Section 4.8, and the majority of the ADRs are not associated with a risk considered important for inclusion in the list of safety concerns in the RMP. The majority of ADRs were Grade 1 (mild) or Grade 2 (moderate) in severity; Grade 3 (severe) ADRs were only reported in 0.2% (5/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 0.2% (3/1,968) of participants in the placebo ring group (Module 2.7.4, Section 14.1). No Grade 4 (life-threatening) or Grade 5 (death) ADRs were reported. Furthermore, the majority of ADRs resolved despite continued investigational product use.

Venous thromboembolic events

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

In the Phase III trials, serious adverse events (SAEs) related to venous thromboembolic events (VTE) were reported for three (3/2,619; 0.11%) participants in the Dapivirine Vaginal Ring-004 group, and for no (0/1,968) participants in the placebo ring group. Additional risk factors were present in all three cases, including high body mass index, use of contraceptives, acute HIV-1 infection, and pulmonary tuberculosis. None of these events was considered to be related to the investigational product by the Investigator (Module 2.7.4, Section 8.1.1.7). No additional events of VTE have been reported since the previous lock point of 30 September 2016 up to the current data lock point of 30 Sep 2021.

In nonclinical oral toxicity studies, shortened partial thromboplastin time was observed in some animal species, but only at high systematic exposures that were associated with changes in the liver. These exposures were far higher than those in women using the Dapivirine Vaginal Ring, and since liver toxicity has not been observed in women using the Dapivirine Vaginal Ring, these findings are not considered relevant for human use of this product (Module 2.4, Section 4.3.4).

The accurate background incidence of VTE in women of reproductive age is difficult to quantify and is affected by many risk factors, including older age, obesity, surgery, trauma, immobilization, pregnancy and postpartum period, oral contraceptives, hormone replacement therapy, inflammatory diseases, infections, HIV infection, heart failure and certain types of cancer, and certain inherited conditions. The calculated incidence rate of VTE in completed trials up to the data lock point, is 4.77 per 10,000 person years. This compares favourably with the incidence rate reported in a meta-analysis performed in 2006 in which the incidence of VTE in women of reproductive age was reported likely to be in the range of 5 to 10 per 10,000 person-years[39].

Based on the low incidence, the low systemic exposure following vaginal administration of dapivirine with the wide safety margins compared with the exposure following oral administration, and the presence of other risk factors, the cases of VTE observed in the Phase III trials are not considered to be indicative of an important identified risk with the use of the Dapivirine Vaginal Ring and is likely a chance finding. Accordingly, reports of VTE will be managed

by routine pharmacovigilance (PV) activities and new case reports received will be summarised in Periodic Benefit Risk Evaluation Reports (PBRERs).

Use in elderly

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Physiologically, the female elderly population is considered similar to postmenopausal women. Postmenopausal women between 45 and 65 years of age were studied in the Phase IIa trial MTN-024/IPM 031 CSR, demonstrating no clinically relevant effect of age on dapivirine pharmacokinetics, and the array and severity of reported TEAEs is considered expected for the enrolled population.

Based on the low systemic exposure following vaginal administration of dapivirine, no interactions with any co-morbidities or co-medications used in the elderly population are expected, and neither are changes in liver and kidney function in the elderly expected to affect safety or efficacy of the Dapivirine Vaginal Ring. Therefore, no new safety concerns are anticipated in this population.

Overdose

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Based on the physico-chemical characteristics and release profile of the Dapivirine Vaginal Ring, the very low systemic exposure levels, as well as the data collected from the use of the Dapivirine Vaginal Ring over periods of up to 84 days, it is considered highly unlikely that the Dapivirine Vaginal Ring has the potential for overdose. While a release of the entire dose of 25 mg contained in one ring can be excluded based on release characteristics of the ring, even an exposure to the entire 25 mg contained in one Dapivirine Vaginal Ring within 1 day or over the period of 1 month would result in systemic exposures much lower than the maximum tolerated oral dose of 300 mg twice daily. The risk of overdose from inserting more than one ring is considered very low. No cases of overdose have been reported during any of the clinical trials.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the Risk Management Plan

Important identified risk: HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use

In the IPM 027 trial, the primary analysis (data lock point of 16 October 2015), following the identification of additional seroconverters as a result of post-hoc testing, showed a reduction in the risk of HIV 1 infection of 35. % (95% CI, 9 to 54; $P = 0.011$) relative to the placebo ring.

In updated analysis to determine the HIV-1 seroconversion rates in the m-ITT population during the entire double-blind period of the IPM 027 trial, a risk reduction of 37% (95% CI, 12 to 55; $P = 0.006$) was observed, (Module 2.7.3, Section 2.1.2.1).

In trial MTN-020, a risk reduction of 26.75% (95% CI, 0.5 to 46.1; $P = 0.046$) was observed (Module 2.7.3, Section 2.2.2.1).

Therefore, some women acquired HIV-1 after being instructed to use the Dapivirine Vaginal Ring-004 in combination with safer sex practices. This may have occurred due to several reasons, including lack of adherence to ring use and lack of adherence to safer sex practices in combination with the Dapivirine Vaginal Ring-004, as well

as non-vaginal exposure to HIV-1. The use of vaginally applied products and other vaginal practices, such as dry sex practices, were discouraged during clinical trials.

Benefit-risk impact:

Lack of adherence to product use and lack of adherence to safer sex practices in combination with the Dapivirine Vaginal Ring-004 (including risk compensation behaviour) directly affect the efficacy of the Dapivirine Vaginal Ring-004.

In the IPM 027 trial non-adherence was defined as a dapivirine ring residual level of > 23.5 mg and/or a plasma concentration < 95 pg/mL, (if both assessments were available; otherwise based on available assessment). Where both assessments were available, the proportion of non-adherent participants ranged between 15.8% (127/805) and 26.2% (304/1,159) at post-baseline trial visits.

In the MTN-020 trial, the proportion of participants with a dapivirine plasma concentration < 95 pg/mL or a dapivirine residual level in used rings > 23.5 mg at post-baseline trial visits (if both assessments were available; otherwise based on the available assessment) ranged between 11.9% (60/503) and 30.5% (110/361), (Module 2.7.3, Section 2.2.2.2.4).

The achieved risk reduction of HIV-1 infection appears dependent on adherence to product use; lower or no risk reduction of HIV-1 infection was observed in the non-adherent subset of participants in both Phase III trials. Adherence and consistent use throughout the entire month are critical to achieve HIV-1 risk reduction, (Module 2.7.3, Sections 2.1.2.3.4.1 and 2.2.2.3.4).

The risk reduction for HIV-1 infection with the Dapivirine Vaginal Ring-004 was approximately 30% in the Phase III clinical trials; therefore, combined use with safer sex practices is key to further decrease the risk of HIV-1 infection. In addition, safer sex practices may limit the potential for the acquisition of STIs and protect from HIV-1 infection in situations where the Dapivirine Vaginal Ring-004 is not effective, including infection via anal sex. Self-reported condom use did not change during the clinical trials despite the provision of condoms and counselling, suggesting a lack of adherence to safer sex practices in general. While risk compensation was not observed in the Phase III trials with the Dapivirine Vaginal Ring-004 and has not been seen in the PrEP Open-Label Extension (OLE) studies, lower adherence to safer sex practices cannot be excluded. Therefore, the Dapivirine Vaginal Ring-004 will be introduced as part of a combination of HIV prevention strategies in the intended markets.

Additionally, since participants had regularly scheduled visits which included periodic screening and treatment for STIs during the Phase III trials, it is unknown what impact untreated STIs may have on efficacy. Routine risk communication and additional risk minimisation measures will include messaging which will focus on the need for safer sex practices to minimize the risk of acquiring an STI, as well as the early recognition of the signs and symptoms associated with an STI and the need to receive treatment as soon as possible.

The effect of other vaginal practices on efficacy and safety of the ring is not known.

Important potential risk: Development of non-nucleoside reverse transcriptase inhibitor resistance in women with unrecognized or acute HIV-1 infection

In the IPM 027 and MTN-020 trials, following the detection of HIV-1 infection, Dapivirine Vaginal Ring-004 use was immediately stopped, and an exit visit arranged approximately 4 to 6 weeks after investigational product discontinuation. In IPM 027, genotypic resistance testing was performed at all visits where HIV-1 ribonucleic acid (RNA) levels were at a level sufficient to allow sequencing of the RT gene. For the MTN-020 trial, results of viral genotyping were available mostly for the visit at which HIV-1 infection was detected, (i.e., the seroconversion visit).

Results of population-based viral genotyping indicated that apart from a higher prevalence of the E138A mutation, HIV-1 isolates of participants who seroconverted in the two Phase III trials (IPM 027 CSR and MTN-020 CSR) indicated a similar proportion of any NNRTI resistance associated mutations in women exposed to the Dapivirine Vaginal Ring and the placebo ring. The imbalance in the prevalence of the E138A mutation at seroconversion in IPM 027 was not statistically significant, (Dapivirine Vaginal Ring-004: 9/84, 10.7%; placebo ring: 2/58, 3.4%; P = 0.20, Fisher's Exact Test, Clinical Virology Report, Version 4.0).

Genotypic predictions of susceptibility indicated a high proportion of viruses fully susceptible to the approved NNRTIs efavirenz (EFV), etravirine (ETV), nevirapine (NVP) and rilpivirine (RPV) (approximately 90%). Additionally, the phenotypic susceptibility results in viruses encoding E138A were supportive of the genotypic susceptibility predictions for EFV, ETV, NPV, and RPV, showing a small incidence of intermediate or high-level resistance for ETV and RPV, but not for EFV and NPV, the more commonly used NNRTIs in sub-Saharan Africa.

When looking at combinations of NNRTI mutations, in the IPM 027 trial only one participant in the Dapivirine Vaginal Ring-004 had virus with two mutations (K101E and E138A), compared to two participants in the placebo ring group who had virus with two or more mutations. These two viruses in the placebo ring group included the mutations Y181C and Y188C, which by themselves are associated with high-level or intermediate level resistance to EFV and NPV, respectively. In the MTN-020 trial, more participants in the Dapivirine Vaginal Ring-004 group had dual mutations (Dapivirine Vaginal Ring-004: 5/68, 7.4%; placebo ring: 1/96, 1.0%); however, in three of these instances in the Dapivirine Vaginal Ring-004 group, at least one of the mutations was a polymorphic variant and other mutations were accessory NNRTI resistance-associated mutations (RAMs). Only one virus (K103S, V106M) was associated with high-level resistance to EFV and NPV (but remained susceptible to ETV and RPV).

Results of next generation sequencing (NGS) showed a high degree of correlation with the population based sequencing performed in the Phase III trials and confirmed that the majority of viruses from participants with HIV-1 seroconversion did not have NNRTI resistance associated mutations identified (wild-type virus: IPM 027: Dapivirine Vaginal Ring-004: 48/57, 84.2%; placebo ring: 34/41, 82.9%; MTN-020: Dapivirine Vaginal Ring-004: 57/63, 90.5%; placebo ring: 81/93, 87.1%) (Clinical Virology Report, Version 4.0).

Eighteen (18/941; 1.9%) participants seroconverted while using the Dapivirine Vaginal Ring-004 during trial IPM 032 (IPM 032 CSR). Seventeen of the 18 participants had a successful population-based sequencing assessment at seroconversion. Wild-type virus was detected in plasma from 12 (12/17; 70.6%) participants; five participants (5/17; 29.4%) were found with single NNRTI RAMs (A98G, K101E, E138A, and two with K103N).

Next Generation Sequencing analysis was performed retrospectively on nine available seroconversion samples, including four of the five participants with virus encoding NNRTI RAMs in the IPM 032 trial. The analysis confirmed the population-based genotyping findings and indicated highly homogeneous infections, consistent with recent infection. The only additional finding was of G190E present in 1.7% of consensus sequences in the virus with A98G.

Phenotypic susceptibility testing for IPM 032 was limited due to sample availability, however, was successfully performed in five instances. Results, which included viruses with A98G or K103KN, did not show any reduction in susceptibility to dapivirine (geometric mean FC: 0.64, range 0.23 – 1.08). For other NNRTIs, only the virus encoding K103N showed a significant increase in FC to efavirenz and nevirapine (FC: 8.93 and 41.1, respectively) but not to the NNRTIs with similar structures to dapivirine (FC etravirine: 0.62; rilpivirine: 0.43), (IPM 032 CSR Addendum).

In the MTN-025 trial, thirty-three (33/1365; 2.4%) participants seroconverted after receiving at least one Dapivirine Vaginal Ring-004 (MTN-025 CSR). Virus from 27 of the participants (27/33; 81.8%) did not have any NNRTI

RAMs and the pattern of mutations in the other six showed a diverse set of mutations: one each with A98G alone, E138A with V179D, V106M with V179D and three with K103N alone (Clinical Virology Report, Version 4.0).

One of two participants who did not use the Dapivirine Vaginal Ring-004 and seroconverted had virus encoding NNRTI RAM, K103N (Clinical Virology Report, Version 4.0).

Next generation sequencing was performed retrospectively on samples from all 33 participants at seroconversion. Of 32 valid results, there was only one participant with a virus encoding a minority species NNRTI RAM not detected using population-based genotyping (Y188H in 3% of NGS sequences). Overall, the NGS analysis did not indicate any significant accumulation of NNRTI RAMs or any significant presence of minority-species NNRTI RAMs in the Virology Population.

Phenotypic susceptibility analysis was performed successfully on seroconversion samples from all 33 participants. None of the 27 viruses without any known NNRTI mutations showed any significant increase of IC50 to dapivirine (FC: geometric mean: 0.65, range: 0.37 – 1.29) or to other NNRTIs (geometric mean FC: efavirenz: 0.86; etravirine: 0.85; nevirapine: 1.06; rilpivirine: 0.65). Viruses with NNRTI RAMs at seroconversion showed either full susceptibility or only modest FC for dapivirine (FC range 0.74 – 2.78), etravirine or rilpivirine (geometric mean FCs: 0.66, 0.62 respectively). High-level resistance to efavirenz and nevirapine was observed according to genotypic predictions, (MTN-025 CSR Addendum).

Benefit-risk impact:

In trial IPM 027, the only difference between NNRTI RAMs at seroconversion was in a higher proportion of E138A variants in the Dapivirine Vaginal Ring-004 group, which was not statistically significant. This difference was not found in trial MTN-020. The E138A variant is a common polymorphism in subtype C HIV-1, the subtype represented most commonly among the seroconversions; and the incidence was similar to that observed in epidemiologic studies of treatment-naïve HIV-1 infected patients.

The mechanism by which the proportional imbalance in the E138A mutation in IPM 027, and of viruses with dual NNRTI mutations in MTN-020, occurred is not clear. These imbalances could have occurred due to the transmission of virus already encoded with these mutations, due to selective pressure by dapivirine following HIV infection, or they could have occurred by chance. Additionally given the small numbers, the prevalence of polymorphic variants among the identified NNRTI resistance-associated mutations, and considering that the mutations identified in the Dapivirine Vaginal Ring-004 group were all identified in the placebo ring group in the Phase III trials, as well as the background prevalence of these mutations in the community, it seems unlikely that these mutations arose due to dapivirine selective pressure, although no definitive conclusions can be drawn.

The most prevalent NNRTI resistance associated mutation identified across both trials was E138A, a known polymorphic substitution, which has been observed in up to 8% of viruses from ARV-naïve patients infected with HIV-1 subtype C[40,41]. E138A is known to be weakly selected by ETV and RPV, two close analogues of dapivirine[42]. All of the E138A substitutions observed in the IPM 027 trial occurred in participants with HIV-1 subtype C virus (IPM 027 CSR). Furthermore, when considering the results of tests at the earliest time point of detection of the E138A substitution and the subsequent evolution of observed NNRTI mutations at the additional testing time points in the IPM 027 trial (tests also at visits prior to seroconversion where HIV-1 RNA was positive and at the exit visit approximately 6 weeks after the seroconversion visit) it is noted that in virus whereE138A was detected prior to the seroconversion visit, there was no selection of additional resistance-associated mutations at subsequent visits despite continued Dapivirine Vaginal Ring-004 use up to the seroconversion visit in these participants with established infection.

Importantly, the E138A substitution is not associated with reduced susceptibility to NVP and EFV[42], which are the more widely used NNRTIs in sub-Saharan Africa. Across both Phase III trials, genotypic predictions of susceptibility indicated a high proportion of viruses fully susceptible to approved NNRTIs and phenotypic susceptibility results in viruses encoding E138A were supportive of the genotypic susceptibility predictions.

Next-generation sequence analysis in both Phase III trials demonstrated a very high level of correlation with the results from the population-based genotypic analysis, supporting the population-based genotypic analysis finding that approximately 90% of viruses at the seroconversion visit did not encode NNRTI resistance associated mutations.

However, since participants in the Phase III trials were closely followed, it is not known what the likelihood of the emergence of resistance would be in women who are using the vaginal ring in a real world setting and who may have undetected HIV-1 infection over a longer period.

The virology analyses from the two OLE trials (IPM 032 and MTN-025) in which clinical follow up (visits scheduled 3 monthly) more closely mirrors the visit schedule anticipated when the product is marketed, extended the findings in the Phase III trials. The results were consistent with and supported Phase III indications that RAMs detected at seroconversion were likely reflective of locally circulating viral variants and did not require explanation through post-infection development of resistance pathways, (IPM 032 CSR, MTN-025 CSR).

Further characterization of viruses from the Phase IIIb extension studies, IPM 032 and MTN-025 used NGS and phenotypic analyses. Limited analyses were possible in IPM 032, however across the studies a high level of correlation between the NGS findings and the results from the population-based genotypic analysis was observed.

Additionally phenotypic analyses showed that all tested viruses without any known NNRTI RAMs did not show any change in susceptibility to dapivirine, reducing the possibility of novel pathways for resistance. Furthermore, there was limited resistance to dapivirine even in the presence of NNRTI RAMs. Phenotypic results from tests with other NNRTIs supported the conclusion that the use of dapivirine had limited effects on cross-resistance prevalence. Indeed, findings of resistance were more common with efavirenz and nevirapine, absent for etravirine and rilpivrine, and was driven by the presence of K103N or V106M, both of which contributed markedly to the high transmission rate of NNRTI resistance when and where the trials were performed.

Furthermore, the follow-up seroconverter studies (IPM 007 and MTN-015), which included assessment of the virologic outcomes after initial antiretroviral therapy during infection, did not show any decline in proportions of virologic suppression in participants with previous DVR exposure compared with placebo. Furthermore, in instances of virological failure, the resistance pathways were as expected after failure of an efavirenz or nevirapine containing ARV regimen, (IPM 007 CSR Addendum; MTN-015 Summary Report Addendum).

The balance of evidence indicates a low risk of the Dapivirine Vaginal Ring-004 selecting new RAMs impacting future treatment options in participants experiencing HIV-1 seroconversion during Dapivirine Vaginal Ring-004 use, particularly since integrase strand-transfer inhibitors are now the first choice for initial ARV therapy.

In summary, currently available data point to a low potential for de novo selection of resistance by dapivirine. This is supported in particular by the limited pattern of genotypic variants and no clear pattern identified of a favoured resistance pathway(s). This taken together with epidemiologic reports of the prevalence of the E138A substitution in ARV-naïve persons and the increased prevalence of NNRTI resistance-associated mutations since the introduction of ART in sub-Saharan Africa suggests that these mutations were likely encoded in virus that was transmitted. Additionally, as the prevalence of NNRTI RAMs in sub-Saharan Africa increased above the WHO limit (10%), a shift to the use of an integrase strand-transfer inhibitor as first line treatment for HIV was mandated. This reduces the possibility of Dapivirine Vaginal Ring-004 use influencing this new treatment strategy.

Important potential risk: Development of pelvic inflammatory disease

Pelvic inflammatory disease can result in significant morbidity, and although it can be managed on an outpatient basis, more severe cases may require hospitalization for optimal treatment. The main complications of PID include the development of tubo-ovarian abscess, chronic pelvic pain, infertility, or ectopic pregnancy.

The incidence of PID in the Phase III trials was low overall, with PID being reported in 1.8% (48/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 2.7% (54/1,968) of participants in the placebo ring group (Module 2.7.4, Section 8.1.1.10.3).

The low incidence of PID observed in the Phase III trials, despite the high incidence of STIs reported in these trials (Module 2.7.4, Table 40), is likely due to effective management of STIs and genital tract infections as a result of either presumptive treatment or specific treatment in response to a confirmed etiological STI diagnosis, as screening for STIs was done regularly during the Phase III trials. Consequently, it is not known whether there could be an increased level of risk (beyond the risk associated with a preceding STI) for the development of PID in Dapivirine Vaginal Ring users with untreated STIs or women with asymptomatic STIs who are not regularly screened and treated. However, data from the open-label extension trial IPM 032 in which participant follow up and STI management more closely mirrors real life experience, indicates a low overall incidence of PID of 0.6% (6/941) despite a high STI incidence of 17.3% (163/941) at screening and 16.4% (154/941) at the last product use visit. All TEAEs of pelvic inflammatory disease were Grade 2 (moderate) in severity and were considered resolved during the IPM 032 trial, (Module 2.7.4, Section 9.1.5.1).

Benefit-risk impact:

There is no clear evidence from clinical trials evaluating the Dapivirine Vaginal Ring of an increased risk of PID associated with its use, and in those participants who developed PID, no participant required permanent discontinuation of the Dapivirine Vaginal Ring-004. The majority of participants could successfully complete treatment for PID despite continued Dapivirine Vaginal Ring-004 use.

However, because effective treatment and screening was performed regularly in the Phase III trials, it is unknown whether women using the Dapivirine Vaginal Ring-004 might be predisposed to a higher risk of developing PID if they acquire an STI and/or genital infection which is undetected for a considerable period of time.

Missing information: Safety during pregnancy

This is considered missing information because existing or planned pregnancy has been an exclusion criterion in clinical trials with Dapivirine Vaginal Ring-004. Women were required to use a reliable method of contraception and those who became pregnant during clinical trials had the investigational product discontinued at the time pregnancy was first diagnosed.

Benefit-risk impact:

Given the intended target population for use of the Dapivirine Vaginal Ring-004, exposure during pregnancy is expected to occur in the post marketing setting. Therefore, this is considered important missing information. A clinical trial to assess the safety of the Dapivirine Vaginal Ring-004 and oral TDF/FTC tablet use in pregnant women, including follow-up of infants up to 1 year of age, is ongoing (MTN-042). Final results from this trial are expected in Q3 2025.

Missing information: Safety during breastfeeding

Breastfeeding has been an exclusion criterion in clinical trials with Dapivirine Vaginal Ring-004.

Benefit-risk impact:

Given the intended target population for use of the Dapivirine Vaginal Ring-004, exposure during breastfeeding is expected to occur in the post marketing setting. Therefore, the use in breastfeeding women is considered important missing information. A clinical trial in lactating, but not breastfeeding women (MTN-029/IPM 039 CSR) has been completed. Low concentrations of dapivirine (C_{max} < 1.5 ng/mL) in breast milk was identified, which decreased rapidly (approximately 64%) within 48 hours following removal of the ring from the vagina. Infant exposure to dapivirine did not occur in this trial.

The estimated potential daily levels of infant exposure to dapivirine were low (approximately 75 ng/kg/day) compared to the maximum tolerated dose after multiple oral doses in adults of 300 mg dapivirine twice daily for 14 days (equivalent to 12 mg/kg/day for a 50 kg female). The estimated daily dapivirine intake by an 8 kg breastfed infant was calculated at approximately 594 ng/day based on the daily consumption of 150 mL/kg/day breast milk and a mean dapivirine intake of 74.32 ng/kg/day. Infant exposure to dapivirine is therefore expected to be below 1 µg/day.

A clinical trial in 148 breastfeeding women-infant pairs assessing safety and exposure to dapivirine in both mothers and infants was completed, (MTN-043). As expected, dapivirine breast milk concentrations were higher than plasma concentrations by approximately 80%. The results of maternal pharmacokinetic parameters evaluated were similar to those of the general adult female population observed in earlier trials of the Dapivirine Vaginal Ring-004. Infant exposure to dapivirine was low with quantifiable dapivirine plasma concentrations observed in only a minority (15%) of infant participants, and when quantifiable, infant plasma concentrations were very low and likely of no clinical significance. Dapivirine Vaginal Ring-004 was well tolerated with no product related SAEs in mothers and no product related AEs in infants. No adverse events led to permanent Dapivirine Vaginal Ring-004 discontinuation.

Based on the results of the MTN-029/IPM 039 and MTN-043 trials and considering that the post-partum period is a high-risk period for acquisition of HIV, the Dapivirine Vaginal Ring-004 can be used in breastfeeding women, and it was therefore agreed to remove from the list of safety concerns, missing information: safety during breastfeeding, see Section SVII.2.

Missing information: Long-term use beyond 24 months of treatment

The two Phase III trials had a planned duration of 24 months (IPM 027 CSR) and a minimum duration of 12 months (MTN-020 CSR), respectively. In MTN-020, an endpoint-driven trial, the maximum duration of exposure was 36 months in a subset of participants.

Benefit-risk impact:

In the post marketing setting, women may use the Dapivirine Vaginal Ring as long as they are sexually-active and at risk of HIV-1 infection. Therefore, the Dapivirine Vaginal Ring is a medicinal product intended for long-term use, and the collection of long-term data beyond 24 months of use is considered important to detect any TEAEs related to long-term exposure. Additional data was collected in two Phase IIIb open-label extension trials (IPM 032 and MTN-025) in HIV-negative women who had participated in the Phase III trials. A subset of women (n = 105) from trial IPM 027, who were still using the Dapivirine Vaginal Ring-004 and then directly rolled over into trial IPM 032, where they continued to receive the Dapivirine Vaginal Ring-004, had continuous exposure to dapivirine for a period longer than 24 months, with 94/105 (89.5%) of the participants having ≥ 36 months of continuous use. Overall exposure in this cohort of 105 participants amounted to 336.97 person years. Analysis of data from this cohort did not reveal any new safety concerns. The study product was well tolerated in this cohort with no permanent or temporary discontinuation of the Dapivirine Vaginal Ring-004 due to AEs. When considering ADR terms identified for the Dapivirine Vaginal Ring-004, by preferred term, rates were generally similar in the cohort

who immediately rolled over and those participants with deferred enrolment in IPM 032. No product related TEAEs were reported in participants who immediately enrolled in IPM 032 from IPM 027. There were no reported events of pelvic inflammatory disease in this cohort despite a slightly higher rate of STIs. However, given the lower number of participants in this cohort (n = 105) compared to the overall enrolled population (n = 941), these data should be interpreted with caution (Module 2.7.4, Section 9.1.1.1).

Missing information: Use in sexually-active females under 18 years of age

The Dapivirine Vaginal Ring could potentially be prescribed to adolescent females and girls younger than 18 years of age, an age group at high risk of HIV infection. However, from previously completed clinical trials, only limited data in females younger than 18 years of age are available.

Benefit-risk impact:

Since women below 18 years of age are at high risk for HIV infection, with only limited clinical data, the safety, efficacy and adherence to Dapivirine Vaginal Ring use in this age group is considered important missing information. Data on use of the Dapivirine Vaginal Ring is limited to a relatively small number of younger sexually-active females under 18 years of age, hence the benefit-risk profile is not considered well characterised in this population.

A clinical trial with the Dapivirine Vaginal Ring in adolescent females between 15 and 17 years of age in the US (MTN-023/IPM 030 CSR) has been completed. Seventy-three participants were enrolled in the Dapivirine Vaginal Ring-004 group and 23 participants in the placebo vaginal ring group. Dapivirine vaginal and plasma concentrations observed in this population were similar to those observed in women of reproductive age 18 years of age and older. The proportion of participants with any reported adverse event was similar between groups with the majority of adverse events reported as Grade 1 (mild) and Grade 2 (moderate) in severity. Furthermore, adverse events reported within the SOC Reproductive system and breast disorders were mostly transient and were mainly mild or moderate in severity. No adverse events warranted premature discontinuation of vaginal ring use in the opinion of the Investigator. Overall, the results pointed to the Dapivirine Vaginal Ring-004 being well tolerated with a similar safety profile observed in this population as has been observed in trials of women of reproductive age 18 years of age and older.

An additional clinical trial evaluating the safety of and adherence to the Dapivirine Vaginal Ring (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 was completed (MTN-034 (REACH). A total of 239 participants (79 adolescent girls less than 18 years of age and 160 young adult women 18 to 21 years of age) were enrolled. The Dapivirine Vaginal Ring-004 was well tolerated, with no product related SAEs or AEs leading to permanent Dapivirine Vaginal Ring-004 discontinuation. The majority of AEs were of mild (Grade 1) or moderate (Grade 2) severity. Results from this trial allowed further characterisation of the safety of the Dapivirine Vaginal Ring in this younger population.

Based on the results of the MTN-023/IPM 030 and MTN-034 trials and considering that adolescent girls and young women are a particular high-risk population for acquisition of HIV, use of the Dapivirine Vaginal Ring-004 in women 16 years and older should be considered. It is therefore proposed to expand the indication to HIV-uninfected women 16 years and older.

Missing information: Local drug-drug interaction with vaginally administered clindamycin and metronidazole

Two drug-drug interaction trials have been conducted with concurrent use of the Dapivirine Vaginal Ring-004 and vaginally administered miconazole or clotrimazole (IPM 028 CSR and IPM 036 CSR, respectively). There are no data available regarding drug-drug interactions with vaginally administered clindamycin and metronidazole.

Benefit-risk impact:

Vaginally administered metronidazole and clindamycin are not generally included as a treatment option for genital and/or STIs in clinical management guidelines published by the respective health ministries or health departments in the target countries in sub-Saharan Africa in which a marketing authorisation will be sought. The only exception is a recommendation in the Zimbabwe STI management guideline in which vaginally administered metronidazole gel is recommended as an alternative choice to oral metronidazole in pregnant women[43- 49]. Since systemically administered antimicrobials are the preferred first line treatment option in non-pregnant women in all of the target countries and considering the low potential of vaginally administered dapivirine to cause systemic drug-drug interactions, the impact of this missing information on the benefit-risk profile is considered low.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated Risk Management Plan

Safety during breastfeeding previously classified as missing information was removed from the list of safety concerns.

Reference is made to Procedure No. EMEA/H/W/002168/II/0025/G: Type II, Category C.I.4 variation which serves to provide the clinical study report (CSR) for the MTN-043 (B-PROTECTED) study, and therefore resolves an MEA PAM associated with the additional risk minimisation activity described in the Risk Management Plan (RMP) for dapivirine vaginal ring 25mg, where safety in breastfeeding women was considered to be missing information. Based on the results from MTN-043 and previous safety evidence on safety in breastfeeding women, it was proposed to remove the missing information on safety in breastfeeding women from the list of safety concerns. The Variation was approved on 11 July 2024. In addition, the following statement is now included in Section 4.6 of the SmPC:

Breastfeeding

Dapivirine has been shown to be excreted in human milk. Clinical studies have shown that dapivirine concentrations in breast milk were approximately 1.8-fold higher than in maternal plasma. In one clinical study that enrolled 148 breastfeeding mothers and their infant pairs, absolute infant exposure to dapivirine was low with the majority (85%) of infants not having a quantifiable dapivirine plasma concentration at any study visit. No product-related adverse reactions were noted in infants of mothers who used the Dapivirine Vaginal Ring.

The Dapivirine Vaginal Ring can be used during breastfeeding.

Long-term use beyond 24 months of treatment classified as missing information was removed from the list of safety concerns

Reference is made to Procedure No. EMEA/H/W/002168/II/0027: Type II, Category C.I.6.a. As there are no additional PhV activities and risk minimisation measures needed, the missing information “Long-term use beyond 24 months of treatment” was removed from the RMP.

Benefit-risk impact:

The Dapivirine Vaginal Ring is a medicinal product intended for long-term use, and long-term data beyond 24 months was collected in the two Phase IIIb open-label extension trials (IPM 032 and MTN-025) in HIV-negative women who had participated in the Phase III trials. The Dapivirine Vaginal Ring was well tolerated and with a favorable safety profile. No permanent or temporary discontinuation of the Dapivirine Vaginal Ring was reported due to AEs (Module 2.7.4, Section 9.1.1.1). The results support the long-term use beyond 24 months of treatment.

Use in sexually-active females under 18 years of age previously classified as missing information was removed from the list of safety concerns.

Reference is made to Procedure No. EMEA/H/W/002168/II/0027: Type II, Category C.I.6.a. providing the clinical study report of the MTN-034 (REACH) trial. Two clinical trials, MTN-023/IPM 030 and MTN-034 trials, evaluating use of the Dapivirine Vaginal Ring-004 in adolescents and young women populations, have been completed.

MTN-023/IPM 030 was conducted in the US in adolescent females between 15 and 17 years of age. Seventy-three participants were enrolled in the Dapivirine Vaginal Ring-004 group and 23 participants in the placebo vaginal ring group. Dapivirine vaginal fluid and plasma concentrations of dapivirine observed in this population were similar to those observed in adult women of reproductive age. The proportion of participants with any reported adverse event was similar between groups with the majority of adverse events reported as Grade 1 (mild) and Grade 2 (moderate) in severity. No adverse events warranted premature discontinuation of vaginal ring use in the opinion of the Investigator. Overall, the results indicate that the Dapivirine Vaginal Ring-004 was well tolerated with a similar safety profile observed in this population as has been observed in trials of adult women of reproductive age.

In the MTN-034 trial, a total of 239 participants (79 adolescent girls less than 18 years of age and 160 young adult women 18 to 21 years of age) were enrolled .

The Dapivirine Vaginal Ring-004 was well tolerated, with no product related SAEs or AEs leading to permanent Dapivirine Vaginal Ring-004 discontinuation. The majority of AEs were of mild (Grade 1) or moderate (Grade 2) severity.

The safety profile of Dapivirine Vaginal Ring-004 in adolescent girls and young women in MTN-034 (REACH) trial was similar to overall observations during placebo-controlled Phase III studies and other phase I, II and III clinical trials of Dapivirine Vaginal Ring-004 in the general population as well as the MTN-023/IPM 030 trial in adolescent girls in the USA. Similarly, for Truvada®, the safety profile was similar to its safety profile in placebo-controlled studies of Truvada®. Both Dapivirine Vaginal Ring-004 and Truvada® were well-tolerated, displayed a favorable safety profile and were found to be highly acceptable among adolescent girls and young women.

Benefit-risk impact:

Adolescent girls and young women in sub-Saharan Africa continue to remain disproportionately affected by HIV[91]. Given the already established favourable safety profile in adults and similar findings in adolescent girls, as well as the results of pharmacokinetic parameters previously evaluated in adolescent girls 15 – 17 years of age (MTN-023/IPM 030) being comparable to adult women, the Dapivirine Vaginal Ring-004 should be considered for an indication of use in HIV-uninfected women 16 years and older. Consequently, the use of the Dapivirine Vaginal Ring in sexually-active females under 18 years of age is removed as missing information.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important identified risk: HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use

Lack of adherence to product use

Potential mechanisms:

The Dapivirine Vaginal Ring-004 provides sustained release of dapivirine when used continuously during the month of use, resulting in dapivirine vaginal fluid concentrations well in excess of those required for inhibition of HIV-1 replication in vitro. However, dapivirine concentrations in vaginal fluid decline rapidly following removal of the ring. Considering the rapid decline in vaginal fluid concentrations upon ring removal, the ring should be used continuously and immediately replaced each month with a new ring.

The primary site of action of dapivirine is most likely within CD4+ T-cells in the tissues of the lower female reproductive tract. Since measurement of dapivirine concentrations in vaginal tissues is difficult due to uncertainty of where within the tissue measured drug concentrations are actually located, vaginal fluid concentrations were used as a surrogate (Module 2.5, Section 2.3.3).

The Dapivirine Vaginal Ring-004 delivers concentrations > 1000-fold higher than the in vitro IC_{99} for inhibition of HIV-1_{BAL} infection of mucosal tissue in human cervical explant cultures (IC_{99} = 3.3 ng/mL [10 nM]) within hours after ring insertion. Dapivirine levels exceed the IC_{99} > 3,000-fold within 24 hours after ring insertion, with peak levels in vaginal fluid occurring within 14 days of ring insertion and a slow decline afterwards, with concentrations after 28 days of continuous use still being > 3,000-fold in excess of the IC_{99}. Upon removal of the ring, vaginal fluid concentrations declined rapidly with a half-life of approximately 20 hours (Module 2.5, Section 3.2 and Section 4.1).

Evidence source(s) and strength of evidence:

Self-reported adherence rates to product use of women participating in the clinical trials have been proven to be unreliable. Therefore, more objective methods to assess adherence to Dapivirine Vaginal Ring use have been investigated, by measuring dapivirine concentrations in plasma at monthly (28 days) visits or determination of dapivirine residual levels in used rings after one month (4 weeks). As there is no absolute definition of adherence, analyses have been performed with different cut-off values for dapivirine concentrations in plasma and residual dapivirine levels in used rings, defining different extents of adherence.

Two pre-defined objective measures of adherence to ring use were used to define adherent/non-adherent populations in adherence-based analyses in the Phase III program. These measures help to identify non-adherence which were defined as > 23.5 mg of dapivirine residual levels in used rings and/or a plasma concentration of < 95 pg/mL.

Of note, limitations remain with both of these methods, as they may demonstrate drug release from the ring and into the plasma but do not allow for determination of whether the Dapivirine Vaginal Ring was inside the vagina at the time of exposure to HIV. Specifically, even though a woman may have been considered largely adherent to product use, reflected in the aforementioned adherence measures, removal of the ring for a short time just before an exposure to HIV-1 may have resulted in infection.

In addition to analysis at the point of seroconversion, HIV-1 RNA analysis has been used to more closely determine the time of HIV exposure and identify the corresponding used ring and plasma sample.

Characterization of the risk:

In the IPM 027 trial, in the modified intent-to-treat (m-ITT) population, the updated primary analysis (data lock point of 16 October 2015) demonstrated a reduction in the risk of HIV 1 infection of 35.07% (95% CI, 9.05 to 53.64; *P* = 0.0114) was observed relative to the placebo ring.

Updated analysis to determine the HIV-1 seroconversion rates in the m-ITT population during the entire double-blind period of the IPM 027 trial indicated a risk reduction of 36.81% (95% CI, 11.95 to 54.65; *P* = 0.0067).

In trial MTN-020, a risk reduction of 26.75% (95% CI, 0.49 to 46.08; *P* = 0.046) was observed.

Based on the time to first HIV-1 RNA detection, a risk reduction of 35.0% (95% CI, 8.97 to 53.59; *P* = 0.0122) was observed in IPM 027 as of the data lock point of 16 October 2015, and 36.43% (95% CI 11.43 to 54.38; *P* = 0.0074) for the complete double-blind period. In the MTN-020 trial a risk reduction of 26.73% (95% CI, 0.47 to 46.07; *P* = 0.0466) was observed, based on time to first HIV-1 RNA detection.

These data taken together indicate that some women acquired HIV-1 infection despite being instructed to use the Dapivirine Vaginal Ring-004 in combination with safer sex practices.

The risk of HIV-1 infection is considered related in part due to lack of adherence, e.g., when women do not use the ring consistently over the entire period of one month. Not using the ring even for a short period of time, e.g., removal before intercourse, or delaying the insertion of a new ring after the removal of the used ring after 1 month of use, may increase the risk for HIV-1 infection following exposure.

In the IPM 027 trial, for the complete double-blind period, the proportion of non-adherent participants (dapivirine ring residual level of > 23.5 mg or a plasma concentration < 95 pg/mL) ranged between 15.0% (147/982) and 26.6% (309/1,162) at post-baseline trial visits. Post hoc time-varying product-adherence analysis on the m-ITT population comparing dapivirine ring adherent periods to the placebo ring, demonstrated a statistically significant reduction in the risk of HIV-1 infection of 39.27% (95% CI, 12.42 to 57.88; *P = 0.0076*) for the complete double-blind period.

In the MTN-020 trial, the proportion of participants with a dapivirine plasma concentration < 95 pg/mL or a dapivirine residual level in used rings > 23.5 mg at post-baseline trial visits (if both assessments were available; otherwise based on the available assessment) ranged between 13.6% (108/797) and 30.3% (109/360).

In the MTN-020 trial post-hoc time-varying adherence analysis based on the full m-ITT population was performed with the cut-off value of ≤ 23.5 mg for the dapivirine residual level in used rings and the cut-off value of ≥ 95 pg/mL for the dapivirine plasma concentration. In this analysis, since dapivirine residual level data was not available from the start of the trial both dapivirine residual levels in used rings and plasma concentrations were used to determine adherence to ring use in the period after 07 August 2013, and adherence was determined based only on the dapivirine plasma concentrations in the period before 07 August 2013. In the Dapivirine Vaginal Ring-004 group, a statistically significantly reduction in the risk of HIV-1 infection of 43% (95% CI, 17.9 to 59.8; *P* = 0.002) relative to the placebo ring group was shown during the periods when the participants were considered adherent, (Module 2.7.3, Section 2.2.2.3.4.1).

In both Phase III trials, the increase in the percentage of the risk reduction demonstrated by time-varying adherence analysis, suggest that HIV-1 infection risk reduction is higher when participants are adherent to ring use.

Given the limitations of the methods for determining adherence at time of exposure and that the subgroup considered as “adherent” based on the above-mentioned criteria represents various degrees of adherence to ring use, the true extent of non-adherence is not known. Accordingly, the maximum level of HIV-1 infection risk reduction via vaginal exposure with consistent ring use cannot be determined based on the available data.

Risk factors and risk groups:

Two factors which showed a trend towards higher non-adherence as defined by above-mentioned criteria were identified, the participant's age and self-reported partner awareness of ring use.

For IPM 027, for the complete double-blind treatment period, the risk reduction for the subgroup women 21 years or younger showed a trend towards lower efficacy compared to women older than 21 years, although not statistically significant: 40% (95% CI, 10 to 60) in women older than 21 years of age and 20% (95% CI, -46 to 57) in women 18 to 21 years of age (P-value for interaction effect = 0.45), (Module 2.5, Section 5.1.2.1.1).

Overall, the proportion of non-adherent participants (with a dapivirine plasma concentration < 95 pg/mL or a dapivirine residual level in returned used rings > 23.5 mg) at any post-baseline trial visit ranged between 15.0% (147/982) and 26.6% (309/1162) in trial IPM 027 and 11.9% (60/503) and 30.5% (110/361) in trial MTN-020, (Module 2.5, Section 5.1.3.1).

Most participants self-reported that the ring was acceptable and not difficult to insert. At baseline in both trials, approximately 65% to 70% of participants reported not being worried about using the ring. This number increased to > 96% at the end of the product use period, indicating that time and use of the Dapivirine Vaginal Ring-004 increased acceptance over time. This was therefore unlikely to be a key driver for non-adherence.

Additionally results of multivariable analysis in IPM 027 showed that being married ($P = 0.016$) and having no genital symptoms/STIs at baseline ($P = 0.013$) resulted in lower HIV-1 seroconversion rates, (Module 2.7.3, Section 2.1.2.1.2).

There was thus some evidence of reduced adherence among participants in the younger age group (based on dapivirine residual levels in returned used rings and dapivirine plasma concentrations) and may explain the reduced efficacy in the younger age group as there is no biological rationale to explain this finding.

Adherence to the Dapivirine Vaginal Ring-004 use in the real-life setting may be better than observed during clinical trials, as suggested by studies with oral PrEP. Adherence to oral PrEP (TDF/FTC) was higher in open-label trials after a demonstration of safety and efficacy than had been seen in the initial blinded, placebo-controlled trials[50]. Knowledge of the real value of PrEP motivated individuals who recognized their elevated HIV-1 risk and likely contributed to higher adherence. Consistent with these findings in trials of oral PrEP, preliminary results from the IPM 032 and MTN-025 trials indicate improved adherence of the Dapivirine Vaginal Ring-004 when used by African women in an open-label setting.

Preventability:

Routine risk communication and additional risk minimisation strategies will be employed to promote adherence to product use in women using the Dapivirine Vaginal Ring and include male partner engagement where appropriate.

Impact on the benefit-risk balance of the product:

Improved adherence to product use is expected to result in increased efficacy of the Dapivirine Vaginal Ring-004, translating into higher risk reduction of HIV-1 infection.

Lack of efficacy information will be collected by routine PV activities, and followed-up with a specific questionnaire to determine the reasons for lack of efficacy. The information on the impact of lack of adherence to product use on the benefit-risk balance and the reasons for non-adherence will be used to design further risk minimisation measures, if necessary.

Public health impact:

The Dapivirine Vaginal Ring is expected to have a significant public health benefit by reducing the number of new HIV-1 infections and will thereby impact the HIV-1 epidemic. However, women who become infected with HIV-1 due to lack of adherence to product use will contribute to the HIV epidemic and may pass the virus to their sexual partner(s), to their children during pregnancy, childbirth and breastfeeding, and other people through other routes. Minimisation of the risk of HIV-1 acquisition during vaginal sexual intercourse, including infection resulting from non-adherence to ring use, which directly affects efficacy, is key to achieve optimal public health impact.

Lack of adherence to safer sex practices in combination with the Dapivirine Vaginal Ring (including risk compensation behaviour)

Potential mechanisms:

The potential maximum risk reduction for HIV-1 infection with the Dapivirine Vaginal Ring is not known, but is unlikely to be 100%, therefore, the Dapivirine Vaginal Ring is indicated to be used in combination with safer sex practices which provide an independent means of reduction of risk for HIV-1 infection. Since these methods have different mechanisms of action, the greatest risk reduction is expected to be achieved when the Dapivirine Vaginal Ring is used in combination with safer sex practices. Moreover, safer sex practices can also reduce the risk of HIV-1 infection via other routes, such as anal sex. Additionally, it will reduce the incidence of STIs (an independent risk factor for HIV infection). The impact of untreated STIs on the efficacy of the Dapivirine Vaginal Ring is unknown, since participants had regularly scheduled visits which included periodic screening and treatment for STIs during the Phase III trials.

Evidence source(s) and strength of evidence:

Self-reported data on condom use is available from the Phase III trials, indicating that safer sex practices were inconsistently followed.

Risk compensation is difficult to assess in a randomized, double-blind, placebo-controlled clinical trial setting, where treatment assignment and the effect size, if any, are unknown and participants regularly receive safer sex counselling. The potential for risk compensation behaviour as a consequence of using the Dapivirine Vaginal Ring may only become apparent in the post marketing setting. Although some data on risk compensation behaviour is available from post marketing studies with oral PrEP and VMMC[51,53,56], risk compensation is not expected in women in sub-Saharan Africa who generally have limited control over the risk of acquiring HIV infection[54,55].

Characterisation of the risk:

Lack of adherence to safer sex practices occurs when women engage in risky sexual behaviour, for example vaginal intercourse without using condoms, resulting in an increased risk of HIV-1 infection.

In the IPM 027 trial, 28.6% (373/1,306) of participants in the Dapivirine Vaginal Ring-004 group, and 30.4% (198/652) of participants in the placebo ring group reported having always used a condom for vaginal sex. The percentage of women reporting that they never used a condom for vaginal sex was 21.2% (277/1,306) of participants in the Dapivirine Vaginal Ring-004 group and 23.0% (150/652) of participants in the placebo ring group, and the remainder had used a condom sometimes or often, (Module 2.7.3, Section 2.1.4.1). In the MTN-020 trial, at baseline male or female condoms or both were used by 59.1% (775/1,312) of the participants in the Dapivirine Vaginal Ring-004 group and 55.7% (733/1,316) of the participants in the placebo ring group (Module 2.7.3, Section 2.2.3.1).

Post-hoc analysis of the impact on efficacy of an STI in the interval before HIV-1 RNA was first detected indicated that a higher proportion of participants with a positive STI result had a detectable HIV-1 RNA result across both

Phase III trials, but that the proportion of participants in the Dapivirine Vaginal Ring-004 group remained lower than that of the placebo ring group. Participants reported using condoms inconsistently and the rates of self-reported condom use did not change throughout the trial, even with specific safer sex counselling and dispensing of condoms.

While it is not known whether risk compensation may occur with the Dapivirine Vaginal Ring in the post marketing setting, data from studies with oral PrEP and VMMC have not shown any evidence of an increase in risk-taking sexual behaviors[51,53]. A review of PrEP generally found limited concern generally regarding risk compensation, and in some cases, it was even shown that use of PrEP may encourage sexual mindfulness and lead to safer behavior[56].

Risk factors and risk groups:

Lack of adherence to safer sex practices, as evidenced by inconsistent use of condoms, was observed throughout the entire study population in the Phase III trials.

Epidemiological studies provide evidence that in general, use of PrEP in sub-Saharan African women does not result in risk-compensating behaviors[51-53]. However, some studies indicate there may be specific sub-populations such as young women and/or sex workers or men who have sex with men[57], who express willingness to engage in more risky behaviour when using PrEP, e.g., by increasing their number of sexual partners, or being less adherent to the use of condoms[56].

Preventability:

Routine risk communication and additional risk minimisation strategies will be employed to promote adherence to safer sex practices in women using the Dapivirine Vaginal Ring and include awareness of the partner(s) involved, where appropriate. These measures will include messaging which will focus on the need for safer sex practices to minimise the risk of acquiring an STI as well as the early recognition of the signs and symptoms associated with an STI or HIV-1 infection, and the need to receive treatment as soon as possible.

Impact on the benefit-risk balance of the product:

Improving the understanding of safer sex practices and the need to use them in addition to the Dapivirine Vaginal Ring will contribute to reducing the risk of HIV-1 infection.

Lack of efficacy information will be collected by routine PV and followed-up with a specific questionnaire to determine the reasons for lack of efficacy. The information on the impact of lack of adherence to product use on the benefit-risk balance and the reasons for non-adherence will be used to design further risk minimisation measures, if necessary.

Public health impact:

The Dapivirine Vaginal Ring is expected to have a significant public health benefit by reducing the number of new HIV-1 infections and will thereby have a positive impact on the HIV-1 epidemic. Minimisation of the risk "lack of adherence to safer sex practices in combination with the Dapivirine Vaginal Ring (including risk compensation behaviour)" is key to achieve optimal public health impact.

As evidenced by the high incidence of new HIV infections, adherence to safer sex practices, which requires partner participation/consent, is a great challenge in the sub-Saharan African population. Therefore, additional female-initiated HIV prevention tools are urgently needed.

Vaginal practices

Potential mechanisms:

Vaginal practices may result in changes in the dapivirine concentrations in vaginal fluid, or cause injuries such as vaginal irritation, inflammation or abrasion, which may affect tolerability, safety and efficacy of the Dapivirine Vaginal Ring. Furthermore, these practices could promote removal of the ring or accidental expulsion of the ring, and therefore affect adherence to the product.

As some vaginal cleansing or drying methods are associated with the disruption of vaginal flora, or inflammatory reactions and epithelial damage that can result in genital lesions, dry sex practices may be a potential risk factor for the acquisition of STIs and HIV. While some studies have demonstrated that certain dry sex practices can increase the risk of HIV acquisition, a causal relationship between dry sex practices, as a collective term, and HIV acquisition has not been established[58,59].

Evidence source(s) and strength of evidence:

Vaginal practices were discouraged during the Phase III clinical trials.

Epidemiological data describing the prevalence of vaginal practices in the overall population is available. However, challenges remain in terms of evaluating a causal association between such practices and HIV acquisition due to inconsistency in the definition of various vaginal practices and the need for greater specificity in terms, when evaluating such practices[59].

Characterisation of the risk:

The practice of “dry sex” refers to the drying and tightening of the vagina for sexual intercourse, and the main reason given for the practice of dry sex is to increase sexual pleasure. Methods of drying are numerous and may include vaginal douching (with water, soaps, or antiseptics), drying with cloths, insertion of objects/substances into the vagina (e.g., powders, stones, and leaves), and drinking substances that are believed to have a drying effect[58].

Epidemiological data indicate that several vaginal practices are common in sub-Saharan Africa. In a meta-analysis, the percentage of women reporting any current dry sex practice at baseline ranged from 18% to 95%, depending on country and studied population[59]. In South Africa, the prevalence of dry sex practices was relatively low, ranging between 18% and 27% depending on the region. However, such practices have also been reported for other countries where the Dapivirine Vaginal Ring is intended to be marketed including Kenya, Uganda, Tanzania, Malawi, and Zimbabwe[59].

Risk factors and risk groups:

There are regional differences in the prevalence of dry sex practices, e.g., low prevalence in South Africa but high prevalence in Zimbabwe. In addition, such practices are more common in specific subgroups of women, such as female sex workers[59].

Preventability:

Routine risk communication and additional risk minimisation strategies will be employed to discourage the use of vaginal practices in women using the Dapivirine Vaginal Ring.

Impact on the benefit-risk balance of the product:

The impact of vaginal practices on the benefit-risk balance is not known.

Public health impact:

The impact of vaginal practices on public health is not known.

Important potential risk: Development of NNRTI resistance in women with unrecognized or acute HIV-1 infection

Potential mechanisms:

In the presence of an NNRTI, active replication of the virus present in women with unrecognized or acute HIV-1 infection, could potentially give rise to the selection of mutations associated with NNRTI drug resistance.

Evidence source(s) and strength of evidence:

The virology population in trial IPM 027 includes 82 (79/1,307; 6.3%) participants confirmed to have been HIV infected in the m-ITT population who were randomized to the Dapivirine Vaginal Ring-004 group during the complete double-blind period, as well as five participants who seroconverted during the open-label period, (87/1,307; 6.7%). Also included are 61 participants randomized to the placebo ring group, (61/652; 9.4%). The virology population in the MTN-020 trial includes (71/1,313, 5.4%) participants in the Dapivirine Vaginal Ring-004 group and (97/1,316; 7.4%) participants in the placebo ring group.

The main HIV-1 subtype represented in the IPM 027 virology population was subtype C, (Dapivirine Vaginal Ring-004: 77/84, 88.5%; placebo ring 54/61, 88.5%). Other subtypes represented included subtype A1 (Dapivirine Vaginal Ring-004: 2/87, 2.3%; placebo ring: 2/61, 3.3%) and subtype D (Dapivirine Vaginal Ring-004: 3/87, 3.4%; placebo ring: 1/61, 1.6%).

Similar to trial IPM 027, most of the viruses in the MTN-020 trial were classified as subtype C (Dapivirine Vaginal Ring-004: 64/71, 90.1%; placebo ring: 90/97, 92.8%). Other subtypes identified included small proportions of subtypes A1 (Dapivirine Vaginal Ring-004: 3/71, 4.2%; placebo ring: 2/97, 2.1%), subtype B (placebo ring: 1/97, 1.0%), subtype A1/D recombinant (Dapivirine Vaginal Ring-004: 1/71, 1.4%; placebo ring: 2/97, 2.1%). and subtype D (Dapivirine Vaginal Ring-004: 1/71, 1.4%; placebo ring: 1/97, 1.0%). The subtype distribution observed in both trials is consistent with that observed in the geographic regions where the trial was conducted.

In trial IPM 027 population-based genotyping was successfully performed on virus extracted from plasma of participants at seroconversion in all but three participants, (Dapivirine Vaginal Ring-004: 84/87, 96.6%; placebo ring: 58/61, 95.1%).

In the MTN-020 trial, population-based genotypes were successfully obtained for 164/168 (97.6%) HIV-1 seroconversions, (Dapivirine Vaginal Ring-004: 68/71, 95.8%; placebo ring: 96/97, 99.0%).

In the open-label extension trial IPM 032 there were 26 participants who seroconverted; 18 (18/941; 1.9%) of these seroconversions occurred while using the DVR-004, three participants were retrospectively found to be HIV-1 infected at enrolment while three others stopped ring use while HIV-1 RNA negative but became infected later.

In trial MTN-025, 33 participants seroconverted after using at least one Dapivirine Vaginal Ring-004, (Clinical Virology Report, Version 4.0).

NNRTI mutational patterns

In trial IPM 027 there were similar proportions of participants with any mutations, identified at HIV-1 seroconversion, between ring user groups, (Dapivirine Vaginal Ring-004: 13/84, 15.5.0%; placebo ring: 8/58, 13.8%). All NNRTI resistance associated mutations observed in the Dapivirine Vaginal Ring-004 group were also observed in the placebo ring group. Additionally, a wide distribution of NNRTI mutations in the placebo ring group was noted, which included the non-polymorphic mutations E138Q, Y181C and Y188C not found in the Dapivirine Vaginal Ring-004 group. Importantly, Y181C is the NNRTI RAM most frequently selected by dapivirine in vitro, therefore the absence of any viruses with Y181C in the Dapivirine Vaginal Ring-004 group is reassuring.

With the exception of the E138A substitution which was observed with a higher frequency in the Dapivirine Vaginal Ring-004 group, a similar mutational frequency was observed for any individual NNRTI mutation between groups. Although an imbalance was noted, the difference in prevalence of E138A between groups did not reach statistical significance (Dapivirine Vaginal Ring-004: 9/84, 10.7%; placebo ring: 2/58, 3.4%; *P* = 0.20, Fisher's Exact Test).

In the MTN-020 trial, there were also similar proportions of participants with any NNRTI RAMs between groups, (Dapivirine Vaginal Ring-004: 8/68, 11.8%; placebo ring: 9/96, 9.4%). Apart from the E138A mutation, all other NNRTI mutations were observed at most on two occasions in each group. As in trial IPM 027, the most frequently observed mutation was E138A, which is associated with low-level resistance to RPV and "potential low-level resistance" to ETV (Stanford HIVdb, Version 8.4). However, in contrast to findings in trial IPM 027, there was no difference in prevalence between treatment groups (Dapivirine Vaginal Ring-004: 3/68, 4.4%; placebo ring: 5/96, 5.2%).

When considering combinations of NNRTI mutations at HV-1 seroconversion, in the IPM 027 trial only one virus in the Dapivirine Vaginal Ring-004 group was encoded with two NNRTI mutations, namely K101E and E138A. There were two viruses with multiple NNRTI RAMs in the placebo ring group and included the mutations associated with high level or intermediate resistance to EFV and NVP, Y181C (n = 1) and Y188C (n = 1).

In the MTN-020 trial, more participants in the Dapivirine Vaginal Ring-004 group had dual mutations (Dapivirine Vaginal Ring-004: 5/68, 7.4%; placebo ring: 1/96, 1.0%); however, in three of these instances in the Dapivirine Vaginal Ring-004 group, at least one of the mutations was a polymorphic variant and other mutations were accessory NNRTI RAMs.

Differences were thus noted in the mutational patterns in the Phase III trials, since in IPM 027 where there was no imbalance in the proportion of participants with more than one mutation present. Conversely there was an imbalance in the prevalence of variant E138A with more in the Dapivirine Vaginal Ring-004 group in trial IPM 027, which was not the case in the MTN-020 trial.

Next generation sequencing (NGS) analyses were performed to identify NNRTI RAMs which could potentially not have been detected by population-based sequencing. Available samples from both Phase III trials of HIV-1 seroconversions in the Dapivirine Vaginal Ring-004 and placebo ring groups at or within 14 days of seroconversion, were submitted for analysis. This analysis was however limited by availability of samples, Valid analyses were available for seroconversion samples from 101 (101/148; 68.2%) participants (Dapivirine Vaginal Ring-004: 57/87, 65.5%; placebo ring: 44/61, 72.1%). Missing test results in this retrospective analysis were due either to unavailability of a stored sample or the absence of participant consent for the additional analysis.

In the IPM 027 trial, NGS analyses indicated that virus populations displayed a high degree of homogeneity, with variants generally detected at 100% prevalence in any one sample. Consistent with population based genotyping results most of the participants did not have NNRTI RAMs detected using NGS analysis and the proportions of participants with any NNRTI RAM were similar to those obtained with population-based sequencing (Dapivirine Vaginal Ring-004: 9/57, 15.8%; placebo ring 7/41, 17.1%).

Additionally, NGS analyses indicated that the individual mutations and mutational patterns detected were the same as those detected using population-based sequencing apart from two viruses (one from each ring user group) that encoded minority mutations at codon 190. In the Dapivirine Vaginal Ring-004 group, G190A was detected at seroconversion at a prevalence of 5% in virus from one participant, whereas in the placebo ring group G190A and G190E were each detected at 2% prevalence in virus isolated from one participant.

In the MTN-020 trial valid analyses were available for seroconversion samples from 156 (156/168; 92.9%) of seroconversions (Dapivirine Vaginal Ring-004: 63/71, 88.7%; placebo ring: 93/97, 95.9.0%). Similar to findings in

the IPM 027 trial, results of NGS analyses were consistent with population-based sequencing and confirmed that most of the participants did not have any NNRTI RAMs detected (wild-type virus: Dapivirine Vaginal Ring-004: 57/63, 90.5%; placebo ring: 81/93, 87.1%). There were similar proportions of participants with NNRTI mutations in the ring user groups, (Dapivirine Vaginal Ring-004: 6/63, 9.5%; placebo ring: 12/93, 12.9%).

There were more viruses with two mutations in the Dapivirine Vaginal Ring-004 group (Dapivirine Vaginal Ring-004: 4/63, 6.3%; placebo ring: 1/93, 1.1%). However, more viruses in the placebo ring group had one mutation: (Dapivirine Vaginal Ring-004: 2/63, 3.2%; placebo ring: 11/89, 12.4%).

Minor differences in mutation counts were detected by NGS in the MTN-020 trial. In the Dapivirine Vaginal Ring-004 group, a minority species harbouring E138K prevalent at 1% was identified that was not detected using population-based genotyping. In the placebo ring group, minority species detected included the following mutations not detected using population-based genotyping: K103T (1% prevalence); K103E (3% prevalence); E138A (9% prevalence); Y181C (1% prevalence); and G190E (2% prevalence), (Clinical Virology Report, Version 4.0).

In trial IPM 032, seventeen of the 18 participants, who became HIV-1 infected while using the DVR-004, had a successful population sequencing assessment. Virus from five participants (5/17; 29.4%) were found with single NNRTI RAMs (A98G, E138A, K101E and two with K103N). Limited Next Generation Sequencing analysis was performed retrospectively on nine available seroconversion samples, including four of the five with virus encoding NNRTI RAMs. The analysis confirmed the population-based genotyping findings and indicated highly homogeneous infections consistent with recent infection. The only additional finding was of G190E present in 1.7% of consensus sequences in the virus with A98G. Phenotypic susceptibility testing, successful in five instances including viruses with A98G or K103KN, did not show any reduction in susceptibility to dapivirine (geometric mean FC: 0.64, range 0.23 – 1.08), (IPM 032 CSR Addendum).

In trial MTN-025 virus from 27 of the participants with seroconversion after receiving investigational product (27/33; 81.8%) did not have any NNRTI RAMs and the pattern of mutations in the other six showed a diverse set of mutations: one each with A98G alone, E138A with V179D, V106M with V179D and three with K103N alone. Next generation sequencing yielded valid results for 32 participants. Only one participant with a virus encoding a minority species NNRTI RAM not detected using population-based genotyping (Y188H in 3% of NGS sequences) was identified. Overall, the NGS analysis did not indicate any significant accumulation of NNRTI RAMs or any significant presence of minority-species NNRTI RAMs. Phenotypic susceptibility analysis was performed successfully on seroconversion samples from all 33 participants. None of the 27 viruses without any known NNRTI mutations showed any significant increase of IC50 to dapivirine (FC: geometric mean: 0.65, range: 0.37 – 1.29) or to other NNRTIs (geometric mean FC: efavirenz: 0.86; etravirine: 0.85; nevirapine: 1.06; rilpivirine: 0.65). Viruses with NNRTI RAMs at seroconversion showed either full susceptibility or only modest FC for dapivirine (FC range 0.74 – 2.78), (MTN-025 Summary Report Addendum).

Currently available data indicate a low potential for de novo selection of resistance by dapivirine. This is supported in particular by the limited pattern of genotypic variants and no clear pattern identified of a favoured resistance pathway(s).

Genotypic susceptibility

Genotypic susceptibility scores were obtained from the amino acid sequences for reverse transcriptase (RT) using the Stanford HIV-1db, Version 8.4. In trial IPM 027, genotypic predictions indicated similar between group full susceptibility to the approved NNRTIs, with full susceptibility predicted in 86.0% (ETV and RPV) and 94.7% (EFV and NVP) of HIV-1 seroconversions in the Dapivirine Vaginal Ring-004 groups.

The proportions of virus with various levels of NNRTI susceptibility were generally similar across the two ring user groups, particularly in relation to susceptibility to the key NNRTI drugs available in sub-Saharan Africa (EFV and NVP). As expected, the presence of E138A contributed to increased predictions of potential low-level resistance to ETV and low-level resistance to RPV in the Dapivirine Vaginal Ring-004 group.

Similar to trial IPM 027, the genotypes with NNRTI RAMs in MTN-020 indicated that full susceptibility to the approved NNRTIs EFV, ETV, NVP, and RPV was predicted in the majority of HIV-1 seroconversions for both ring user groups. Intermediate or high-level resistance to NNRTIs was predicted to be uncommon but numbers were too small at these resistance levels to differentiate between the Dapivirine Vaginal Ring-004 and placebo ring groups. High-level resistance was found to both EFV and NVP in three (3/68; 4.4%) participants in the Dapivirine Vaginal Ring-004 group compared with one (1/96; 1.0%) participant in the placebo ring group. This was due mainly to the presence of K103N or K103S + V106M, (Clinical Virology Report, Version 4.0).

Longitudinal genotypic analysis over time

Population based genotypic analysis over time of paired viral analyses (52 from Dapivirine Vaginal Ring-004 group; 26 from placebo ring group) performed at the first visit when HIV-1 RNA was detected and the seroconversion timepoint indicated that no new NNRTI RAMs developed. These visits were separated on average by 34.7 and 30.6 days in the dapivirine and placebo ring groups respectively. As the HIV-1 RNA status of the participants was only determined retrospectively, ring use was ongoing during this period.

Paired viral analyses (63 from Dapivirine Vaginal Ring-004 group; 41 from placebo ring group) from the time of seroconversion to the exit visit identified two viruses with mutations that were first detected at the exit visit. These mutations were observed as mixtures, G190G/A in one participant and K103K/N with V106V/M in another. These mutations were detected 42 and 63 days, respectively, after the seroconversion visit when ring use was stopped. Next generation sequencing analysis performed at the seroconversion visit detected a minority G190A species (5% prevalence) at the seroconversion visit.

When considering participants who were randomized to receive investigational product when already HIV infected at enrolment (but no evidence of seroconversion), a total of seven participants were found retrospectively to have HIV-1 RNA present in plasma on starting investigational product treatment (Dapivirine Vaginal Ring-004: n = 5, placebo ring: n = 2). The virus in participants randomized to Dapivirine Vaginal Ring-004 was therefore exposed to what was essentially a sub-optimal regimen consisting of dapivirine monotherapy, although delivered via the vaginal ring and with very low systemic exposure.

At HIV-1 seroconversion, population-based genotyping was available for six participants, five of whom had HIV-1 RNA ≥ 2,000 copies/mL. Five of the six viruses from the participants with HIV-1 RNA detected at enrolment did not have any NNRTI RAMs. The one observed mutation at enrolment, E138A, was in a Dapivirine Vaginal Ring-004 user. This mutation was also observed at the first visit after starting investigational product and at the exit visit for this participant, (Clinical Virology Report, Version 4.0).

Phenotypic analysis of dapivirine susceptibility and cross resistance to approved NNRTIs

In trial IPM 027, participants from the virology population with virus that encoded NNRTI RAMs had successful analysis of dapivirine susceptibility in 18 instances (Dapivirine Vaginal Ring-004: 11/13; placebo ring: 7/8).

Among the viruses encoding any NNRTI RAM (included A98G, K103N, E138A alone or E138A with K101E), individual fold change (FC) values to dapivirine showed either no difference or only modest elevation above control levels in most instances in the Dapivirine Vaginal Ring-004 group as indicated by the geometric mean half maximal

inhibition concentration (IC_{50}) increase (FC – [standard deviation – SD]: Dapivirine Vaginal Ring-004 n = 11: 3.06 [1.55]).

For viruses encoding E138A alone, minor FC increases to dapivirine were noted (E138A: geometric mean Dapivirine Vaginal Ring-004 n = 8: 2.92 FC; placebo ring n = 1: 0.94 FC). For the one virus with the dual mutation, the possibility that the inclusion of K101E with E138A resulted in a small additional effect on FC cannot be excluded (K101E, E138A: 5.10 FC); however, the clinical importance of this is unclear.

Phenotyping results of NNRTI mutations in the placebo ring group demonstrate the possibility of high-level resistance to dapivirine arising from transmission of virus encoded with the genotypic patterns of V106M with Y188C, and V108I, Y181C with H221Y. These two viruses gave outlier FC values which elevated the geometric mean FC in the placebo ring group, (V106M and Y188C: 24.83 FC; V108I, Y181C and H221Y: 120.21 FC).

The geometric mean value for participants with one mutation showed similar FC relative to wild-type viruses in both groups (geometric mean dapivirine FC: Dapivirine Vaginal Ring-004 n = 10: 2.91 FC; placebo ring n = 5: 2.39 FC).

In the MTN-020 trial virus from all submitted samples (Dapivirine Vaginal Ring-004: n = 8; placebo ring: n = 9) had successful phenotypic dapivirine susceptibility analysis. Similar to trial IPM 027, among the viruses encoding any NNRTI RAM, the average FC showed no resistance or limited susceptibility reduction in most instances as indicated by the geometric mean IC_{50} FC (FC [SD]: Dapivirine Vaginal Ring-004: 3.29, 3.84; placebo ring: 1.74, 2.42).

Four viruses in the Dapivirine Vaginal Ring-004 group and one virus in the placebo ring group were associated with > 5 FC. Three of these viruses had variants at RT codon 103, (K103N, n = 2; K103S, n = 1) associated with resistance to EFV and NVP but not RPV and ETV. The FC for the two K103N mutants in the Dapivirine Vaginal Ring-004 group (5.7 and 19.3 FC) were both greater than that observed for the K103N encoding virus tested from the placebo ring group (1.72 FC). The reason for the higher FC for the two K103N encoding viruses in the Dapivirine Vaginal Ring-004 group is unclear.

Viruses with K101E occurred in both ring-user groups, either with E138G (Dapivirine Vaginal Ring-004) or E138A (placebo ring) and both viruses showed modest FC (5.45 and 5.10 FC, respectively).

Susceptibility to the approved NNRTIs EFV, ETV, NVP, and RPV, was also assessed in available viruses from participants in trial IPM 027, where the profile included the most prevalent mutation observed, E138A. Other viruses were not analysed for susceptibility as phenotypic correlation for NNRTI RAMs have been well established for the approved drugs in this class. In the tests with viruses encoding E138A, no- to modest FC was observed for the NNRTIs efavirenz, etravirine, nevirapine and rilpivirine (FC range: 0.6 to 2.9). Only slightly higher FC values were observed with the mutation combination of E138A and K101E (FC EFV: 3.78; ETV: 2.98; NVP: 5.30; RPV: 2.40).

In the MTN-020 trial all eight viruses with E138A present (Dapivirine Vaginal Ring-004: n = 3; placebo ring: n = 5) underwent testing against EFV, ETV, NVP, and RPV. There was little difference in the FC for NNRTI susceptibility to viruses with NNRTI RAM patterns that included E138A between the Dapivirine Vaginal Ring-004 and placebo ring groups (any E138A: geometric mean FC Dapivirine Vaginal Ring 004 n = 3, placebo ring n = 5: EFV: 1.08, 1.46; ETV: 1.27, 1.65; NVP: 1.07, 2.48; RPV: 1.12, 1.74, respectively). Overall, there was no clear difference between the groups despite the presence of second mutations in all three viruses investigated from the Dapivirine Vaginal Ring 004 group, (Clinical Virology Report, Version 4.0).

Limited phenotypic susceptibility testing was performed in trial IPM 032. Testing was successful in five instances including viruses with A98G or K103KN and did not show any reduction in susceptibility to dapivirine (geometric mean FC: 0.64, range 0.23 – 1.08). For other NNRTIs, only the virus encoding K103N showed a significant increase

in FC to efavirenz and nevirapine (FC: 8.93 and 41.1, respectively) but not to the NNRTIs with similar structures to dapivirine (FC etravirine: 0.62; rilpivirine: 0.43).

In the MTN-025 trial phenotypic susceptibility analysis was performed successfully on seroconversion samples from all 33 participants. None of the 27 viruses without any known NNRTI mutations showed any significant increase of IC50 to dapivirine (FC: geometric mean: 0.65, range: 0.37 – 1.29) or to other NNRTIs (geometric mean FC: efavirenz: 0.86; etravirine: 0.85; nevirapine: 1.06; rilpivirine: 0.65). Viruses with NNRTI RAMs at seroconversion showed either full susceptibility or only modest FC for dapivirine (FC range 0.74 – 2.78), etravirine or rilpivirine (geometric mean FCs: 0.66 and 0.62, respectively). High-level resistance to efavirenz and nevirapine was observed according to genotypic predictions.

Characterisation of the risk:

In vitro experiments conducted in various cell types, in which a number of laboratory-adapted and clinical isolates of HIV-1 were exposed to increasing concentrations of dapivirine demonstrated the development of a number of mutation classified as major NNRTI resistance-associated mutations by the Stanford HIV RT and Protease Sequence Database. These included the RT mutations K101E/N, K103N, V106I, V108I, E138G/K/Q/R, V179E/F/I, Y181C/I, Y188H/L, G190A/E, and M230I. A number of additional mutations in the RT were also noted. The following mutations showed a greater than 10-fold change in susceptibility to dapivirine: L100I, K101P, K103N, E138R, Y181C/I/V, Y188L, G190E/Q, F227C, M230I/L, V106A+F227C and E138A+F227C. The most frequently occurring mutation observed in in vitro passage experiments was the Y181C mutation, which was not observed in any Dapivirine Vaginal Ring-004 exposed participants in the two-Phase III trials (IPM 027 and MTN-020), (Module 2.7.2.4, Section 1.1.1.4).

The proportion of participants who had seroconverted during the two Phase III trials, and had virus identified harbouring NNRTI RAMs, was low and similar between the Dapivirine Vaginal Ring-004 and placebo ring groups, apart from a numeric imbalance noted in the proportion of participants with the E138A substitution (higher proportion in Dapivirine Vaginal Ring group) in the IPM 027 trial only. This imbalance did not reach statistical significance (Clinical Virology Report, Version 4.0).

In the IPM 027 trial, in all instances where the E138A substitution was identified and genotyping could be performed at a visit(s) prior to the seroconversion visit, the E138A substitution was already present at the earlier visit. Furthermore, there was no selection of additional resistance associated mutations at later time points. Additionally the E138A variant is a known polymorphic substitution, which is more common in HIV-1 subtype C than subtype B virus, has been observed in up to 8% of viruses from ARV-naïve patients[40,41]. However, E138A is weakly selected by ETV and RPV, two close analogues of dapivirine. It reduces ETV[60,61] and RPV susceptibility about 2-fold[62].

When considering participants with virus harbouring more than one NNRTI mutation, in the MTN-020 trial an imbalance was noted in participants in the Dapivirine Vaginal Ring-004 group who had more viruses with more than one NNRTI RAM. This imbalance was not noted in the IPM 027 trial. Since the numbers were small and considering that a number of polymorphic variants were detected in three of the five viruses in the Dapivirine Vaginal Ring-004 group, the significance of this finding is unclear.

Next generation genotype sequencing (NGS) analysis indicated that the viruses assessed had a high level of homology with most mutations and variants observed with 100% prevalence within any given quasi-species. Additionally, the NGS analyses provided support for the results from the population-based genotyping that most of the viruses at seroconversion did not harbour NNRTI RAMs even at low sensitivity and identified more additional mutations (not identified by population-based sequencing) in the placebo ring users across both Phase III trials. Furthermore, no clear redistribution of amino acids to accommodate the development of favoured resistance pathways among viruses from Dapivirine Vaginal Ring-004 exposed participants could be identified. Altogether, these findings are consistent with little or no effect of dapivirine selective pressure on the virus population established immediately after HIV-1 infection.

Across completed trials at HIV-1 seroconversion, genotypic analyses indicated that virus retained susceptibility to the approved NNRTIs. High-level resistance to EFV and NVP, the most commonly used NNRTIs in sub-Saharan Africa, was infrequent in both groups and, when it occurred, it was due to mutations at codon 103 (asparagine or serine) in the Dapivirine Vaginal Ring-004 group.

In the Phase III trials for the dual-mutant viruses with the E138A substitution, all three viruses in the Dapivirine Vaginal Ring-004 group predicted low-level or potential low-level resistance to all NNRTIs, except for the combination of E138A with V179T, when full susceptibility to EFV and NVP was predicted. The dual mutants in both groups when K101E was included with E138A or E138G, had high-level resistance to RPV and intermediate resistance to EFV predicted. The presence of dual mutations with E138A generally did not predict any worse resistance level than for E138A alone with the exception of the dual mutations with K101E found in both trial groups.

Additionally, phenotypic analysis of viruses with the E138A variant to determine its impact on susceptibility to approved NNRTIs indicated either little or modest increases in mean geometric FC of the four NNRTIs tested.

These data suggest the use of dapivirine had limited effects on the prevalence of cross-resistance particularly when considering the increasing prevalence of NNRTI resistance mutations in the region where the trials were performed.

Longitudinal genotypic analysis over time indicated that no new NNRTI RAMs developed between the first visit at which HIV-1 RNA was detected and the seroconversion visit, despite maintaining exposure to dapivirine. These findings of no new NNRTI RAMs developing despite the continued use of dapivirine in the presence of HIV-1 infection over an average use period of approximately 5 weeks, provide further support that there is a low potential for selection of NNRTI RAMs by the Dapivirine Vaginal Ring-004.

In paired viral analyses from the time of seroconversion visit to the trial exit visit, two viruses were identified, by population-based sequencing, with mutations at the exit visit for the first time. These mutations which were observed as mixtures G190GA and K103KN with V106VM, were detected 42 days and 63 days after the seroconversion visit, at which visit dapivirine use was discontinued. NGS analyses of virus from these participants only detected the G190A mutation as 5 % minority species at the seroconversion visit. In both these instances plasma HIV-1 RNA was initially very high (> 10^6 copies/mL) on first detection but significantly reduced at seroconversion indicative of increased immune pressure by the developing anti-HIV-1 immune response. The mechanism by which these mutations emerged therefore is not clear and could represent immune mediated inhibition of transmitted wild-type virus and mutant virion mixtures or due to selective pressure by dapivirine during a period when dapivirine exposure levels were declining in the washout phase after discontinuing ring use.

Based on the available data, the potential for dapivirine to exert selective pressure in the presence of HIV-1 infection over a relatively short period of up to 5 weeks is considered low and the NNRTI mutations observed at seroconversion more likely represent transmitted virus with the mutations already encoded, especially given the increased prevalence of NNRTI resistance mutations in Africa following the introduction of ART in the region,

and/or could have been selected as a consequence of selective pressure from the developing anti-HIV immune response given the acute HIV infection setting[63].

This conclusion is supported by the fact that the substitutions observed in in vitro experiments which mimicked the low concentrations of dapivirine anticipated following vaginal administration, were not observed with higher frequencies in participants in the Dapivirine Vaginal Ring-004 group compared to the placebo ring group in the Phase III trials (Clinical Virology Report, Version 4.0).

Furthermore, data from both seroconverter trials, IPM 007 and MTN-015 did not demonstrate any differences in HIV-1 disease progression or ARV treatment response between participants who used the Dapivirine Vaginal Ring-004 in the parent trials MTN 020 and MTN-025 compared with those participants who used a placebo ring. NNRTI RAMs detected at the point of virologic failure in these studies and results of phenotypic susceptibility testing were consistent with what would be expected in virus from a failing first line EFV or NVP based treatment regimen.

Background incidence/prevalence of non-nucleoside reverse transcriptase inhibitor resistance:

Findings reported by Gupta et al. in 2012[63], suggest a significant increase in prevalence of drug resistance over time since ARV rollout in regions of sub-Saharan Africa. This increase was largely driven by increases in NNRTI resistance observed in studies from East and Southern Africa where substantial increases were noted, notably in East Africa (36% per year [21 to 52]; $P < 0{\cdot}0001$) and Southern Africa (23% per year [7 to 42]; $P = 0{\cdot}0049$)[63].

Similarly, results of studies presented at the XXIV International HIV Drug Resistance Workshop, 21 to 22 February 2015, Seattle, Washington, indicated that the prevalence of NNRTI mutations is rising in South Africa[63].

A national surveillance study from all nine provinces in South Africa, provided an analysis of drug resistance mutations in 2012. Overall, the prevalence of resistance by drug class was estimated at 5.4% (3.7% to 7.6%) for NNRTIs, 1.1% (0.5% to 2.4%) for nucleoside reverse transcriptase inhibitors and 0.9% (0.3% to 2.6%) for protease inhibitor-associated drug resistance. However, four provinces had a prevalence of NNRTI resistance that was greater than 5%[63].

Results were also reported from three rounds of an annual population-based HIV surveillance program in rural KwaZulu-Natal in South Africa from 2010 to 2012. Prevalence of any significant drug resistance was estimated to be 5%. The mutations observed were predominantly related to the NNRTI class of drugs and included most frequently the K103N mutation, followed by V106M and G190A[64].

Additionally, prevalence of HIV drug resistance reported in women from Durban, KwaZulu-Natal in South Africa, who were screened for HIV prevention trials, was above 5%. Of women with resistant virus, 62% had single-class NNRTI resistance. The most frequently observed NNRTI mutations in descending order of frequency were the K103N, V106M, and Y181C substitutions[65].

Risk factors and risk groups:

Women who could potentially be at higher risk are those who are not regularly tested to confirm HIV-1 seronegative status.

Preventability:

The importance of adherence to Dapivirine Vaginal Ring use and the need for frequent HIV testing is considered important to prevent the development of NNRTI resistance-associated mutations. Early detection of HIV infection and the withdrawal of Dapivirine Vaginal Ring use in any user who is suspected of being HIV infected are key to limiting the potential for development of NNRTI mutations. A high index of suspicion of acute HIV infection in any user who experiences an at-risk event and subsequently has non-specific symptoms of signs and symptoms of a viral

infection, should be maintained. Key messages regarding this aspect will be described in the Healthcare Professional (HCP) Guide and User Guide being developed and made available in the countries in Africa where a marketing authorisation will be sought.

Impact on benefit-risk balance of product:

Apart from the higher prevalence of E138A, resistance data from HIV-1 isolates of participants who seroconverted in the two Phase III trials (IPM 027 and MTN-020) indicated a similar proportion of individual NNRTI associated mutations in women exposed to the Dapivirine Vaginal Ring and the placebo ring (Clinical Virology Report, Version 4.0).

However, when considering the stability of the genotype from longitudinal analyses of the observed NNRTI RAMs, the known epidemiology of the E138A polymorphism in HIV-1 subtype C, the fact that this substitution was not selected by dapivirine during in vitro experiments and the inconsistent findings in respect of disproportionality between the user groups in the two Phase III trials, this suggests that the prevalence of the E138A mutation was likely due to transmitted virus with the E138A substitution already encoded.

When considering participants with virus harbouring more than one NNRTI mutation, in the MTN-020 trial an imbalance was noted in participants in the Dapivirine Vaginal Ring-004 group (5/68 [7.4%] versus 1/96 [1.0%]) who had more viruses with more than one NNRTI RAM. This imbalance was however not noted in the IPM 027 trial. Considering the small numbers and that a number of polymorphic variants were detected in three of the five viruses with more than one mutation in the Dapivirine Vaginal Ring-004 group, as well as the fact that this finding was not observed in both Phase III trials, the reasons for these observations are unclear.

Genotypic predictions of susceptibility indicated a high proportion of viruses fully susceptible to EFV, ETV, NVP, and RPV (approximately 90%). Importantly, the E138A substitution on its own is not associated with reduced susceptibility to NVP and EFV[42], which are the more widely used NNRTIs in sub-Saharan Africa.

Genotypic susceptibility scoring of viruses in IPM 027 using NGS indicated that full susceptibility to the EFV and NVP was expected in approximately 95% of HIV-1 seroconversions in the Dapivirine Vaginal Ring-004 group. As expected, the proportion of participants with fully susceptible virus was slightly less for ETV and RPV (both 86%), due mainly to the algorithm's score for the mutation E138A, which is associated with potential low-level resistance to ETV and to low-level resistance to RPV.

Additionally, results of phenotypic susceptibility testing, in viruses encoding E138A in the IPM 027 trial, were supportive of the genotypic susceptibility predictions for EFV, ETV, NVP, and RPV, showing a small incidence of intermediate or high-level resistance. A range of susceptibilities from full susceptibility to modest FC was observed for the approved NNRTIs (geometric mean FC range: 0.6 to 2.9). However, when considering E138A with K101E as additional mutation (the mutation combination of E138A and K101E was observed in one participant in the Dapivirine Vaginal Ring group) there was a slightly higher FC range observed across the approved NNRTIs tested (range 2.40 to 5.30). The clinical relevance of the latter finding is unknown.

Despite the greater prevalence of dual-mutant viruses with E138A encoded in the Dapivirine Vaginal Ring-004 group in the MTN-020 trial, the FC values for all viruses with E138A present, were within the range observed in the placebo ring group with or without additional mutations being present. This finding is consistent with the observation that the additional mutations were at polymorphic codons that do not contribute significantly to resistance.

When considering longitudinal genotypic analyses in trial IPM 027, none of the 52 paired viral analyses, performed between the seroconversion timepoint and the first visit when HIV-1 RNA was detected, indicated that new RAMs developed. This suggests a low potential for de novo selection of resistance in the first 30 days after HIV-1 RNA detection. Although emergence of resistance in virus from two of 63 participants (G190G/A and K103K/N with V106V/M) was observed at the trial exit visit when not observed at the seroconversion visit, these are considered unusual mutations for dapivirine to select. Additionally, the findings in the placebo group of minority species G190A and G190E, both associated with high-level or intermediate resistance to EFV and NVP (Stanford HIVdb, Version 8.4), demonstrate that there was circulation of G190 resistance variants in the community. Furthermore, the contribution of the immune system with strong immune selective pressure in an acute HIV infection setting is unclear.

Further support for the low potential for selection of NNRTI RAMs by the Dapivirine Vaginal Ring-004 comes from the results of population-based genotyping among participants already infected at enrolment (but without HIV-1 seroconversion). These participants were exposed to dapivirine in the presence of HIV infection over a period of approximately five weeks. Since the Dapivirine Vaginal Ring was discontinued upon identification of HIV-1 seroconversion in the Phase III clinical trials, and follow-up visits were scheduled approximately 4 weeks apart, the duration of exposure to dapivirine while infected with HIV-1 was however limited. Consequently, the likelihood of emergence of NNRTI resistance in women who use the Dapivirine Vaginal Ring while being infected with HIV-1 in a real-world setting, where HIV infection may go undetected for a longer period of time, is unknown.

Additionally, the results of population based genotyping, NGS and phenotypic susceptibility testing from the open-label extension trials IPM 032 and MTN-025 were similar to the observations in the Phase III trials, indicating highly homogeneous viral species, good correlation between the population based genotyping and NGS, limited effects of dapivirine on the development of cross resistance to other drugs in the NNRTI class and that in viruses without any known NNRTI RAMs observed, there was no change in susceptibility to dapivirine, reducing the possibility of novel pathways for resistance development.

The development of any mutations associated with NNRTI resistance and their establishment in the viral reservoir could later contribute to reduced clinical response and treatment failure after initiating ART. Consequently, future therapeutic options in a proportion of women who become HIV-1 infected while using the Dapivirine Vaginal Ring may be reduced. This is particularly true in resource limited settings.

Participants who seroconverted in IPM 027 and MTN-020 and the follow-on trials IPM 032 and MTN-025 could choose to undergo follow-up in the studies IPM 007 and MTN-015, to monitor their responses on ART.

Data from both studies (IPM 007 and MTN-015) did not indicate any differences in HIV-1 disease progression and ARV treatment response between participants who used the Dapivirine Vaginal Ring-004 in the parent studies compared with those who used a placebo ring. In IPM 007, of the participants who had received ARVs for at least 6 months at the 12-month visit (i.e., had the opportunity to achieve an optimal treatment response), 94.4% (17/18) of the participants who used the Dapivirine Vaginal Ring-004 in IPM 027 had HIV-1 RNA < 200 copies/mL, compared with 77.8% (5/7) of the participants who used a placebo ring (IPM 007 CSR, Section 11.1). Of those participants who used the Dapivirine Vaginal Ring-004 in IPM 032, 100.0% (20/20) of the participants had HIV-1 RNA < 200 copies/mL.

Similarly, in MTN-015, ARV treatment response of participants who received at least 6 months of ARV therapy indicated 70.3% (26/37) of the participants who used the Dapivirine Vaginal Ring-004 had HIV-1 RNA < 200 copies/mL, compared with 76.6% (46/60) of participants who used a placebo ring in MTN-020. Of the MTN-025 participants, 88.2% (15/17) of the participants who used the Dapivirine Vaginal Ring-004 achieved HIV-1 RNA < 200 copies/mL (MTN-015 Summary Report, Section 7.2).

Additionally, the pattern of mutations identified at virologic failure in the IPM 007, and MTN-015 trials demonstrate mutations consistent with selection by the ARV drugs used in the EFV or NVP containing treatment regimen.

Overall, available data from the clinical trials point to a high proportion of any NNRTI RAM in placebo ring users at HIV-1 seroconversion (IPM 027: 14%; MTN-020: 9.4%) reflecting a high prevalence of circulating mutations available for transmission and furthermore genotypic NNRTI mutation patterns as well as longitudinal analysis of these mutations suggest a low potential for de-novo selection of NNRTI RAMs by dapivirine (Clinical Virology Report, Version 4.0).

Potential public health impact:

Development of NNRTI resistance mutations in a setting of HIV prevention may contribute to the pool of resistant virus in the community which can be transmitted. Additionally, these mutations have the potential to confer cross resistance to other NNRTIs and limit treatment options available to HIV-1 infected participants who may require second line and potentially salvage therapy regimens earlier than anticipated. This is likely to increase the cost and administrative burden for the provision of ART in resource limited settings, since newer therapies may either not be available or not available in lower-cost generic fixed-dose combinations, which may further complicate adherence challenges and hence the goal of attainment of a high proportion of patients with virological control at a population level.

In their July 2017 guidance document[66], the WHO recommended that when country prevalence of NNRTI resistance exceeds 10%, a public health response should be triggered in that country and consideration given to an alternative, non-NNRTI treatment regimen for individuals starting ART. These alternative guidelines suggest the use of the integrase inhibitor, dolutegravir, as first-line treatment for all adults starting ARV treatment for the first time.

This recommendation has now been widely adopted and alleviates to some extent concerns regarding the impact of NNRTI mutations in participants who seroconvert using an NNRTI-based means to reduce the risk of infection.

Important potential risk: Development of pelvic inflammatory disease

Potential mechanism:

The pathogenesis of PID starts with the presence of a vaginal or cervical infection, which thereafter ascends to the upper genital tract. Such an infection is often sexually transmitted and may be asymptomatic[67].

The mechanisms by which microorganisms ascend to the upper genital tract, is unclear. Several mechanisms have been postulated. Although cervical mucus provides a functional barrier against upward spread, the protective effect of this barrier may be reduced by vaginal inflammation and by hormonal changes that occur during ovulation and menstruation[68].

Antibiotic treatment of STIs can disrupt the balance of vaginal microflora, resulting in the overgrowth of normally non-pathogenic organisms and then ascend to the upper genital tract structures. Furthermore, opening of the cervix during menstruation, along with retrograde menstrual flow, may also play a role. In sexually-active women, intercourse may contribute to the ascent of infection through uterine contractions occurring during orgasm[68]. Bacteria may also be carried along with sperm into the upper genital tract[69].

Inflammation and or epithelial disruption of the vagina and cervix potentially resulting from mechanical abrasion of these surfaces from use of the Dapivirine Vaginal Ring, may lead to a breakdown of the protective cervical barrier. However, data from the Phase III clinical trials do not reveal a significant impact of the Dapivirine Vaginal Ring on vaginal pH and vaginal flora, which could predispose to infection or inflammation, nor was its use associated with significant pelvic examination findings (Module 2.7.4, Sections 8.4.2 and 8.4.3).

Evidence source(s) and strength of evidence:

The low incidence of PID observed in the Phase III program, despite the high incidence of STIs reported in the Phase III program (Module 2.7.4, Table 40), is likely due to effective management of STIs and genital tract infections as a result of either presumptive treatment or specific treatment in response to a confirmed etiological STI diagnosis as a result of nucleic acid amplification tests that were scheduled to be performed regularly throughout trial conduct (3-monthly in IPM 027 and 6-monthly in MTN-020).

However, it is not known whether there could be an increased level of risk (beyond the risk associated with a preceding STI) for the development of PID in Dapivirine Vaginal Ring users with untreated STIs, or women with asymptomatic STIs who are not regularly screened and treated.

Characterisation of the risk:

Pelvic inflammatory disease encompasses a range of inflammatory disorders of the female upper genital tract. Numerous sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis* are implicated. Microorganisms that comprise the vaginal flora (e.g., *Gardnerella vaginalis* and *Haemophilus influenzae*) have also been implicated in the development of PID[67]. Many cases of chlamydia and gonorrhoea infections are asymptomatic in women, and many go undiagnosed and untreated[70]. Results from randomized controlled trials, suggest that chlamydia screening is associated with a decreased incidence of PID[71,72]. Although BV has been associated with PID, whether the incidence of PID can be reduced by identifying and treating women with BV is unclear[73].

The incidence of PID in the Phase III trials was low overall, with PID being reported in 1.8% (48/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 2.7% (54/1,968) of participants in the placebo ring group (Module 2.7.4, Section 8.1.1.10.3). Participants with PID could be adequately managed using available treatment guidelines, despite the continued use of the Dapivirine Vaginal Ring-004 in the majority of cases. The majority of cases of PID reported for participants in the Phase III trials, were Grade 2 (moderate) in severity. Grade 3 (severe) PIDs were reported in 0.1% (2/2,619) of participants in the Dapivirine Vaginal Ring-004 group and 0.2% (3/1,968) of participants in the placebo ring group (ISS Phase III, Table 14.4.1.7). No event of PID resulted in the permanent discontinuation of the investigational product and temporary discontinuation of the investigational product was uncommon, only being reported in 0.1% (3/2,619) and 0.3% (5/1,968) of participants with PID in the Dapivirine Vaginal Ring-004 and placebo ring groups, respectively (ISS Phase III, Table 14.4.1.36), indicating that the Dapivirine Vaginal Ring-004 was well tolerated in the majority of women with acute PID. Additionally, PID was reported as an SAE requiring hospitalization in only one (1/1,968; 0.1%) participant in the placebo ring group during the Phase III trials (ISS Phase III, Table 14.4.1.11).

Following a review of reported cases of PID and assessing an association between a diagnosis of an STI in the preceding 3 months prior to a diagnosis of PID being made in any participant in the Phase III trials, and the hypothetical contribution that the presence of the vaginal ring could have in the pathogenesis of the PID event, only 16 (16/110; 14.5%) such participants could be identified that had a preceding STI and who had a subsequent diagnosis of PID. This low incidence is similar to published literature data of the incidence of PID in women with a preceding STI[74], and this together with the favourable treatment outcomes in participants with PID who continued Dapivirine Vaginal Ring-004 use, do not suggest a significant contribution by the Dapivirine Vaginal Ring-004 in the pathogenesis of PID in these cases reported during conduct of the Phase III trials.

These findings are further supported by data from the open-label extension trial IPM 032 in which participant follow up and STI management more closely mirrored real life experience. A low overall incidence of PID of 0.6% (6/941) was observed, despite a high STI incidence of 17.3% (163/941) at screening and 16.4% (154/941) at the last product use visit. Additionally, all TEAEs of pelvic inflammatory disease were Grade 2 (moderate) in severity and were considered resolved during the clinical trial, (Module 2.7.4, Section 9.1.5.1).

However, PID may result in significant morbidity, and although it can be managed on an outpatient basis, more severe cases may require hospitalization for optimal treatment. The main complications of PID include the development of tubo-ovarian abscess, chronic pelvic pain, infertility, or ectopic pregnancy.

Impaired fertility is a major concern in women with a history of PID. Infection and inflammation can lead to scarring and adhesions within tubal lumens. The rate of infertility increases with the number of episodes of infection. The risk of ectopic pregnancy is increased by 15% to 50% in women with a history of PID. Ectopic pregnancy is a direct result of damage to the fallopian tube. Tubo-ovarian abscess is reported in as many as one third of women hospitalized for PID. Acute rupture of a tubo-ovarian abscess with resultant diffuse peritonitis is a rare but life-threatening event that requires urgent abdominal surgery[68].

In real world setting, acute PID is difficult to diagnose because of the wide variation in symptoms and signs associated with this condition. Many women with PID have subtle or non-specific symptoms or are asymptomatic. Delay in diagnosis and treatment probably contributes to inflammatory sequelae in the upper reproductive tract. Many episodes of PID go unrecognized. Although some cases are asymptomatic, others are not diagnosed because the patient or the healthcare provider fails to recognize the implications of mild or non-specific symptoms or signs[75].

No specific data on PID incidence worldwide are available. However, in 2005 the WHO estimated that approximately 448 million new cases of curable STIs occur annually in individuals 15 to 49 years of age. Factors contributing to the difficulty of determining the actual worldwide incidence and prevalence of PID are multifactorial but include resource limitations in the health systems and access to care as well as the subjective nature of diagnostic criteria.

The annual rate of PID in high-income countries has been reported to be as high as 10 to 20 per 1,000 women of reproductive age. Public health efforts implemented in Scandinavia to decrease the prevalence of STIs, have been shown to reduce the incidence of PID[68]. These PID incidence rates are similar to the incidence rates observed in the Phase III trial population, despite the high incidence of STIs that were observed.

Risk factors and risk groups:

Risk factors for development of PID include, multiple sexual partners, a history of prior STIs, a history of sexual abuse, gynaecological surgical procedures that may result in damage to the cervical barrier (such as endometrial biopsy, curettage, and hysteroscopy), and the use of intrauterine devices (IUDs)[68].

The risk is increased in younger females, due to increased cervical mucosal permeability, a larger zone of cervical ectopy, lower prevalence of protective anti-chlamydial antibodies, and possibly higher risk-taking sexual behaviour[68]. The comparative incidence of PID from the pooled Phase III trial data in the ≤ 21 years of age versus > 21 years of age groups, respectively, was 1.9% (11/583) of participants versus 1.8% (37/2,036) of participants in the Dapivirine Vaginal Ring-004 group, and 1.5% (6/405) of participants versus 3.1% (48/1,563) of participants in the placebo ring group, respectively (ISS Phase III, Table 14.4.1.4A).

In a report published in 1996[74], the risk of PID in the year after an episode of treated STI was considered high, but the highest period of risk was assessed to be in the first few weeks. The shape of the risk curve indicated that some PID cases may have resulted from treatment-resistant infections, or possibly from untreated re-infections. Overall, the risk of PID was estimated to be about 9% during a 1-year period following treatment for gonorrhoea or chlamydia, with a steep rise in risk within the first 45 days[74].

The risk for PID associated with IUD use, is primarily confined to the first 3 weeks after insertion, and treatment outcomes did not generally differ between women with PID who retained the IUD and those who had the IUD removed[76-78]. These studies primarily included women using copper or other non-hormonal IUDs.

Since IUD use as a contraceptive option was limited and the incidence of PID was low overall in the Phase III trials, the risk of PID associated with concomitant Dapivirine Vaginal Ring and IUD use could not be reliably determined.

Preventability:

Routine risk communication will include precautionary statements added to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) regarding the need for early treatment of any suspected STI or genital infection, and the need to consider interruption of use of the Dapivirine Vaginal Ring in any woman who has a recent gynaecological procedure, until such time as healing of the genital tract has taken place. Additional educational information will be provided in the proposed HCP Guide and User Guide as part of risk minimisation activities. This messaging will include advice on signs and symptoms to look out for to facilitate the early recognition of PID, and the need for early treatment for symptomatic genital infection, the need for partner treatment to prevent re-infection, and the importance of safer sex practices.

Impact on benefit-risk balance of product:

The low overall incidence of PID observed in the Phase III trials, despite a high incidence of STIs, does not suggest an increased risk of developing PID in women who used the Dapivirine Vaginal Ring. Additionally, the impact of PID on continued use of the Dapivirine Vaginal Ring was negligible, as no participant required permanent discontinuation of the Dapivirine Vaginal Ring following a diagnosis of PID, and the majority of participants could successfully complete treatment for PID despite continued Dapivirine Vaginal Ring use.

Since effective treatment and screening for STIs was performed regularly in the Phase III trials, it is unknown whether women using the Dapivirine Vaginal Ring might be predisposed to a higher risk of developing PID if they acquire an STI and/or genital infection which is undetected for a considerable period of time.

However, data from the recently completed IPM 032 study showed a low incidence of pelvic inflammatory disease, despite the high incidence of STIs. This indicates that STIs can be effectively managed in Dapivirine Vaginal Ring users, without a high risk of an ascending pelvic infection when following a visit schedule which more closely mirrors anticipated real life clinical follow up.

Potential public health impact:

The significant burden of disease attributed to PID largely stems from the long-term complications of tubal infection: tubal factor infertility, ectopic pregnancy, and pelvic adhesions, which can lead to chronic pelvic pain[79].

Women in resource-poor countries, especially those in sub-Saharan Africa, may experience an increased rate of complications and sequelae due to a lack of access to care and/or inability to afford optimal care.

Pelvic inflammatory disease can significantly add to the burden and costs to healthcare systems. Approximately 125,000 to 150,000 hospitalizations occur yearly in the US because of PID, despite a decline in PID rates over the last decade[79].

SVII.3.2 Presentation of the Missing Information

Missing information: Safety during pregnancy

Evidence source:

Clinical data in pregnant women are limited, since pregnant women were excluded and participants who became pregnant during the clinical trials discontinued use of the investigational product (Module 2.7.4, Section 12.4.1). Across completed trials in adult women, the proportion of participants with adverse pregnancy outcomes similar between the Dapivirine Vaginal Ring-004 group and placebo ring group (Table Part II: Module SVII-1). Since pregnancy testing was performed at monthly (28 days) intervals, overall exposure to dapivirine of the developing embryo, including potential local exposure at the pre-implantation stage and subsequently systemic exposure, was limited. Pregnancy outcome data with follow-up of infants up to 1 year of age have shown no developmental abnormalities reported up to the data lock point.

Table Part II: Module SVII-1: Cumulative Summary of Pregnancy Outcomes from completed trials of Adult Women 18 years and older

Pregnancy outcome	**Dapivirine Vaginal Ring-004 (28 Days)**	**Placebo Ring (28 Days)**
	n (%)	**n (%)**
Number of pregnancies	**240**	**122**
Number of expected pregnancy outcomes	**243**	**125**
Live birth	140 (57.6%)	78 (62.4%)
Spontaneous abortion	47 (19.3%)	24 (19.2%)
Non-therapeutic (elective) abortion	36 (14.8%)	15 (12.0%)
Stillbirth/intrauterine fetal demise	6 (2.5%)	3 (2.4%)
Ectopic pregnancy	2 (0.8%)	1 (0.8%)
Maternal death	-	1 (0.8%)
False positive urine test/pregnancy not confirmed	4 (1.6%)	1 (0.8%)
Possible chemical pregnancy/pregnancy not confirmed	3 (1.2%)	1 (0.8%)
Pregnancy not confirmed[a]	1 (0.4%)	0
Outcome unavailable	4 (1.6%)	1 (0.8%)

n= the number of pregnancy outcomes for each category
[a] Obstetric ultrasound four months after positive pregnancy test indicated that the participant was not pregnant but had an ovarian cyst.
Only trials that had pregnancies reported were summarized. Data of IPM 015, IPM 027, IPM 032, MTN-020 and MTN-025 were included. Per participant, multiple pregnancy outcomes were possible.
Source: Module 2.7.4, Section 12.4.1, Table 45

Additionally, the observational study, MTN-016, assessed pregnancy and infant outcomes for a subset of the participants who became pregnant in MTN-020 (ASPIRE) and MTN-025 (HOPE), the two parent trials that evaluated the Dapivirine Vaginal Ring-004, and who enrolled in the study, (MTN-016 EMBRACE Summary Report).

For participants who ever used a ring and became pregnant in the parent trial and chose to enroll in MTN-016, there were 77 (77/88; 87.5%) full-term births reported for the dapivirine group and 45 (45/56; 80.4%) in the placebo ring group. Three (3/88; 3.4%) premature live births were reported for the dapivirine group and eight (8/56; 14.3%) in the placebo ring group. Four (4/88; 4.5%) stillbirths were reported in the dapivirine group and two (2/56; 3.6%) in the placebo ring group.

No major structural congenital abnormalities were reported in infants. Twenty-eight (28/133; 21.1%) neonates were born with a low birth weight, 18 (18/80; 22.5%) in the dapivirine group and 10 (10/53; 18.9%) in the placebo ring group with no statistically significant difference between the groups (odds ratio: 1.25, 95% CI, 0.53 to 2.97; P = 0.6153).

Mean standardized infant Z-scores for weight, length and head circumference were determined for infants at each visit. No statistically significant difference was observed between the dapivirine and placebo groups, indicating no reductions in infant growth among women with inadvertent exposure to dapivirine in early pregnancy compared to women in the placebo group.

Nonclinical studies of dapivirine do not indicate direct or indirect harmful effects, with respect to reproductive toxicity, that are relevant to use of the Dapivirine Vaginal Ring. No toxicity was seen in embryofoetal development studies in rats and rabbits performed via the vaginal route (up to 3.3 mg/mL using a dose volume of 0.2 mL/kg in rats, and up to 2 mg/mL using a dose volume of 1.0 mL in rabbits) (Module 2.4, Section 4).

In nonclinical studies with oral administration in rats, some effects on the developing foetus were observed at maternally toxic doses (≥ 80 mg/kg) of dapivirine, while there were no effects at the maternally non-toxic dose of 20 mg/kg/day. No effects on embryofoetal development were observed in rabbits at doses up to 90 mg/kg. In a pre- and postnatal development study in rats, no effects were observed at oral doses of dapivirine of 5 or 20 mg/kg/day. Transient reductions in body weight gain and food consumption in the mothers and slight reductions in body weight and body weight gain in the offspring were observed at 80 mg/kg/day (Module 2.4, Section 4.6).

Given the absence of relevant nonclinical findings and low systemic exposure to dapivirine in women using the Dapivirine Vaginal Ring, it is considered unlikely that the use of the Dapivirine Vaginal Ring during pregnancy presents any significant risk to the developing embryo or foetus.

Population in need of further characterisation:

There is a great medical need for HIV infection risk reduction in pregnant women, since pregnant women are at increased risk of HIV infection[7-10]. In addition, there is a risk that HIV-positive women transmit the virus to the unborn child during pregnancy, or to the baby at delivery and during breastfeeding[80].

Studies in Uganda, Rwanda, and Zimbabwe have shown that pregnant women are at a higher risk of HIV infection than lactating or non-pregnant women[6]. A prospective study in Uganda found HIV incidence rates were 2.3 per 100 person-years during pregnancy, 1.3 per 100 person-years during breastfeeding, and 1.1 per 100 person-years in non-pregnant and non-lactating women[8]. This finding appears more likely to be a result of physiological changes during gestation than to social and behavioural changes during pregnancy[7]. Moreover, maternal HIV infection during pregnancy also increases the risk for transmission to the unborn child. In a recent meta-analysis, pooled mother-to-child-transmission rates were 2.8-fold higher for women with incident HIV infection during pregnancy, compared to those with previous HIV infection[81].

The benefit/risk of using the Dapivirine Vaginal Ring should therefore be considered in the context of the high incidence of HIV infection among pregnant and postpartum populations. A clinical trial to assess the safety of the Dapivirine Vaginal Ring and oral TDF/FTC tablet use in pregnant women, including follow-up of infants up to one year of age, is ongoing (MTN-042). This trial is being conducted under the regulatory sponsorship of

NIH/NIAID/DAIDS. The database was locked on 23 August 2024, and a final clinical study report is expected Q3 2025.

Missing information: Local drug-drug interaction with vaginally administered clindamycin and metronidazole

Evidence source:

In vitro experiments indicate that in the liver dapivirine primarily undergoes oxidative metabolism by cytochrome P450 (CYP450; primarily CYP3A and, to a lesser extent, by the CYP2C family), followed by glucuronidation by uridine 5'-diphospho-glucuronosyltransferase (UGT), specifically UGT1A and -2B isoenzymes. Dapivirine is a substrate of CYP1A1 and CYP3A4 enzymes, but is not a substrate of CYP1A2, CYP1B1, CYP2B6, CYP2C8 or CYP2C19, or of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9 or UGT2B7

Dapivirine was not a substrate of the drug transporters P-gp, BCRP, MRP1, MRP4, and ENT1 in vitro at concentrations observed in the vaginal fluid and had no inhibitory effects on the activity of these transporters at maximal vaginal concentrations and maximal plasma concentrations.

In vitro dapivirine showed varying degrees of inhibition of CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. At maximal plasma concentrations, dapivirine is not an inhibitor of UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9 and 2B7. In vaginal tissue no UGT enzyme activity was detected. Dapivirine was not an inducer via AhR (CYP1A2), CAR (CYP2B6) and PXR (CYP3A4) at 0.3 µM (0.1 µg/mL), (Module 2.4, Section 3.4).

Clindamycin, one of the "lincoamides" is metabolized primarily by CYP3A4, and to a lesser extent by CYP3A5. In vitro studies have shown that clindamycin only moderately inhibits CYP3A4[86].

Although metronidazole (nitroimidazole derivative) was previously reported as an inhibitor of CYP3A4 based on assumptions inferred from isolated case reports, controlled in vitro and in vivo studies show that metronidazole does not significantly inhibit CYP3A4/5 activity. Additionally, a study in humans examined S-warfarin and tolbutamide as probes for the CYP2C9 isoenzyme. Metronidazole interacted with S-warfarin, but not tolbutamide. This lessens the likelihood of a potential CYP2C9 interaction, which was originally postulated. It is unknown whether metronidazole alters transport proteins[87].

Since the systemic exposure to dapivirine observed in women using the Dapivirine Vaginal Ring-004 is very low (< 2 ng/mL), it is unlikely to result in a significant impact on the hepatic metabolism of systemically co-administered drugs.

Vaginally administered products typically have low systemic absorption with little effect of hepatic metabolism, therefore, local metabolism in the vagina would likely be a primary mediator of any potential pharmacokinetic interaction of these drugs.

In vaginal tissue, CYP450, but not UGT enzyme activity was detected. Dapivirine inhibited several CYP450 and UGT enzymes and therefore there is the potential for drug-drug interactions with co-administered vaginal products that are metabolized by these enzymes in vaginal tissue.

Therefore, potential effects of dapivirine on the enzyme activity in local vaginal tissues that may lead to drug-drug interactions with other drugs cannot be entirely excluded.[88,89]

Population in need of further characterisation:

Information regarding the effect of concomitant use of dapivirine and metronidazole or clindamycin on CYP hepatic and local tissue metabolism, is not available. Given that the treatment guidelines for genital infection and/or STI in the countries in sub-Saharan Africa targeted for a marketing authorisation application, all recommend use of oral metronidazole in non-pregnant women and generally do not recommend use of vaginally administered clindamycin. No formal local drug-drug interaction trials with dapivirine and vaginally administered metronidazole or clindamycin are planned at this time.

Anticipated risk/consequence of the missing information:

Systemic drug-drug interactions are not anticipated with systemically co-administered metronidazole or clindamycin and the Dapivirine Vaginal Ring-004. Considering that vaginally administered metronidazole and clindamycin are not expected to be used frequently in the countries in which a marketing authorisation will be sought, the anticipated risk of this missing information is considered low and routine risk communication and the additional risk minimisation measures (HCP and User Guides), are considered adequate to address this safety concern. Routine risk communication will clearly indicate that concurrent use of vaginally administered metronidazole and clindamycin is not recommended. Additionally, the User Guide will inform the user to consult her clinic or doctor before concurrent use of any vaginally administered medicine and the HCP guide will indicate that no data are available on the concurrent use of either vaginally administered metronidazole or clindamycin.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII-1: Summary of Safety Concerns

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 Local drug-drug interaction with vaginally administered clindamycin and metronidazole
HIV-1 = human immunodeficiency virus type 1; NNRTI = non-nucleoside reverse transcriptase inhibitor	

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

Clinical investigations have demonstrated that the Dapivirine Vaginal Ring 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 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 as indicated in Table Part III-1.

III.1 Routine Pharmacovigilance Activities

Routine PV is a set of activities required to fulfil the legal requirements for PV (Directive 2001/83/EC and Regulation [EC] No 726/2004). The Pharmacovigilance System Master File describes these activities. Signal detection, as part of routine PV, will be an important element in identifying new risks for the product.

Routine PV activities beyond adverse reactions reporting and signal detection:

- The applicant plans to use a specific questionnaire to obtain structured information on the following suspected adverse reaction of special interest: Lack of efficacy (Annex 4).

This specific questionnaire is designed to identify reasons for HIV-1 acquisition, such as lack of adherence to product use and/or lack of adherence to safer sex practices (including risk compensation behaviour), or HIV-1 infection through a route other than vaginal sexual intercourse.

A medical contact centre service will be implemented and fully operational prior to the launch of the product in the first intended market. This call centre will facilitate the receipt of safety reports, product complaints and usability issues from consumers and healthcare professionals and will allow integration of these reports into the global safety database by manually emailing the report form to the dedicated safety mailbox. The in-country tollfree telephone numbers, if available, for the medical contact centre will be made available on the company website and in the country specific HCP and User guides subject to in-country approval. The PV system will be designed to allow upscaling as demand increases and to incorporate new technological advances which may enhance pharmacovigilance activities.

III.2 Additional Pharmacovigilance Activities

There are no imposed Category 1 or 2 trials. The following trials are included in Category 3 as required additional PV studies for the Dapivirine Vaginal Ring.

Missing information on the safety of Dapivirine Vaginal Ring use during pregnancy will be assessed by data collected in the ongoing MTN-042 trial. This trial is a Phase IIIa, randomized, open-label safety and pharmacokinetic trial of Dapivirine Vaginal Ring and oral TDF/FTC tablet use in pregnancy. The protocol was amended and now describes a three-cohort, open-label trial with a 2:1 randomization ratio (Dapivirine Vaginal Ring: oral TDF/FTC tablet) for Cohort 1 and 2 and 4:1 randomisation ratio for Cohort 3. Essentially Cohorts 3 and 4 have been collapsed into one cohort. The trial used a stepwise reverse gestational age study schema with dosing occurring within pre-defined gestational age ranges. The rationale for the use of this schema was that the lowest risk associated with dapivirine use would be anticipated later in pregnancy, well after organogenesis is completed. The entire trial enrolled approximately 550 healthy, HIV-negative women 18 to 45 years of age across the gestational age ranges.

1.8.2 Risk Management Plan

Approximately 150 women at 36 to 37 weeks of gestation were enrolled first and followed through delivery with an interim safety review performed prior to enrolment of the next gestational age range. No safety concerns have been identified to date. This trial was initiated on 09 January 2020 and the database was locked on 23 August 2024. A final clinical study report is expected in Q3 2025.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III-1: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				
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 is expected Q3 2025
CSR = clinical study report; FTC = emtricitabine; MTN = Microbicide Trials Network; TDF = tenofovir disoproxil fumarate				

PART IV 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 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 in a real-world setting. The study plans to enroll 500 women who will use the Dapivirine Vaginal Ring 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 Part IV-1: 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 (IPM 055) Observational study in healthy HIV-negative young women ages 18-25 years. (ongoing)	• 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	Expected completion of study conduct Q4 2024	Final CSR expected Q3 2025

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The majority of safety concerns will be addressed with routine risk minimisation measures (Table Part V-1), namely by providing text in the product information, the SmPC, and PIL (Module 1.3).

Additional risk minimisation measures will include information provided in the form of a HCP Guide and User Guide, which will address all the safety concerns mentioned in Table Part II: Module SVIII-1.

The HCP Guide and User Guide will facilitate HCP education and assist in provision of counselling to the (potential) user. The User Guide written in lay language will assist the user in understanding the risks and missing information associated with the Dapivirine Vaginal Ring, and how these can be minimised.

As part of routine PV activities, a specific follow up questionnaire (Lack of Efficacy Form) has been developed to be completed when unsolicited reports of lack of efficacy, i.e., HIV seroconversion are received. The aim of this form is to collect additional information in all vaginal ring users who become HIV infected. A periodic analysis of information received will assist in further characterising the important identified risk of HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use in younger women.

As an additional risk minimisation measure linked to receipt of such lack of efficacy reports, direct or indirect contact through third parties (e.g., the distributor of the product in the intended markets) will be made periodically (e.g., 6 monthly) with an identified primary contact at the healthcare facility receiving supplies of the Dapivirine Vaginal Ring-004, to inquire if there have been any cases of HIV-1 infection in Dapivirine Vaginal Ring-004 users and whether such reports have been submitted through the established reporting channels. It is envisaged that the Lack of Efficacy Forms will be distributed to the reporter by the PV vendor when reports of lack of efficacy are received. The Lack of Efficacy Form will also be made available to Healthcare Practitioners on the Applicant's dedicated PrEP ring web page.

Routine and additional risk minimisation measures are further described in the sections below.

V.1 Routine Risk Minimisation Measures

Table Part V-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation 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.
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.
Development of PID	Routine risk communication: Prescribing Information (Summary of Product Characteristics), Section 4.4. Patient Information Leaflet, Section 2.
Safety during pregnancy	Routine risk communication: Prescribing Information (Summary of Product Characteristics), Section 4.6. Patient Information Leaflet, Section 2.
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.
HIV-1 = human immunodeficiency virus type 1; NNRTI = non-nucleoside reverse transcriptase inhibitor; PID = pelvic inflammatory disease	

V.2 Additional Risk Minimisation Measures

Healthcare Professional Guide

The Dapivirine Vaginal Ring will be provided as part of an overall HIV-1 prevention strategy. Accordingly, the HCP Guide will assist the HCP to provide counselling guidance on different options for HIV-1 prevention and help to perform a risk assessment to identify the best option(s) depending on each woman's individual situation to reduce her risk of HIV-1 infection.

The HCP Guide will instruct HCPs on product use and characteristics. The information is intended to facilitate provision of counselling to users and where applicable, her partner(s). Additionally, understanding of a woman's individual situation in terms of gender equality, respect of individual sexual health and rights as well as personal preferences is critical to advise on the best possible prevention options or combinations thereof.

The HCP Guide will include the following key points to support the HCPs during counselling of users:

- The importance of adherence to product use to achieve a reduction in risk of HIV-1 infection: continuous use during one month and immediate replacement of the used ring with a new ring after 1 month.
- The Dapivirine Vaginal Ring is a part of a comprehensive HIV-1 prevention strategy and should be used in combination with safer sex practices and is only effective in preventing HIV-1 infection arising from vaginal intercourse.
- Prior to initiating treatment, the HCP should enquire about the use of any vaginal products and/or vaginal practices and recommend to avoid any vaginal practices or treatments which may potentially interfere with the efficacy or safety of the Dapivirine Vaginal Ring.
- The potential risk of the selection of NNRTI resistance associated mutations and hence the importance of quarterly monitoring of HIV-1 serostatus to avoid continuing use of the Dapivirine Vaginal Ring in case of seroconversion, as wells as what signs and symptoms to look out for during HIV seroconversion (acute HIV infection). Symptoms usually associated with acute HIV are described and likened to an influenza-like illness, with the most commonly reported symptoms being fatigue (tiredness), fever (high body temperature), sore throat, rash, headache, loss of appetite, myalgia (painful muscles), arthralgia (painful joints), and enlarged lymph nodes.
- The Dapivirine Vaginal Ring does not have any contraceptive effect and does not protect against transmission of other STIs.
- The importance of ensuring early identification and treatment of STIs and other genital infections, which might increase the risk of HIV infection prior to initiating treatment, and during use of the Dapivirine Vaginal Ring.
- Advice to give to women on what actions to take in case the Dapivirine Vaginal Ring is accidentally expelled or damaged.
- Information that safe use in pregnancy has not been established.

Additionally, the following statements will be included for HCPs:

- Prior to initiating preventative treatment with the Dapivirine Vaginal Ring, testing for HIV infection should be performed according to applicable local guidelines.

- In the absence of HIV-1 RNA PCR testing to detect the presence of HIV infection in women who may be in the window period prior to initiation of treatment, a clinical decision should be made regarding the benefit of providing treatment that could potentially avert infection versus the potential risk of development of mutations associated with NNRTI drug resistance.

Objectives:

The objective of the HCP Guide is to provide information for counselling to address the safety concerns in Table Part II: Module SVIII-1, and to minimise the potential adverse outcomes in the user with emphasis on adherence and the importance of quarterly reconfirmation of HIV-1 negative status during use of the Dapivirine Vaginal Ring.

Rationale for the additional risk minimisation activity:

The HCP Guide is proposed to further minimise the identified or potential risks associated with the aforementioned safety concerns, with messaging included to allow early identification and treatment of the important potential risk of PID and any preceding genital infections to minimise their impact. The information included will allow for the provision of face-to-face counselling to each woman using the Dapivirine Vaginal Ring, rather than relying on users to read the PIL.

Target audience and planned distribution path:

Healthcare professionals who are planning to prescribe the Dapivirine Vaginal Ring. The target list of these HCPs and the planned distribution path are to be determined depending on the local healthcare system and relevant regulations. The Applicant has submitted the material to the respective in-country regulatory authorities that have already approved the Dapivirine Vaginal Ring for use. Approval is being sought to make these materials available electronically on the dedicated Dapivirine Vaginal Ring website. Distribution pathways need to be negotiated with in-country regulatory authorities, but materials could potentially be distributed with product shipment, during HCPs workshops and during product demonstration sessions at the demonstration project stage.

Plans to evaluate the effectiveness of the interventions and criteria for success:

“Lack of efficacy” information will be collected using routine PV activities and followed up with a specific questionnaire. Data from the questionnaire will be analysed on a regular basis, considering the number of “lack of efficacy” reports over time and suspected reasons for prevention failure. This information will be provided in the Periodic Safety Update Report (PSUR) and/or PBRER as required by applicable regulatory agencies.

To facilitate the receipt of lack of efficacy reports, direct or indirect contact through third parties (e.g., the distributor of the product in the intended markets) will be made periodically (e.g., 6 monthly) with an identified primary contact at the healthcare facility receiving supplies of the Dapivirine Vaginal Ring-004, to inquire if there have been any cases of HIV-1 infection in Dapivirine Vaginal Ring-004 users and whether such reports have been submitted through the established reporting channels.

Additionally, healthcare professional surveys, to help understand any knowledge gaps about correct product use and the safety concerns regarding the product, will be undertaken 12 months after product launch and periodically thereafter at a frequency no less than 12 monthly. These surveys will assist with optimisation of the material, if necessary, in order to facilitate a better understanding about the risks associated with product use.

User Guide

The User Guide is an educational material that will instruct the user and her partner(s), if applicable, on how to properly use the Dapivirine Vaginal Ring. It will also provide information on the importance of the early recognition

and treatment of genital infections as well as the signs and symptoms associated with acute HIV infection to potentially limit the use of the Dapivirine Vaginal Ring in women who are suspected of being HIV infected.

Objectives:

The objective of the User Guide is to provide relevant health information to the user and her partner(s), if applicable, regarding the safety concerns summarized in Table Part II: Module SVIII-1, and to minimise potential adverse outcomes in the user. It will contain explanations on how to use the product appropriately emphasizing the importance of the correct use of the product, including adherence to product use, adherence to safer sex practices, and avoidance of vaginal practices.

Rationale for the additional risk minimisation activity:

An illustrative instruction for the user is proposed because reading capabilities may vary across the population using the Dapivirine Vaginal Ring, and simple, validated language supported by icons is likely needed to ensure all women understand how to properly use the product. The User Guide addresses all safety concerns, and, in addition, it contains language requesting the user to consult her HCP regarding use during pregnancy and breastfeeding.

Target audience and planned distribution path:

The ring user and her partner(s), if applicable. Counselling is to be provided by HCPs before the first-time prescription of the product and as needed afterwards. The Applicant has submitted the material to the respective in-country regulatory authorities that have already approved the Dapivirine Vaginal Ring for use. Approval is being sought to make these materials available electronically on the dedicated Dapivirine Vaginal Ring website, accessible to consumers. Distribution pathways need to be negotiated with in-country regulatory authorities but materials could potentially be distributed with product shipment, during end-user workshops and during product demonstration sessions.

Plans to evaluate the effectiveness of the interventions and criteria for success:

At the first 3-month visit following the visit at which the vaginal ring was first prescribed the prescriber will confirm in a randomly selected number of users, the user's understanding of correct product use and when a lack of understanding is demonstrated, this assessment will be repeated at the next scheduled follow up visit. This assessment will be undertaken in the form of a survey. It is expected that 100% of users will demonstrate an understanding of correct product use at the time of the second assessment.

Additionally, healthcare professional surveys to help understand any knowledge gaps in user knowledge about correct product use will be undertaken periodically to allow optimization of the User Guide when appropriate. Formal user testing studies of materials may also be undertaken dependent on feedback received from HCP's providing counselling. It was envisaged that a log was to be maintained at the main pharmacy where the product will be dispensed and that this log would track distribution of the User Guide, however this no longer is feasible given the already overburdened health care systems in the target markets, especially considering the impact of the current COVID-19 pandemic, thereby potentially leading to unreliable information.

V.3 Summary of Risk Minimisation Measures

Table Part V-3: 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
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:	Additional pharmacovigilance activities:

1.8.2 Risk Management Plan

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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)*	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
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		

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR DAPIVIRINE VAGINAL RING (DAPIVIRINE)

This is a summary of the RMP for the Dapivirine Vaginal Ring. The RMP describes important risks that a women may experience while using the Dapivirine Vaginal Ring. The plan explains how these risks can be minimised, and how more information will be collected to better understand the risks and unknown effects caused by use of the Dapivirine Vaginal Ring.

This summary of the RMP for the Dapivirine Vaginal Ring should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

A Patient Information Leaflet and User Guide containing information about the safe use and possible side effects is provided to women who decide to use the Dapivirine Vaginal Ring.

Healthcare professionals will also receive more detailed information to guide the appropriate use in those women who decide to use the Dapivirine Vaginal Ring. This guide will be adapted for the different countries where the Dapivirine Vaginal Ring is marketed (HCP Guide – country specific).

I THE MEDICINE AND WHAT IT IS USED FOR

The medicine contained in the vaginal ring is called dapivirine. This medicine makes it more difficult for the most common form of the HIV, HIV-1, to multiply inside human cells and so prevents HIV infection during vaginal sex. It is intended to be used in sexually-active women, who are 16 years of age and older, and who also use safer sex practices. The Dapivirine Vaginal Ring is placed inside the vagina where the dapivirine is slowly released. Only small amounts of dapivirine are absorbed into the blood and rest of the body.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Risks that have already been identified or possible risks that may be due to use of the Dapivirine Vaginal Ring and what steps will be taken to limit these risks as far as possible, as well as what will be done to better understand these risks, are described below.

Steps that can be taken to limit these risks are:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet for users of the Dapivirine Vaginal Ring, and a document called the SmPC which is intended for HCPs.
- Important advice on the medicine's packaging.
- The authorised pack size – the amount of medicine in a pack is chosen to make sure that the medicine is used correctly.
- The medicine's legal status – for example, whether a prescription is needed to get the medicine.

The points mentioned above describe the standard (routine) steps that, when taken together, help to reduce (minimise) risks when using the Dapivirine Vaginal Ring (routine risk minimisation measures).

Additional measures to minimise risks are described in the section below as additional risk minimisation measures.

1.8.2 Risk Management Plan

The additional risk minimisation measures will include the use of educational materials such as an HCP and a User Guide to promote adherence to correct product use and to minimise any potential harm.

The HCP Guide will provide educational information to HCPs on the correct use of the product, explain what information is unknown and any risks associated with the product. The information is also provided to help the HCP to counsel a potential user and if applicable, her partner(s).

The HCP Guide will explain the following key points which can be used during counselling of users:

- The importance of continuous use of the vaginal ring during one month and immediate replacement of the Dapivirine Vaginal Ring with a new ring after 1 month.
- The Dapivirine Vaginal Ring should be used in combination with safer sex practices and that it can only protect against HIV infection from vaginal sex.
- Because limited information is known about the effect of vaginal practices such as douching and dry sex practices on dapivirine, it is recommended to avoid any vaginal practices which may potentially interfere with the Dapivirine Vaginal Ring.
- The importance of regular monitoring of HIV status to avoid starting or continuing to use the Dapivirine Vaginal Ring if HIV infected, and what signs and symptoms to look out for during HIV seroconversion (early stages of HIV infection).
- The Dapivirine Vaginal Ring does not prevent pregnancy and does not protect against transmission of other STIs.
- The importance of recognizing and receiving treatment early when STIs or other infections in the vagina occur, which might increase the risk of HIV infection.
- Provide advice on what actions to take in case the Dapivirine Vaginal Ring accidentally falls out of the vagina or is damaged.
- Information that it is not known if the Dapivirine Vaginal Ring is safe to use in women who are pregnant.

The User Guide is an educational material developed for the ring user and will instruct her and her partner(s), if applicable, on how to properly use the Dapivirine Vaginal Ring and mention the relevant safety concerns associated with the product. Key messages in the User Guide can also be used by the HCP during counselling of a prospective vaginal ring user.

The following information will be included:

- A description of what a normal Dapivirine Vaginal Ring looks like and what to do if the ring is damaged or broken or looks different to what is expected.
- An instruction that the Dapivirine Vaginal Ring should only be inserted into the vagina.
- The Dapivirine Vaginal Ring may only protect from HIV-1 during vaginal sex and does not protect from HIV-1 infection during anal sex or other forms of sexual contact as well as other ways of becoming infected with HIV (e.g., sharing needles when using recreational drugs).
- The Dapivirine Vaginal Ring does not protect a man from getting HIV-1 infected.
- Safer sex practices (such as use of condoms) should always be used at the same time as using the Dapivirine Vaginal Ring and that male and female condoms can be safely used together with the Dapivirine Vaginal Ring.

- The Dapivirine Vaginal Ring should be kept in the vagina at all times, (even during menstruation and especially during vaginal sex), until it is replaced with a new one after 1 month.
- It is safe to use the Dapivirine Vaginal Ring with tampons during menstruation. If tampons are used and later removed, it should be ensured not to accidently remove the vaginal ring as well.
- If the Dapivirine Vaginal Ring accidently falls out or is removed and this happens in a clean place (e.g., in the bed or in a cloth), the vaginal ring should immediately be rinsed in clean water and inserted again into the vagina. If the vaginal ring has touched something dirty (e.g., toilet) the vaginal ring should not be re-used but rather a new vaginal ring has to be inserted.
- The Dapivirine Vaginal Ring does not prevent pregnancy.
- Instructions to inform the HCP about any vaginal products regularly used to clean the vagina.
- A recommendation not to use products to clean the vagina when using the Dapivirine Vaginal Ring.

Additionally, the User Guide will provide information on what to do if the user thinks she may be HIV infected and what the signs and symptoms are of early HIV infection, as well as what to do if she suspects she may be pregnant or wishes to become pregnant. Testing of a user's understanding on how to use the product correctly will be undertaken from time to time.

If important information about the safe use of the Dapivirine Vaginal Ring is not yet known or available, it is listed under "missing information" below.

In addition, several sources of information are regularly reviewed to look for reports of "side effects" or "adverse reactions" in women who are using the Dapivirine Vaginal Ring. Any safety issues in connection with the Dapivirine Vaginal Ring are assessed, and if necessary, immediate action can be taken, in addition to usual activities to ensure the safe use of the product. These activities are called routine PV activities.

II.A List of Important Risks and Missing Information

Important risks of the Dapivirine Vaginal Ring are risks that users (and their partners, if applicable) should be aware of. Risks may be considered important identified or potential risks. Identified risks are risks for which there is enough proof of a link between the risk and the use of the Dapivirine Vaginal Ring. Potential risks are risks for which there is not enough proof of a link and therefore further information should be collected to better understand the risk.

The most important identified risk is becoming HIV-1 infected because of incorrect use of the Dapivirine Vaginal Ring and not using it in combination with other safer sex practices.

It is also important to understand that not everything is known about the Dapivirine Vaginal Ring. Information that was not collected before and may need to be collected is considered missing information.

Potential risks and missing information include the following:

- Developing resistance to this type of medicine and medicines closely related to it. If women continue to use the Dapivirine Vaginal Ring after unknowingly becoming infected with HIV-1, the HIV in the body may undergo changes and may make other medicines that are used to treat HIV infection less effective, (potential risk).
- The possibility of developing an infection in the lower belly (pelvic region) if there is an unrecognized infection in the vagina which is not treated soon enough, (potential risk).
- How safe the medicine is when used by women who are pregnant (missing information).

- Whether the use of other vaginal medicines (such as clindamycin and metronidazole) together with the Dapivirine Vaginal Ring affects either medicine or causes side effects because these medicines are used at the same time.

Table II-1: Lists of Important Risks and Missing Information

List of important risks and missing information	
Important identified risks A risk that has adequate proof (evidence) of being linked to the Dapivirine Vaginal Ring and could affect the balance between the benefit of using the Dapivirine Vaginal Ring compared with experiencing the risk	The risk of becoming infected with HIV-1 if the Dapivirine Vaginal Ring is not used properly and is not used in combination with safer sex practices.
Important potential risks A risk where there is a suspicion but no confirmation of a link between the risk and the use of the Dapivirine Vaginal Ring that could affect the balance between the benefit of using the Dapivirine Vaginal Ring versus experiencing the risk	• Developing resistance to this type of medicine and medicines closely related to it. If continuing to use the Dapivirine Vaginal Ring after unknowingly becoming infected with HIV-1, the virus may undergo changes and may make other medicines that are used to treat HIV infection less effective. • The possibility of developing an infection in the lower belly (pelvic region) if an infection in the vagina is not treated soon enough.
Missing information Information about use of the Dapivirine Vaginal Ring which is not yet well understood	• How safe the medicine is when used in women who are pregnant. • Whether the use of other vaginal medicines (such as clindamycin and metronidazole) together with the Dapivirine Vaginal Ring affects either medicine or causes side effects because these medicines are used at the same time.
HIV-1 = human immunodeficiency virus type 1	

II.B Summary of Important Risks

Table II-2: Summary of important risks and missing information

Summary of important risks and missing information	
Important identified risk: HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use	
Evidence for linking the risk to the medicine Clinical studies have showed that if you use the Dapivirine Vaginal Ring correctly, the risk of becoming infected with HIV-1 is less.	The Dapivirine Vaginal Ring does not prevent HIV-1 infection in all of the women who use the Dapivirine Vaginal Ring. Clinical studies showed that the Dapivirine Vaginal Ring prevented HIV-1 infection in approximately 30% of all women who participated in those trials, and in women older than 21 years of age the Dapivirine Vaginal Ring prevented HIV-1 infection in 42.9%. There are several possible reasons for this result, including not using the Dapivirine Vaginal Ring all the time as instructed and not using additional safer sex practices. The Dapivirine Vaginal Ring does not protect against STIs other than HIV-1. Safer sex practices will protect against other STIs. Furthermore, it is unknown if an untreated STI will reduce the ability of the Dapivirine Vaginal Ring to protect against HIV-1 infection. It is also unknown what effect the use of products to clean the vagina or prepare the vagina before sexual activity (vaginal practices) can have on the Dapivirine Vaginal Ring, and whether this would make the medicine less effective in preventing HIV-1 infection, therefore, it is not recommended to use such practices when using the Dapivirine Vaginal Ring.
Risk factors and risk groups	In general, all users who do not use the Dapivirine Vaginal Ring as instructed will have less protection from getting HIV-1 infection when having vaginal sex. Women between 18 and 21 years of age: Some clinical trials found that the Dapivirine Vaginal Ring did not show the same level of protection from HIV-1 infection for women between 18 and 21 years of age when compared to older women. While there are no known differences in how the Dapivirine Vaginal Ring works in different age groups, the reduced effect of the Dapivirine Vaginal Ring seen in the younger group may be because they were less likely to use the Dapivirine Vaginal Ring correctly, and were also less likely to practice safer sex, since these trials did show that women between 18 and 21 years of age experienced STIs more frequently than older women. It is not known if women who used the Dapivirine Vaginal Ring during clinical trials felt comfortable that it would protect them and therefore took more risks by not also using safer sex practices. These younger women might also engage in vaginal practices and use vaginal medicines to treat vaginal infections.
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Sections 4.1, 4.2 and 4.4. Advice will be provided in the Patient Information Leaflet, Sections 2 and 3, for women who intend to use the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to provide guidance on the best way to use the Dapivirine Vaginal Ring in order to reduce the users' chance of becoming HIV-1 infected.
Additional pharmacovigilance activities	None
Important potential risk: Development of non-nucleoside reverse transcriptase inhibitor resistance in women with unrecognized or acute HIV-1 infection	
Evidence for linking the risk to the medicine	It is currently not known for sure whether using the Dapivirine Vaginal Ring in HIV-1 infected women, increases the chance of the HIV-1 virus changing form (mutating), and thereby possibly making other similar medicines used to treat HIV infection, less effective (development of NNRTI resistance). Results from

Summary of important risks and missing information	
	completed trials showed that apart from one type of NNRTI mutation (namely the E138A mutation), which was higher in the group of women exposed to the Dapivirine Vaginal Ring, the percentage of women who became HIV-1 infected and had any type of NNRTI mutation was similar in women who used the Dapivirine Vaginal Ring or the placebo ring. Additionally, there was a small number but a higher percentage, of women who received the Dapivirine Vaginal Ring who had more than one NNRTI mutation. Overall, the available data suggest a low risk for the Dapivirine Vaginal Ring to cause such changes in the virus. These differences would seem more likely to be due to changes already present in HIV-1 when women were infected however the possibility they may be caused by continuing to use the Dapivirine Vaginal Ring after becoming HIV-1 infected cannot be completely excluded.
Risk factors and risk groups	Women who could potentially be at higher risk are those using the Dapivirine Vaginal Ring and not knowing they are already HIV-1 infected, including those women who do not undergo regular testing to confirm that they are still HIV-negative.
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.4. Advice will be provided in the Patient Information Leaflet, Section 2, for women who intend to use the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to reduce the chances of developing NNRTI mutations.
Additional pharmacovigilance activities	None
Important potential risk: Development of pelvic inflammatory disease (PID)	
Evidence for linking the risk to this medicine	The percentage of women who developed PID who had used the Dapivirine Vaginal Ring in clinical trials was low. Most women who developed PID could be successfully treated and continue using the Dapivirine Vaginal Ring. What is not known is, if a woman has an infection in her vagina and does not receive treatment for it and then continues to use the Dapivirine Vaginal Ring, whether the fact that she has the Dapivirine Vaginal Ring in her vagina can lead to the infection spreading higher up into her belly causing PID.
Risk factors and risk groups	Risk factors for development of PID include, multiple sexual partners, a history of STIs, a history of sexual abuse, recent medical procedures involving the womb or vagina, and use of contraceptive devices in the womb. Adolescent and younger women may also be at higher risk due to differences in their vaginas when compared to older women, and possibly due to taking more risks in their sexual behaviour.
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.4. Advice will be provided in the Patient Information Leaflet, Section 2, for women who intend to use the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to minimise the chances of getting PID and provide advice on symptoms to look out for to assist with early recognition and treatment should a Dapivirine Vaginal Ring user develop PID.
Additional pharmacovigilance activities	None
Important missing information: Safety during pregnancy	

Summary of important risks and missing information	
Risk minimisation measures	Routine risk communication: Guidance will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.6. Advice will be provided in the Patient Information Leaflet, Section 2, for women who plan to become pregnant or may fall pregnant while using the Dapivirine Vaginal Ring. Additional risk minimisation measures: Information will be provided in a Healthcare Professional Guide and a User Guide to make the best possible decision regarding the use of the Dapivirine Vaginal Ring during pregnancy. There is limited information on the use of the Dapivirine Vaginal Ring in pregnant women. As a precaution, it is preferred that the use of the Dapivirine Vaginal Ring during pregnancy is avoided, unless the healthcare provider considers that the woman (and possibly the unborn child too) is at high risk of HIV-1 infection.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: MTN-042 (DELIVER) This trial is ongoing and will collect safety information and monitor the way in which dapivirine is metabolized (absorbed, broken down, and removed from the body) in pregnant women. This trial randomly selected pregnant women to receive either the Dapivirine Vaginal Ring or an oral tablet that is used to prevent HIV infection.
Important missing information: Local drug-drug interaction with clindamycin and metronidazole	
Risk minimisation measures	Routine risk communication: Information will be included in the Prescribing Information (Summary of Product Characteristics) used by healthcare professionals in Section 4.5. Information will be provided in the Patient Information Leaflet, Section 2. Information will be provided in a Healthcare Professional Guide and a User Guide to indicate that there is currently no information on the use of either clindamycin or metronidazole when used in the vagina at the same time as the Dapivirine Vaginal Ring. Users will be reminded to contact their clinic or doctor before using any vaginal medicines at the same time as the Dapivirine Vaginal Ring.
Additional pharmacovigilance activities	None
ARV = antiretroviral; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; NNRTI = non-nucleoside reverse transcriptase inhibitor; PID = pelvic inflammatory disease; PrEP = pre-exposure prophylaxis; TDF = tenofovir disoproxil fumarate; STI = sexually transmitted infection	

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

Study short name: IPM 055 (Implementation Study)

Purpose of the study: Given uncertainties regarding the efficacy of the Dapivirine Vaginal Ring in younger women, this study will assess uptake, and persistence of use over a 12-month period. Additionally, the HIV-1 seroconversion rate will be described. Analyses will be stratified by two age categories, 18-21 years and > 21 years to 25 years. Qualitative assessments of barriers to uptake, adherence, and persistence will be described.

II.C.2 Other Studies in Post-authorisation Development Plan

Study short name: MTN-042 (DELIVER)

1.8.2 Risk Management Plan

Purpose of the study: To describe the maternal and infant safety profile associated with study product (Dapivirine Vaginal Ring-004 or FTC/TDF) exposure during pregnancy and describe the pregnancy outcomes and pregnancy complications associated with such exposure during pregnancy. Additionally, infant levels of study drugs associated with study product exposure during pregnancy will be described and adherence and acceptability to use of either study product will be described.

Part VII ANNEXES

LIST OF ANNEXES

Annex 1 EUDRAVIGILANCE INTERFACE

Annex 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAM

Annex 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Lack of Efficacy Report Form

Dapivirine Vaginal Ring

All confirmed Lack of Efficacy cases should be reported using this form.
This form is intended to be completed by a healthcare professional
Please submit the completed form to IPM-safety@arriello.com

NOTE:
Initial and date any updates to this form including any updates made to the narrative section. Please always send the entire form submitted previously and not just the amended pages.

The information included in this form will be treated as confidential.

I. Report Information

Report type: ☐ Initial ☐ Follow-up **Date of report:** ____ / ____ / ____ *(Example: 29 Feb 2021)*
DD MMM YYYY

Reporter information and contact details:

Name: _____ **Phone:** _____ **Ext:** _____
Professional qualification: _____ **Cell:** _____
E-mail: _____

II. User Information

Country: _____ **Date of Birth:** ____ / ____ / ____
DD MMM YYYY
Marital Status: _____

Race: ☐ Asian ☐ Black ☐ Mixed ☐ Prefer not to say ☐ White
☐ Other, specify: _____

III. Dapivirine Vaginal Ring Use Prior to Seroconversion

Date of first Dapivirine Vaginal Ring insertion			Date of last Dapivirine Vaginal Ring insertion			Last date of Dapivirine Vaginal Ring in situ		
DD	MMM	YYYY	DD	MMM	YYYY	DD	MMM	YYYY

Please provide the batch number for each of the last three Dapivirine Vaginal Rings used

Batch number last vaginal ring used: _____ ☐ NA
Batch number second last vaginal ring used: _____ ☐ NA
Batch number first vaginal ring used: _____ ☐ NA

IV. HIV Diagnosis Information

Date of last negative HIV test: ____ / ____ / ____
DD MMM YYYY
Date of positive HIV test: ____ / ____ / ____
DD MMM YYYY

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Lack of Efficacy Report Form

Dapivirine Vaginal Ring

HIV testing Specify tests used to determine HIV seroconversion	☐ Single HIV Rapid test ☐ Two HIV Rapid tests ☐ Elisa ☐ Other, specify: _____
Was HIV infection confirmed using a confirmatory laboratory test, if so, indicate test used	☐ None ☐ Elisa ☐ HIV RNA PCR ☐ Western Blot ☐ Other, specify: _____

V. Additional Health and Medical Information

1. **Was the user informed about safer sex practices by her healthcare provider?** ☐ Yes ☐ No

   If yes, provide more details:

2. **Since the last visit when the Dapivirine Vaginal Ring was prescribed, did the user engage in any sexual activity other than vaginal intercourse (e.g. anal sex)?** ☐ Yes ☐ No

   If yes, provide more details:

3. **Since the last visit when the Dapivirine Vaginal Ring was prescribed, did the user engage in vaginal intercourse without the Dapivirine Vaginal Ring in situ?** ☐ Yes ☐ No

   If yes, please specify as a percentage of acts of vaginal intercourse, if possible (e.g., 25%, 50%, 100%): _____

4. **Does the user have a main sex partner?** ☐ Yes ☐ No
   a. Does the main partner know that the Dapivirine Vaginal Ring is being used? ☐ Yes ☐ No
   b. Is the HIV status of the main partner known? ☐ Yes ☐ No
   c. If yes, please specify: _____

5. **Since the last visit when the Dapivirine Vaginal Ring was prescribed, did the user engage in vaginal sex with any partners other than the main sex partner partners?** ☐ Yes ☐ No
   a. If yes, please specify how many: _____
   b. Are any sex partners known to be HIV-infected? ☐ Yes ☐ No

6. **Since the last visit when the Dapivirine Vaginal Ring was prescribed, was the ring purposely removed by the user for any reason?** ☐ Yes ☐ No
   a. If yes, please provide reason: _____
   b. What was the longest period of time that the Dapivirine Vaginal Ring was out of the vagina before engaging in the next act of vaginal intercourse? _____

7. **How frequently did the user use condoms at each sex act since the last visit when the Dapivirine Vaginal Ring was prescribed?**

   ☐ Always ☐ More than 50% of the time ☐ Less than 50% of the time ☐ Never

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Lack of Efficacy Report Form

Dapivirine Vaginal Ring

8. Since the last visit when the Dapivirine Vaginal Ring was prescribed, was the user treated for any STI?	☐ Yes	☐ No
a. If yes, on how many occasions: _____		
b. Indicate the aetiological diagnosis of the STI(s), if known: _____		
c. If known, provide details on syndromic treatment or specific treatment received for each STI: _____		
9. Indicate any Contraceptive method(s) used since the last visit when the Dapivirine Vaginal Ring was prescribed:		
☐ Combined contraceptive pill ☐ Condoms ☐ Depo-medroxyprogesterone injection ☐ Norethisterone injection		
☐ Levonorgestrel implant ☐ IUCD non-hormonal ☐ IUCD hormonal ☐ Other: specify _____		
10. Since the last visit when the Dapivirine Vaginal Rings was prescribed, has the user experienced menstruation? If yes, answer the following:	☐ Yes	☐ No
a. Did she have vaginal intercourse during menstruation?	☐ Yes	☐ No
b. Was the Dapivirine Vaginal Ring in situ at all times during menstruation?	☐ Yes	☐ No
c. Did she use tampons during menstruation?	☐ Yes	☐ No
11. Since the last visit when the Dapivirine Vaginal Rings was prescribed, did the user use any medicinal vaginal products?	☐ Yes	☐ No
a. If yes, specify intravaginal medicinal product: _____		
b. If yes, was the Dapivirine Vaginal Ring used concurrently?	☐ Yes	☐ No
12. Since the last visit when the Dapivirine Vaginal Ring was prescribed, did the user engage in any customary/traditional vaginal practices (e.g. use of herbal vaginal products)?	☐ Yes	☐ No
If yes provide more details: _____		
13. Has the user's sexual behavior changed since she started using the Dapivirine Vaginal Ring?	☐ Yes	☐ No
If yes, please provide more details (e.g., less frequent condom use, more sex partners, etc.): _____		
14. Has the user ever experienced accidental expulsion of the Dapivirine Vaginal Ring?	☐ Yes	☐ No
If yes provide more details: _____		

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Lack of Efficacy Report Form

Dapivirine Vaginal Ring

15. Has the user undergone antiretroviral drug resistance testing? ☐ Yes ☐ No

If yes provide the test results, if available:

VI. Action taken by healthcare provider

IMPORTANT: Dapivirine Vaginal Ring must be discontinued upon confirmation of HIV-1 seroconversion

☐ Dapivirine Vaginal Ring use discontinued ☐ Any other action taken?

Please specify:

VII. Medical History

Pertinent medical history (please also include any relevant medical history from sex partner[s]):

Healthcare provider (reporter)

I have verified the data on this report and have determined they are accurate and compatible with source documents/information provided by the user.

By submitting this document, I agree to allow the International Partnership for Microbicides (IPM) and its affiliates to process and store the personal data provided herein only for the purposes of reporting safety information. Personal data are collected, processed, and stored as outlined in our privacy policy.

VIII. Reporter Signature

Reporter Name:	Reporter Signature	Date
		/ / DD MMM YYYY

Annex 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Physician educational material:

- The Summary of Product Characteristics
- Healthcare Professional Guide

The patient information pack:

- Patient Information Leaflet
- A User Guide

Draft key messages of the additional risk minimisation measures for the Healthcare Professional Guide and User Guide are provided below.

Healthcare Professional Guide

This template summarizes key information on safety concerns of the Dapivirine Vaginal Ring for use by healthcare professionals when counselling and advising potential ring users and when reinforcing information previously provided to existing users. It is intended to facilitate the safe and correct use of the Dapivirine Vaginal Ring and includes the following messaging:

1. <u>The Dapivirine Vaginal Ring forms part of a comprehensive HIV-1 prevention strategy</u>

   The Dapivirine Vaginal Ring:

   - is indicated for use in HIV-uninfected women 16 years and older.
   - alone is not fully effective in reducing the risk of HIV-1 infection. An approximately 30% reduction in the risk of HIV-1 infection was shown in the clinical Phase III program.
   - is only effective in reducing the risk of HIV-1 infection during vaginal intercourse.
   - should be offered only after comprehensive counselling on safer sex practices and a discussion on the most effective and safe option of HIV prevention tools suitable for the women to consistently adhere to using it.
   - should always be used with condoms.

2. <u>Adherence to the correct use of the Dapivirine Vaginal Ring</u>

   Risk reduction of HIV-1 infection is correlated with adherence to the correct use of the Dapivirine Vaginal Ring. Advise user on the following:

   - To continuously use the Dapivirine Vaginal Ring over the period of one month and follow with immediate insertion of a new ring.
   - The Dapivirine Vaginal Ring must remain in-situ during vaginal intercourse.
   - The Dapivirine Vaginal Ring should not be removed at the time of menses.
   - Tampons may be used; however, the user should be cautioned to not accidentally remove the ring when removing the tampon.

- In the event of accidental expulsion or removal in a clean environment, the Dapivirine Vaginal Ring may be rinsed in clean water and immediately re-inserted.
- If expulsion or removal occurred in an unhygienic area, the Dapivirine Vaginal Ring should be placed in the empty ring pouch or wrapped in tissue or toilet paper and disposed of in a refuse bin. A new ring should be inserted immediately.
- If the Dapivirine Vaginal Ring is damaged or broken it should not be inserted or reinserted. The incident should be reported to the healthcare professional.
- To report any problems associated with ring insertion (such as discomfort or pain) to the healthcare professional, if these symptoms do not resolve after repositioning of the Dapivirine Vaginal Ring.

3. Risk of HIV resistance

   Use of the Dapivirine Vaginal Ring in the presence of HIV-1 infection could potentially lead to the selection of HIV-1 mutations associated with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance and may limit future options for HIV treatment.

   To reduce the risk of the Dapivirine Vaginal Ring being used in the presence of HIV-1 infection, the following steps are advised:

   - Prior to prescribing the Dapivirine Vaginal Ring for initial use, the user must have a negative HIV test(s) per local testing guidelines.
   - If doubt exists about whether the potential Dapivirine Vaginal Ring user could be HIV infected, despite a negative serological test for HIV, consideration should be given to delay introduction of the Dapivirine Vaginal Ring for one month until such time as repeat HIV testing can be done.
   - Use clinical judgment to evaluate the potential risk of not detecting an early HIV infection versus the benefit of providing the Dapivirine Vaginal Ring for HIV-1 prevention.
   - Perform HIV tests at frequent intervals (e.g., at least every 3 months) while using the Dapivirine Vaginal Ring.
   - Counsel the user to report any clinical symptoms consistent with acute HIV infection, especially for recent exposure (< 1 month). If HIV infection is suspected while women are using the Dapivirine Vaginal Ring:
     - Discontinue use of the Dapivirine Vaginal Ring and recall the user after one month to perform HIV tests per local guidelines.
     - Reinforce counselling messages on safer sex practices while the Dapivirine Vaginal Ring is not being used.
     - The Dapivirine Vaginal Ring may be reintroduced if the user has negative HIV tests after one month.
   - Counsel the user to immediately report to a healthcare practitioner if she has a positive HIV test result and to stop use of the Dapivirine Vaginal Ring.

4. Presence of genital infections

   The Dapivirine Vaginal Ring does not protect against sexually transmitted infections (STIs), other than HIV-1 infection.

In addition, the presence of an STI and/or other genital infections is associated with an increased risk of acquiring HIV infection, and if not treated appropriately, these infections may result in an ascending or complicated genital tract infection.

Prior to initiating treatment with the Dapivirine Vaginal Ring, identify and treat any genital infections which may be present, as per local guidelines.

- Counsel the user on the signs and symptoms that may be associated with genital infections such as: STIs, vulvovaginal infections (non-STI related), and pelvic inflammatory disease in order to ensure early identification and treatment of these conditions.
- Provide counselling on safer sex practices per local guidelines.

5. Vaginal practices and vaginal medications

No data are available that describe the effect of vaginal practices on the safety and efficacy of the Dapivirine Vaginal Ring.

- Prior to prescribing the Dapivirine Vaginal Ring, enquire about past and current use of vaginal products and/or vaginal practices.
- Advise that dry sex practices or douching which may potentially interfere with the efficacy or safety of the Dapivirine Vaginal Ring.
- These vaginal practices, in particular douching, may alter the vaginal/genital microflora and could potentially increase the risk of acquiring genital infections/STIs (including HIV).

The concomitant use of the Dapivirine Vaginal Ring and vaginally administered clotrimazole or miconazole used to treat vaginal candidiasis should be used with caution.

No data on the use of other intravaginal medications, such as metronidazole and clindamycin are available.

6. Pregnancy and breastfeeding

Safe use of the Dapivirine Vaginal Ring during pregnancy has not been established.

- The Dapivirine Vaginal Ring does not have contraceptive properties and therefore does not prevent pregnancy.
- If the user does not wish to fall pregnant, counsel on the use of an appropriate contraceptive method.
- The user must be counselled to immediately inform a healthcare practitioner to discuss continued use of the Dapivirine Vaginal Ring in the event of pregnancy.

Use clinical judgment in deciding whether to recommend continued use of the Dapivirine Vaginal Ring in pregnancy after considering the risk of HIV-1 infection during pregnancy and the risk of possible transmission to the unborn or nursing child.

Dapivirine has been shown to be excreted in human breast milk in low concentrations. Infant exposure is expected to be low (less than 1 µg/day).

User Guide

The purpose of this document is to provide the HCP with additional information during counselling of the user and to assist the user in using the Dapivirine Vaginal Ring correctly and safely. Information is also included to inform the user of the importance of early identification and treatment of genital infections while using the Dapivirine Vaginal Ring. Additionally, information is provided to assist with maintaining a high index of suspicion for acute HIV infection and the need for regular HIV testing to limit the duration of Dapivirine Vaginal Ring use after HIV infection.

1. General information on the use of the Dapivirine Vaginal Ring includes the following messaging:
    - A description of what an unused Dapivirine Vaginal Ring is expected to look like, ie an off-white vaginal ring that is easy to bend
    - The user must have tests which show that they are HIV negative before starting to use the Dapivirine Vaginal Ring and regular HIV testing every 3 months should be done to ensure that the ring is not used if already HIV infected.
    - The Dapivirine Vaginal Ring reduces the chance of a woman getting a HIV-1 infection during vaginal sex.
    - The Dapivirine Vaginal Ring does not protect a man from getting HIV-1 infected.
    - The Dapivirine Vaginal Ring does not prevent pregnancy.
    - The Dapivirine Vaginal Ring is for vaginal use only and must be used continuously for a month until it is replaced with a new ring. If the ring is taken out, the user is no longer protected from HIV-1 infection during vaginal intercourse.
    - The Dapivirine Vaginal Ring should be kept in the vagina (even during menstruation) until it is replaced with a new one after 1 month.
    - It is safe to use the Dapivirine Vaginal Ring with tampons during menstruation. If tampons are used, take care not to accidently also remove the vaginal ring when removing the tampon.
    - The Dapivirine Vaginal Ring should always be used with a male or female condom.
    - Instructions are provided for ring insertion, including the correct positioning of the user to assist with vaginal ring insertion, ring re-insertion and replacement as well as the disposal of the used vaginal ring.
    - Instructions are provided to not use the Dapivirine Vaginal Ring if it is broken, damaged or looks different to what would be expected when the packaging is first opened, if the user knows that they are HIV infected, or is using another type of vaginal ring. Users are also instructed to report any such incidents to the clinic/doctor.
    - The Dapivirine Vaginal Ring may change colour when it comes into contact in with blood or vaginal fluid during use.
    - The Dapivirine Vaginal Ring does not protect you from HIV-1 infection during anal sex or other ways of getting HIV, such as sharing of needles with a HIV infected person.
    - Instructions are provided in terms of what to do should the Dapivirine Vaginal Ring accidently fall out or is removed. If this happens in a clean place (e.g., in the bed or in a cloth), users should immediately rinse the vaginal ring in clean water and can reinsert it into the vagina. If the vaginal ring has touched

something dirty (e.g., toilet) instructions are not to reuse the vaginal ring but rather insert a new vaginal ring.

- The user is also instructed to inform their doctor about any vaginal products they regularly use to clean the vagina and that it is not recommended to use products to clean inside the vagina when using the Dapivirine Vaginal Ring.

2. A section is included which advises the user on what to do if they think they may be HIV-1 infected:
   - If you think you were exposed to HIV, inform your clinic/doctor straight away. They may want to do more tests to make sure you are still HIV negative.
   - If you continue to use the Dapivirine Vaginal Ring while being HIV infected, the HIV may undergo changes which may make it more difficult to treat with available anti-HIV treatments.
   - Basic HIV tests may miss an infection in the early stages. Signs and symptoms of early HIV infection are similar to a flu-like illness. These may be signs of HIV infection:
     - Tiredness
     - Fever
     - Joint or muscle aches
     - Headache
     - Vomiting or diarrhoea
     - Rash
     - Night sweats
     - Enlarged lymph nodes in the neck or groin
   - Tell your healthcare provider about any flu-like illness – either in the month before starting to use the Dapivirine Vaginal Ring, or at any time while using it, especially if you think you may have been exposed to HIV.
3. A section is included which advises on what to do if the user thinks they may have a vaginal infection or sexually transmitted infection
   - The Dapivirine Vaginal Ring does not protect against sexually transmitted infections other than HIV-1 infection.
   - If you suspect you may have a vaginal infection or sexually transmitted infection visit your clinic/doctor for treatment. If left untreated, these infections make it easier for HIV to infect you.
   - Early treatment of these infections may also prevent the spread of infection to other female organs higher up in your abdomen.
   - Symptoms which may indicate an infection include itching in your vagina, discomfort or pain and a discharge from your vagina, and possibly pain or discomfort during sex.
   - Pelvic inflammatory disease is an infection of the female organs in your belly. It usually occurs when sexually transmitted bacteria spread from your vagina to your other female organs higher up in your abdomen.

Contact your clinic/doctor immediately if you experience:

- Pain/severe pain in your lower belly.
- A discharge, with unpleasant smell, from your vagina.
- Pain or bleeding during sex.
- Fever, sometimes with chills.
- Painful or difficulty in emptying your bladder.
- Nausea and vomiting, with an inability to keep anything down.

4. A section is included regarding important matters which might arise requiring the user to contact their clinic/doctor. Users are instructed to contact a clinic/doctor if they are using the Dapivirine Vaginal Ring and they:
    - Miss a period (menstruation).
    - Think you may be pregnant or plan to fall pregnant.
    - Have questions or concerns about ring use.
    - Have pain or discomfort after inserting the ring.
    - Think you may have bene exposed to HIV.
5. A frequently asked questions section is also included in the User Guide and includes the following additional messaging not covered in earlier sections:
    - What to do if the user suspects that she is pregnant - ie remove the ring and contact the clinic/doctor immediately for advice. Discuss other HIV prevention methods with your clinic/doctor.
    - Confirmation is provided that the Dapivirine Vaginal Ring should not be removed before vaginal sex.
    - Confirmation is provided that it is not possible for the ring to get lost inside the user.
    - Confirmation is provided that the Dapivirine Vaginal Ring can be used with any form of contraception/birth control, other than vaginal rings containing contraceptives or diaphragms.