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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

Dapivirine Vaginal Ring 25 mg

International non-proprietary name: dapivirine

Procedure No. EMEA/H/W/002168/0000

### Note

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



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## List of abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AEOI	Adverse event of interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMI	Body mass index
cfu	Colony forming units
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C <sub>max</sub>	Maximum plasma concentration
CTM	Clinical Trial Manufacturing
CVF	Cervicovaginal fluid
CYP	Cytochrome P450
DoE	Design of experiments
DSC	Differential scanning calorimetry
DSMB	Data and Safety Monitoring Board
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FTC	Emtricitabine
FT-IR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GVS	Gravimetric vapour sorption
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HPLC	High performance liquid chromatography
IC <sub>99</sub>	99% inhibitory concentration
IC <sub>99</sub> BaL	99% inhibitory concentration against the HIV-1BaL strain
ICH	International Council for Harmonisation
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES	Inductively coupled plasma atomic emission spectroscopy
IP	Investigational product
IPC	In-process control
IPM	International Partnership for Microbicides

KF	Karl Fischer titration
LDPE	Low density polyethylene
MCC	Medicines Control Council
MEB	Medicines Evaluation Board
m-ITT	Modified intent-to-treat
MPA	Medical Products Agency
MTCT	Mother-to-child transmission
MTD	maximum tolerated oral dose
NA	Not applicable
NMR	Nuclear magnetic resonance
NMT	Not more than
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRA	National Regulatory Authority
PDE	Permitted daily exposure
PDMS	Polydimethylsiloxane
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
PrEP	Pre-exposure prophylaxis
QbD	Quality by design
QC	Quality Control
QTPP	Quality target product profile
RH	Relative Humidity
RNA	Ribonucleic acid
RT	Reverse transcriptase
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of product characteristics
STI	Sexually transmitted infection
SVF	Simulated vaginal fluid
TAMC	Total aerobic microbial count
TasP	Treatment as prevention
TDF	Tenofovir disoproxil fumarate
TEAE	Treatment-emergent adverse event
TGA	Thermogravimetric analysis
TYMC	Total combined yeasts/moulds count
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States (of America)
USP	United States Pharmacopoeia
UV	Ultraviolet
V	Volume of distribution
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
XRPD	X-ray powder diffraction

# 1. Background information on the procedure

## 1.1. Submission of the dossier

The applicant International Partnership for Microbicides Belgium AISBL submitted on 22 June 2017 an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organisation for Dapivirine Vaginal Ring 25 mg.

The eligibility by the World Health Organisation was agreed-upon on 28 April 2016.

Dapivirine Vaginal Ring 25 mg will exclusively be intended for markets outside the European Union.

The applicant applied for the following indication:

*"The Dapivirine Vaginal Ring is indicated for reducing the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-uninfected women 18 years and older in combination with safer sex practices."*

### **The legal basis for this application refers to:**

This application is submitted under Article 58 of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to Article 8(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

This dossier is submitted under Article 58 of (EC) No 726/2004 to the European Medicines Agency (EMA), for a scientific opinion in the context of cooperation with the World Health Organisation.

### **Information on Paediatric requirements**

The requirements of the paediatric legislation (Regulation (EC) No 1901/2006) do not apply to Article 58 applications.

A trial in adolescents is was performed (MTN-023/IPM 030). MTN-023/IPM 030 was a multi-center, two-arm, randomized, double-blind, placebo-controlled pharmacokinetic Phase IIa trial evaluating the safety of the dapivirine vaginal ring in adolescents aged 15-17 years. The study enrolled 96 healthy, HIV-uninfected adolescent females, 15 - 17 years old (inclusive). Participants were randomized in a 3:1 ratio to one of the following study groups: dapivirine (25 mg) vaginal ring or placebo vaginal ring. Each participant will be followed for approximately 25 weeks (24 weeks on study product and a final phone call one week after end of study product use). Secondary objectives of the trial include evaluating acceptability and adherence to a dapivirine (25 mg) vaginal ring when inserted once every 4 weeks for a 24 week period in HIV uninfected adolescent females, and to evaluate local and systemic dapivirine exposure.

The Dapivirine Vaginal Ring was well tolerated in adolescent females when inserted once every 4 weeks and used continuously during 24 weeks. The type and nature of adverse events reported were similar to those reported in trials conducted in women of reproductive age 18 years and older.

### **Scientific advice**

The applicant received the following Scientific advice (including parallel consultations with FDA and WHO Art 58 Advices) on the development relevant for the indication subject to the present application:

<b>Date</b>	<b>Reference</b>	<b>SAWP co-ordinators</b>
19 August 2010	EMA/CHMP/SAWP/686625/2010  Procedure No.: EMA/H/SA/1669/1/2010/III	Dr Armin Koch and Prof. Beatriz Silva Lima were appointed as coordinators.
16 September 2011	EMA/CHMP/SAWP/945073/2011  Procedure No.: EMA/H/SA/1669/1/2010/III	Dr Elmer Schabel and Dr Caroline Auriche were appointed as coordinators.
20 July 2013	EMA/CHMP/SAWP/607732/2013  Procedure No.: EMA/H/SA/1669/1/FU/2/2013/II	Dr Mair Powell and Dr Armin Koch were appointed as coordinators.
24 August 2014	EMA/CHMP/SAWP/629621/2014  Procedure No.: EMA/H/SA/1669/1/FU/3/2014/II	Dr Mair Powell and Dr Armin Koch were appointed as coordinators.
25 May 2015	EMA/CHMP/SAWP/467443/2015  Procedure No.: EMA/H/SA/1669/1/FU/4/2015/II	Prof. Dieter Deforce and Dr Armin Koch were appointed as coordinators.
04 March 2016	EMA/CHMP/SAWP/271072/2016  Procedure No.: EMA/H/SA/1669/1/FU/5/2016/SME/I	Prof. Dieter Deforce and Dr Mair Powell were appointed as coordinators.

The advices pertained to the following quality, preclinical, and clinical aspects:

- Changes in manufacturing and bridging strategy to support the medicinal product for Phase 3 and for commercial supply. Stability data and shelf life. Specifications and characterisation.
- Nonclinical toxicology, virology, safety pharmacology and pharmacokinetic studies. Lack of preclinical or clinical metabolite identification studies or excretion balance studies. Lack of studies on the photosensitization potential. Adequacy of a 6-month intravaginal study with transgenic animals such as Tg(rasH2) to evaluate the carcinogenic potential of Dapivirine when used as microbicide.

- The clinical pharmacology program including studies to evaluate local drug-drug interactions, cardiac safety assessment, condom functionality, male tolerance and special populations.
- Whether the data generated from Phase I and II support progression to phase III. The adequacy of PK and safety data generated from phase 1/2 study IPM-013 to support use past 28 days and instructions regarding ring expulsion or accidental removal in phase III. The instructions in the proposed Phase III study related to ring expulsion or ring loss.
- The Phase III strategy in terms of number of pivotal trials, study designs, endpoints, HIV Testing Algorithm for determining the HIV infection status, population also related to the age range to be included, study duration, safety endpoints, assessment of adherence, and statistical analyses.
- The evidence base to support approval in adolescents and post-menopausal women.
- The design of the clinical study to support use of the Dapivirine Vaginal Ring During Menses and with Concurrent Tampon Use.
- Labelling considerations related to post-insertion time to achieve protective levels, insertion of a new ring, dry sex practices and plan to use PK and residual dapivirine measurement in the ring to characterise dapivirine delivery for labelling.
- The plan to deal with assumed non-adherence observed at research centre 03 in the IPM-027 study by discontinuing all participants at Research Center 03 and increasing the sample size to restore the lost trial power. In addition, the Applicant discussed the possibility to conduct adherence adjusted analyses to support benefit risk assessment.
- The plan to conduct the efficacy and safety analyses of IPM 027 (earlier than originally anticipated) to align these analyses temporally with the release and public dissemination of MTN-020 results to support an earlier benefit risk assessment.

## **1.2. Steps taken for the assessment of the product**

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik      Co-Rapporteur: Janet Koenig

The application was received by the EMA on	22 June 2017
The procedure started on	13 July 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	28 September 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	2 October 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	13 October 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 Aug 2018
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	



A GCP inspection at 5 sites (clinical investigators, sponsor, CROs) in Uganda, South Africa and the USA between 6 November 2017 and 2 February 2018. The outcome of the inspection carried out was issued on	30 April 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	24 September 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	04 October 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	18 October 2018
SAG (Scientific Advisory Group) were convened to address questions raised by the CHMP on  The CHMP considered the views of the SAG as presented in the minutes of this meeting.	03 December 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 April 2019
The CHMP agreed on 2nd list of outstanding issues to be sent to the applicant on	26 April 2019
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	24 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2 <sup>nd</sup> List of Outstanding Issues to all CHMP members on	11 July 2019
The CHMP agreed on 3rd list of outstanding issues to be sent to the applicant on	25 July 2019
The applicant submitted the responses to the CHMP 3rd List of Outstanding Issues on	29 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the 3 <sup>rd</sup> List of Outstanding Issues to all CHMP members on	11 June 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	22 June 2020
The CHMP agreed on 4 <sup>th</sup> list of outstanding issues to be sent to the applicant on	25 June 2019
The applicant submitted the responses to the CHMP 4 <sup>th</sup> List of Outstanding Issues on	01 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the 4 <sup>th</sup> List of Outstanding Issues to all CHMP members on	09 July 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to	23 July 2020

## 2. Scientific discussion

### 2.1. Problem statement

#### 2.1.1. Disease or condition

The claimed therapeutic indication is:

"The Dapivirine Vaginal Ring is indicated for reducing the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-uninfected women 18 years and older in combination with safer sex practices."

#### 2.1.2. Epidemiology

Since the beginning of the epidemic, more than 70 million people have been infected with HIV, of which about 35 million people have died. Globally, 36.7 million [30.8–42.9 million] people were living with HIV at the end of 2016. An estimated 0.8% [0.7–0.9%] of adults and adolescents aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 25 adults (4.2%) living with HIV and accounting for nearly two-thirds of the people living with HIV worldwide (WHO Global Health Observatory (GHO) data).

Globally, in 2015 there were an estimated 17.8 million women living with HIV (15 and older), constituting 51% of all adults living with HIV. Young women and adolescent girls aged 15–24 are particularly affected, with an estimated 2.3 million adolescent girls and young women living with HIV (60% of all young people living with HIV).

There are significant regional differences in both the new HIV infections among women and in the proportion of women living with HIV (15 and older) as opposed to men, and the gaps are even more notable among young women (aged 15–24) versus young men. In sub-Saharan Africa, women comprised 56% of new infections among adults (15 and older); and the proportion was higher among young women aged 15–24, who made up 66% of new infections among young people.

Specific groups of women are disproportionately affected by HIV. An analysis of studies measuring the pooled prevalence of HIV in 50 countries estimated that, globally, female sex workers are approximately 14 times more likely to be infected than other women of reproductive age.

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

For more information, please refer to <http://www.unwomen.org/en/what-we-do/hiv-and-aids/facts-and-figures>.

#### 2.1.3. Biologic features, aetiology and pathogenesis.

HIV-1 infection is a blood-borne infection. HIV is a retrovirus that infects and replicates primarily in human CD4+ T cells and macrophages. HIV can be transmitted via blood, blood products, sexual fluids, other fluids containing blood, and breast milk. Most individuals are infected with HIV through sexual contact, before birth or during delivery, during breast-feeding, or when sharing contaminated needles and

syringes (intravenous drug users). Sexual intercourse is the most common mode of HIV transmission. The risk of transmission per exposure is low; estimates are on the order of 0.1% per contact for heterosexual transmission, but this varies considerably and increases with concurrent ulcerative STDs and high HIV viral load in the infected partner, e.g. due to no or non-efficient antiretroviral therapy.

#### **2.1.4. Clinical presentation, diagnosis.**

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

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

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

#### **2.1.5. Management**

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

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

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

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

Many women in sub-Saharan Africa live in highly patriarchal societies where they have very limited economic options. Because of this gender and social inequality, they cannot reliably negotiate the use of protective methods during sexual encounters, leaving them vulnerable to sexually transmitted infections, including HIV. The fact that many currently available biomedical prevention methods require partner participation/consent or may be associated with the stigma of HIV infection is a key obstacle to consistent use. This, together with the continued high risk of HIV transmission to women in sub-Saharan Africa makes it especially important to develop additional options that enable women to reduce their risk of

HIV infection without the need for male partner negotiation. An effective vaginal microbicide could offer an additional urgently needed female-initiated option for prevention of HIV-infection.

### ***About the product***

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

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

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

The proposed use of Dapivirine Vaginal Ring is as follows:

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

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

### ***Type of Application and aspects on development***

The product development for dapivirine vaginal ring consisted of five Phase I pharmacokinetic and safety trials, two Phase II placebo-controlled trials (IPM 015 and MTN-024/IPM 031), and two pivotal efficacy and safety Phase III trials (IPM 027 and MTN-020). Several additional studies are either ongoing (including two Phase IIIb open-label extension trials IPM 032 (DREAM) and MTN-025 (HOPE)) or have been completed. The development program has been discussed with CHMP at several occasions.

The EMA reflection paper on the nonclinical and clinical development for oral and topical HIV PrEP (EMA/171264/2012) was published during the development of Dapivirine Vaginal Ring-004 and was taken into consideration for the ongoing development plan.

The 2010 and 2011 procedures were parallel Scientific Advice procedures with the FDA, which also included participants of WHO and selected African National Regulatory Authorities (NRAs). Most of CHMP's advice have been taken into consideration by the applicant. However, CHMP advised against discontinuation of Research Center 03, which was not followed by the applicant, and recommended the continuation of study IPM 027 at least until the data from study MTN-020 have been analysed, well understood and communicated, which was also not followed.

## 2.2. Quality aspects

### 2.2.1. Introduction

The finished product is presented as a vaginal delivery system (silicone ring) containing 25 mg of dapivirine

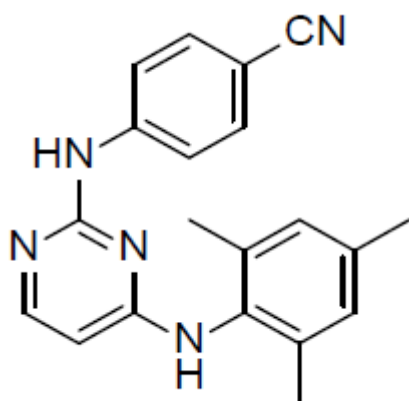
Other ingredients are: dimeticone and silicone elastomer (DDU-4870). The silicone elastomer consists of siloxanes and silicones (dimethyl, vinyl group-terminated), platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane, amorphous fumed crystalline free silica and siloxanes and silicones (dimethyl, methyl vinyl, methyl hydrogen, hydroxyl-terminated).

The product is available in laminated PET-Alu/Adhesive/PP heat-sealed pouches as described in section 6.5 of the SmPC.

### 2.2.2. Active Substance

#### General information

The chemical name of dapivirine is 4-{{[4-(mesitylamino)-2-pyrimidinyl]amino}benzonitrile} corresponding to the molecular formula  $C_{20}H_{19}N_5$ . It has a relative molecular mass of 329.41 g/mol and the following structure:



**Figure 1: active substance structure**

The chemical structure of dapivirine was elucidated by a combination of  $^1H$  and  $^{13}C$  NMR spectroscopy, electrospray ionisation mass spectrometry, Fourier transform infrared spectroscopy, UV spectroscopy, elemental analysis and confirmed by single crystal x-ray crystallography. Dapivirine is achiral.

Dapivirine is a white to off-white/slightly yellow crystalline powder. The solid-state properties of the active substance were investigated by a combination of gravimetric vapour sorption (GVS), thermogravimetric analysis (TGA), differential scanning microscopy, polarised light microscopy, hot stage microscopy, x-ray powder diffraction (XRPD), variable temperature XRPD and single crystal x-ray diffraction. Polymorph screening identified 3 polymorphic forms and an amorphous form. Of these, form I is the most thermodynamically stable and is routinely produced by the manufacturing process. The GVS analysis demonstrates that dapivirine is not hygroscopic. The active substance is practically insoluble in water and only slightly soluble at pH 1.

## ***Manufacture, characterisation and process controls***

Dapivirine is synthesised convergently in synthetic steps using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Potential and actual impurities were well discussed with regards to their origin and characterised. Genotoxic impurities are controlled in starting materials and intermediates in line with ICH M7 and adequate purge data has been provided.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The same route of synthesis has been used throughout development although changes have been made to some solvents, reagents and reaction conditions to improve the efficiency of the process and to reduce the levels of impurities generated. A micronisation step was introduced to improve release properties and ensure even active substance distribution throughout the silicone ring. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in double LDPE bags, sealed and stored within a drum. The LDPE bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

## ***Specification***

The active substance specification includes tests for appearance (visual inspection), identity (FTIR, DSC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), sulphated ash (Ph. Eur.), chloride (titration), particle size distribution (laser diffraction) and microbial enumeration (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set, also in line with available batch data. The limits for residual solvents are acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from several pilot and production scale batches of the active substance manufactured by the proposed commercial process were provided. The results are within the specifications and consistent from batch to batch. Further conforming supportive data from several batches of un-micronised material produced earlier in development was also provided.

## ***Stability***

Stability data from 7 pilot and production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 96 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, identity by DSC, assay, related substances and water content. Particle size distribution and microbial enumeration were also tested on batches at later timepoints. The analytical methods used were the same as for release and were stability indicating. No significant changes to any of the measured parameters and no trends were observed throughout the studies.

Photostability testing following the ICH guideline Q1B was performed on one batch, demonstrating that dapivirine is photostable.

Forced degradation studies were conducted in the solid state at high temperature, and in either acidic, basic or oxidative aqueous solution. Slight degradation was observed under basic conditions and significant degradation was observed under oxidative conditions. These demonstrate that the analytical methods are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 96 months in the proposed container.

### **2.2.3. Finished Medicinal Product**

#### ***Description of the product and Pharmaceutical development***

Dapivirine vaginal delivery system is an off-white, flexible ring containing 25 mg of dapivirine dispersed in a silicone polymer matrix. The finished product is designed to provide delivery of approximately 4 mg of dapivirine topically to the lower female reproductive tract over a period of 28 days. The dimensions of the ring are 56 mm (outer diameter) by 7.7 mm (cross-sectional diameter). The excipients in the formulation are dimeticone and a silicone elastomer system (DDU-4870).

The quality target product profile (QTPP) was defined as a vaginal delivery system suitable for localised sustained release of dapivirine over 28 days. The product should use medical grade excipients, be resistant to swelling and other changes in appearance and performance and should allow for easy insertion, retention, and removal.

Several different dosage forms were developed for delivery of dapivirine to vaginal vault including gels, films and rings. A ring formulation was selected as it provides a convenient option for pre-coital prophylaxis and had met with a high level of acceptance from women in clinical settings. It is intended to be inserted and left in situ for 28 days to provide a prolonged release of dapivirine. The ring is then replaced to ensure continual anti-viral protection.

The critical quality attributes were identified.

The active substance is practically insoluble in aqueous media and is therefore micronised to accelerate dissolution and release from the matrix. Solubility in dimeticone was found to be sufficient to allow wetting of the active substance and dispersion throughout the polymer matrix prior to curing. A range of analytical techniques were used to investigate the active substance properties and distribution following curing including confocal Raman microscopy, scanning electron microscopy and x-ray microtomology with synchrotron radiation. The particles were shown to be evenly distributed throughout the polymer matrix with no difference between core and edge sections in terms of particle size distribution or morphology.

The main component of the finished product is DDU-4870. DDU-4870 is considered to be a novel excipient and details of its production, control, testing procedures, and stability are provided later in this report. In addition, dimeticone is used to pre-disperse the active substance prior to mixing with DDU-4870 and is of Ph. Eur. quality. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report

A bespoke dissolution method was developed as none of the pharmacopoeial methods were viable over the required 28-day analysis period. Either the vaginal ring was too large to be accommodated in the pharmacopoeial apparatus, or significant loss of solvent was observed. Therefore, a method was developed. The proposed dissolution method is able to discriminate between batches made using



different sources of silicone rubber, different curing chemistries, and between micronised and un-micronised active substance. The dissolution profiles of batches used throughout development were shown to be similar using F2 calculations. The dissolution method is considered acceptable for quality control purposes.

The design of the manufacturing process followed QbD principles and was informed by risk assessment of the various process parameters for each unit operation. Parameters for each step were investigated by a combination of univariate and multivariate experiments. For the first 2 steps, parameters are set to ensure homogeneity. DoEs were conducted on factors in the injection moulding step. Statistically significant effects were identified but these were small and unlikely to impact the finished product performance given the wide ranges investigated. Target set-points for the different parameters are well within the ranges studied. No design space is claimed.

The primary packaging is a laminated PET-Alu/Adhesive/PP heat-sealed pouch. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

### ***Manufacture of the product and process controls***

The manufacturing process shown in consists of 4 main steps: masterbatch preparation, pre-mix preparation, injection moulding/curing for ring formation and inspection/packaging. The process is considered to be a non-standard manufacturing process.

The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

The process has been formally validated on 3 consecutive production scale batches. It has been shown that dapivirine is homogeneously distributed throughout the rings and that no in-process control (IPC) for homogeneity is needed after step 2, given the robustness of the process. During development, production scale batches have been manufactured, all producing product of acceptable quality. Therefore, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

### ***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual inspection, cross-sectional and external diameter), identity (HPLC, UV), assay (HPLC), degradation products (HPLC), content uniformity (HPLC), dissolution (in-house with HPLC analysis), weight (gravimetric), compression (compression test), tensile strength (physical stretching) and microbial quality (Ph. Eur.).

There are no specified degradation products, based on batch data, stability data and forced degradation studies where it was demonstrated that dapivirine is very difficult to degrade. The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities which concluded that elemental impurities are sufficiently controlled in the raw materials. Leachables studies on the rings showed that the levels of elemental impurities remained well below the parenteral (worst case) permitted daily exposures (PDEs). Therefore, no controls for elemental impurities are deemed necessary in the finished product specification.

The applicant conducted a risk evaluation for the presence of nitrosamines, considering both active substance and finished product manufacturing processes, excipients and packaging. No risks were identified for any of the components. Extractables and leachables studies on the packaging provide evidence that there is no appreciable risk of contamination with nitrosamines.



The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results were provided for several batches manufactured at 50-100% of production scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

### ***Stability of the product***

Stability data from 10 production scale batches of finished product stored for up to 60 months under long term conditions (30°C / 65% RH) and 5 batches for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. One of these batches was also stored under the long-term conditions expected for an Article 58 procedure (30°C / 75% RH) – up to 48 months' data is available.

Samples were tested for appearance, cross-sectional diameter, external diameter, assay, degradation products, dissolution, weight, compression, tensile strength and microbial limits. Tests were performed at every time-point for 4 of the batches and with reduced frequency for 6 batches which are regarded as supportive. The analytical procedures used are stability indicating.

All test results were within specifications throughout the study under all conditions, despite a slight downward trend in dissolution rate and slight increase in compression. In addition, the applicant has committed to place the first two commercial batches on stability under Article 58 long term conditions (30°C / 75% RH).

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The dissolution rate was adversely affected, showing a reduction in initial release rate and assay also decreased slightly so the product is required to be stored protected from light to avoid this from occurring.

Temperature cycling studies were conducted to assess the impact of temperature excursions during shipping and storage. Samples were cycled without detriment.

Based on available stability data, the proposed shelf-life of 48 months and stored in the original container to protect from light as stated in the SmPC (section 6.3) is acceptable.

### ***Adventitious agents***

No excipients derived from animal or human origin have been used.

### ***Novel excipients***

#### ***DDU-4870***

Although the use of silicone rubbers in medical devices and drug delivery systems is well established, DDU-4870 has not previously been used in any approved medicinal products in the EU and is therefore considered to be a novel excipient.

Adequate in-process controls are applied during the synthesis. Suitable specifications are applied to the raw materials used in the process and adequate information on their production has been provided. DDU-4870 is packaged in polyethylene pails which are certified food-grade. The primary packaging material has no adverse impact on the excipient quality.

### **Specification**

The DDU-4870 specifications applied to the individual components include appearance (visual inspection), identity (FT-IR), particulate analysis (microscopy), extrusion rate (pneumatic gun), microbiological quality (Ph. Eur.), volatile siloxanes (GC), work time (visual inspection) and rheology (rheometer). Tests applied to the cured material consist of specific gravity (density ratio), hardness (durometer), elemental impurities (ICP-OES), tensile strength, elongation and tear strength (all extensometer) and residual platinum (ICP-OES).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data from several batches of the DDU-4870 were provided. The results are within the specifications and consistent from batch to batch.

### **Stability**

Stability data from 5 batches of DDU-4870 stored for up to 24 months under long term conditions (25 °C / 60% RH) and 8 batches stored for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. In addition, re-test data from 16 lots of DDU-4870 stored for up to 3 years was provided. The batches of DDU-4870 are representative of those proposed for commercial finished product manufacture and were packed in the primary packaging proposed for storage.

Based on available stability data, the proposed shelf-life of 12 months stored up to or at 25 °C is acceptable.

## **2.2.4. Discussion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The novel polymer excipient has been adequately described and sufficient data was provided. The non-standard process has been validated in line with the guidelines. Given the extended period of use of the product (28 days) and practical insolubility of the active substance in aqueous media, a bespoke dissolution method was developed. Stability data has been generated from one batch as required for Article 58 procedures to cover use in hotter and more humid parts of the world than the EU. In addition, further stability studies will be conducted on the first two commercial batches.

## **2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## **2.2.6. Recommendations for future quality development**

Not applicable.

## **2.3. Non-clinical aspects**

### **2.3.1. Introduction**

### **2.3.2. Pharmacology**

#### ***Primary pharmacodynamic studies***

Dapivirine is an NNRTI and binds to the p66 subunit of RT, thereby inhibiting its action of DNA synthesis leading to reduced syncytium formation in HIV-1 infected cells. The indication applied for is reducing the risk of infection from male to female. Transmission of infection occurs via semen in which both free virus and infected T-cells are present (cell-free HIV and cell-associated HIV) and both can transmit the infection to target cells. Therefore, antiviral activity should be demonstrated for free virus and for infected cells, leading to reduced infection of target cells.

#### Free virus

In *in vitro* experiments, using laboratory HIV strains X4 and R5, pre-treatment with dapivirine resulted in reduced infection of TZM-bl indicator cells. IC<sub>50</sub> values ranged from 0.15 to 0.84 nM for the different strains. Dapivirine was much more potent in prevention of infection than tenofovir (IC<sub>50</sub> 2.3 to 6.7 µM).

As HIV is also able to infect epithelial and stromal cells present in vaginal and cervical tissue, experiments were performed to determine the ability of dapivirine to block this process. It was shown that dapivirine can effectively block infection of cervical tissue with an IC<sub>50</sub> of 1.5 nM. Near complete inhibition was seen at 10 nM.

Physiological conditions were mimicked by addition of semen or cervical fluid to the *in vitro* test conditions, using free virus and either TZM-bl cells or cervical explants as target for infection. It was shown that dapivirine became less effective in inhibiting infection of TZM-bl cells in the presence of cervical fluid (EC<sub>50</sub> increased from 1.46 to 8.32 nM), and of infection of cervical explant in the presence of semen. However, the differences were not statically significant. Furthermore this effect is not expected to influence the activity of DPV *in vivo*, as the DPV concentration in the vaginal fluid (mean concentration 79.9 µg/ml (243 µM)) was demonstrated to be well in excess to the *in vitro* EC<sub>50</sub> for wt HIV-1 of 3.3 ng/mg (0.9 nM). A further study was performed since underlying data were lacking. This study showed no effect on antiviral activity of dapivirine in the presence of semen or cervical mucus, when tested on TZM-bl cells or ecto-cervical tissue explants in the absence or presence of PM-1 cells.

#### Cell-associated

Antiviral activity was investigated in pre-infected MT-4 and PM-1 cells. After incubation with different concentrations of dapivirine, the activity of supernatant reverse transcriptase was measured. Dapivirine prevented RT activity with EC<sub>50</sub> values of 0.9 nM in MT-4 cells infected with HIV wildtype strain LAI, and with 2.8 to 3.5 nM in PM-1 cells infected with strains X4 and R5. Transmission to target cells was not investigated in these experiments.

Antiviral activity in the more clinically relevant model using peripheral blood mononuclear cells (PBMC) or monocytes/macrophages (M/Ms) freshly isolated from healthy donors showed similar results as in the MT-4 cells.

### Free virus versus cell-associated

An experiment was performed to evaluate the inhibitory activity of dapivirine on infection of target cells, using both free virus (HIV-1<sub>Bal</sub>) and infected cells (PBMCs and macrophages) as source of infection. The test set-up allowed distinction between pre-infected cells and newly infected target cells. It was shown that dapivirine can inhibit infection of target cells from both cell free virus and cell-associated virus, although inhibition was more potent when cell free virus was used. The exact EC<sub>50</sub> values could not be retrieved but are around 1.5 nM for cell free virus and range from 1.8 to 2.3 nM for cell-associated virus. These data indicate that dapivirine is able to inhibit viral infection of cells from both sources as present in semen.

Similar to the previous experiment, it is shown that higher concentrations dapivirine are required to completely block cell-cell transmission of virus (100 nM) than to block free virus from infecting cells (10 nM). For short term treatment of only 24 hours, 10-fold higher drug concentrations were needed to completely block infection. Inhibition of infection was even achieved when dapivirine was added to the cell culture 2 hours after exposure of target cells to virus or infected cells. Continuous exposure to dapivirine is needed for sufficient efficacy.

### In vitro efficacy

The antiviral activity of dapivirine was tested in a panel of group M HIV-1 recombinant isolates and EC<sub>50</sub> values were determined. The EC<sub>50</sub> ranged from less than 0.5 nM (1.67 ng/ml) to 2.6 nM (0.9 ng/ml) for all subtypes tested (A, B, C, D, F and H). the highest EC<sub>50</sub> represents a fold-change of 3.5 as compared to the wild-type strain LAI. Group M viruses containing mutations at positions 98, 101, 106 and 179 showed no significant increase in EC<sub>50</sub> values. However, a group O strain harbouring 3 mutations at positions 98, 179 and 181 did show a significant reduction in activity with a fold-change of 140.

Within group M, subtype E, G, J and K have not been tested (see general question on in vitro efficacy). Also not tested is group N, however since infection is extremely rare with this virus group, this is acceptable.

### Resistance selection

Treatment of wild type infected MT-4 cells with 40, 200 or 1000 nM (13.3, 66.7 or 333 ng/ml) dapivirine resulted in mutated virus breakthrough. The first breakthrough viruses harbored mutations at position 181 (Y181C/I/L), while the mid concentration resulted also Y188L mutant. Mutations at position 190 (G to E) occurred at the highest concentration. A second experiment started with suboptimal dapivirine concentrations which were subsequently increased. Mutation Y 181C was the first to emerge, with L100I, V179F and K101E appearing as concentrations increased. When a mutant strain was used as initial infection (K103N), only additional mutations Y 181C and V179I were observed.

Exposure to dapivirine at low concentrations (0.001 to 100 nM (0.0003 to 33 ng/mL)) resulted in virus breakthrough when MT-4 cells were infected with wild-type HIV-1. The following mutations were found in the RT at positions associated with NNRTI resistance: A98S, V106I, V108A, E138G, V179A, V179I, Y181C, Y181N, G190E and M230I. The study reports for these experiments are not dated, but taken from the document titles, it is anticipated that these experiments were performed in 2003-2005.

More recent experiments (2011 and 2012) were conducted to investigate the selection of resistance mutations after exposure to dapivirine. Three R5 tropic isolates and two clinical isolates were used to infect activated PBMC's. Gradually increasing concentrations up to 1000 nM dapivirine resulted in the emergence of resistance viruses with mutations: K101E, V108I, K103N, E138Q, V179M/E, Y181C and F227Y. When suboptimal concentrations ( $\leq 1$  nM) of dapivirine were used to treat CBMC's infected with clinical isolates of HIV subtypes B and C, the following mutations emerged: V90I, A98S, L100I, K101E, K103M/N, V106I, E138A/G/K/R/E, V179I, Y181C, G190A. Interestingly, although some mutations are

selected in all experiments performed, not all mutations are identical. Therefore all mutations should be considered as possibly of importance in resistance against dapivirine.

From previous experience with other NNRTI treatments of HIV, some mutations have emerged, which play an important role in NNRTI resistance in general (Stanford database). These are L100I, K101P/E, K103N/S, V106A/M, E138K, Y181C/I/V, Y188L/C/H, G190A/S/E/Q, M230L. Combinations of mutations which have proven to confer resistance to NNRTI's are: 179D+103R, 179F+181C, 225H+103N, 227L+106A and 227C+various other.

#### Resistant strains

For the above list of mutations EC50 values should be determined taken into consideration that the concentration of dapivirine in the vaginal fluid ranges from 30 µM to 240 µM (10.000 ng/ml to 80.000 ng/ml). Since this is much higher than the concentration used in any of the experiments selecting for resistance, it is important to know if dapivirine could still be active against the mutant viruses at clinically relevant concentrations. A number of mutant strains was tested which showed that the largest fold-change of 4505 was achieved for a strain with 10 mutations. Overall, the EC50 remained below 100 nM for 80% of the mutant strains. From the antiviral tests to determine EC50 values, the following conclusions can be drawn (see Table 1):

**Table 1 Resistant mutations**

Resistant mutations*	Non-resistant mutations
L100I, K103N, K101P, E138R, Y181C/I/V, Y188L, G190E/Q, F227C, M230I/L, K101E+K103N, K101E+Y181C, V106A+F227C, K103N+Y181C, E138A+F227C, V179F+Y181C, Y181C+G190A, Y181C+F227C	V90I, A98S, K101E, K103M/R/S, V106A/I/M, V108A/I, E138A/G/K/Q, V179A/E/F/I/M, Y181L/N, Y188C/H, G190A/S, F227Y, K103R+V179D, 225H+103N, 227C+106A,

\*It should be noted that resistance is classified as >10-fold change in above table, but it is not clear if this is clinically relevant, since the largest fold change of 4500 still represents a EC50 value far below clinically relevant.

As opposed to the statement of the applicant that resistance to dapivirine is typically dependant on more than one substitution in reverse transcriptase, there are 13 mutations which can be viewed as potentially inducing resistance to dapivirine, and 8 combinations of 2 mutations.

#### Clinical isolates

A selection of 788 clinical HIV-1 isolates was tested for sensitivity to dapivirine. Of these, 433 were classed as NNRTI resistant. A cut-off for resistance of >10-fold decrease in potency as compared to wild-type translates as resistance from an EC50 value of >9 nM (3 ng/ml). Taking this cut-off, 54% of the NNRTI resistant strains was also resistant to dapivirine. When taking a cut-off of 100 nM (33 ng/ml) for resistance, 12% of the NNRTI resistant strains was also resistant to dapivirine. It is not clear what the clinically relevant cut-off for resistance is. The lowest concentration of dapivirine measured in the vaginal fluid at 28 days after insertion of the ring is 10330 ng/ml. Further, no sequence data is provided on the strains tested.

The in vitro efficacy data on HIV-1 subtypes and resistance strains are not sufficient. The data are old and there is a lack of underlying information about subtypes and mutations. Further data are required and requested.

### In vivo efficacy

An in vivo experiment was performed using hu-SCID mouse, infected with human peripheral blood lymphocytes (hu-PBL) previously infected in vitro with HIV-1 strains SF162 (R5-tropic) and 1BX/08 (dual tropic R5X4). Prior to infection, the mice were treated with 2 gel formulations of different viscosities. This study is difficult to interpret, since the correlation between the gels and the vaginal ring is unknown. The concentrations used of 740 and 4700 ng/ml are much higher than the reported EC50 values of 1-3 ng/ml. Despite this, not all animals were protected from infection. This could be due in part to the gel formulations or the physiological conditions of the in vivo experiment as compared to the in vitro tests. Further, only cell-cell transmission was evaluated in the in vivo study, while transmission from free virus is also an important part of transfer of infection. In vivo efficacy should be further demonstrated in clinical trials.

### **Secondary pharmacodynamic studies**

Dapivirine does not interact with any receptor (besides the progesterone and oestrogen receptors, see below), ion channel, enzyme or transporter as tested up to 10 µM. Although the local concentration during use of the vaginal ring will be higher than 10 µM, systemic exposure will be lower. Taking into consideration the lack systemic and local adverse effects and manageable local adverse effects, the receptor screen is sufficient.

Dapivirine is not active against HIV-2, herpes simplex virus types 1 and 2, vaccinia virus, vesicular stomatitis virus, Coxsackie B4 virus, or respiratory syncytial virus. Studies analysing the activity of DPV on hepatitis viruses (HBV and HCV) should be performed and the results provided.

It also has little antibacterial effect, as no inhibition was observed for clinical isolates of the commensal *Lactobacillus* spp, or the pathogenic *Candida*, *Streptococcus*, *Staphylococcus*, *Enterococcus*, *Escherichia coli*, or *Neisseria gonorrhoeae* when tested up to 32 mg/L. The only microorganism that was sensitive to dapivirine with a MIC90 of 2 mg/L (2000 ng/ml) is *Haemophilus ducreyi*, indicating a possible protective or therapeutic effect against chandroid caused by this pathogen.

Dapivirine had no effect on contractile activity of human uterine muscle when tested up to 50 µM. It had also no effect on sperm motility when tested up to 2 mM.

Dapivirine binds with low affinity to the estrogen and progesterone receptor ERα, ERβ, PR-A and PR-B. Very low relative binding values indicate that the natural ligands estrogen and progesterone would be preferentially bound to the receptors. This is further illustrated by the lack of any findings in humans after use of the dapivirine ring that could indicate an agonistic or antagonistic response due to the binding of dapivirine to the receptors.

### **Safety pharmacology programme**

CNS effects of dapivirine (ataxia, horizontal and vertical activity) in Wistar rats were only observed at doses of 80 mg/kg or higher. These effects are not relevant for the clinical situation since the systemic exposure of dapivirine after use of the vaginal ring is very low, and exposure in rats after an oral dose of 20 mg/kg is already 1600-fold higher than human exposure.

Dapivirine has no effect on the central nervous system at clinically relevant doses.

Dapivirine has inhibitory effects on cholinergic nerve-smooth muscle function at concentration far in excess of those achieved systemically in women using the ring.

In in vivo studies in dogs, effects on cardiovascular parameters were only seen at doses resulting in exposure far in excess of clinically relevant concentrations. No effect of dapivirine on action potential was seen in guinea-pig heart muscle cells. An inhibitory effect on hERG channels was observed. At the lowest concentration tested of 0.1 µg/mL, an 8% block in current was seen. This is far in excess of relevant concentrations.

No effects on the cardiovascular system are anticipated at clinically relevant exposures to dapivirine.

No specific study was performed to evaluate effects on the respiratory system. This type of study would normally be required before the first in human clinical trial. Although no effects on the respiratory system have been observed in any of the long-term animal studies, these studies do not evaluate the same parameters as would be done in a safety pharmacology study. However, considering the amount of clinical data available without any apparent effect on the respiratory system, and the low systemic exposure after use of the ring, it is unlikely that dapivirine has any adverse effects on the respiratory system when used as indicated. No further studies are required.

Gastrointestinal effects of dapivirine were studied in Wistar rats. At the lowest dose tested of 40 mg/kg, decreased gastric emptying was observed, which was probably due to the solvent PEG400. At 160 mg/kg, a protective effect on castor oil-induced diarrhea was seen. These effects are not relevant for the current product as they are evident at much higher doses and exposures than those achieved clinically.

### ***Pharmacodynamic drug interactions***

Experiments were performed to investigate the interaction of dapivirine with various antifungal compounds. The interpretation of the results is hampered due to effects of the test system on fungal growth, including the presence of solvents and differences in pH. However, it can be concluded that dapivirine has the potential to reduce the efficacy of antifungal compounds. Interactions with antifungal agents are further discussed in the clinical AR.

Levonorgestrel has no effect on antiviral activity of dapivirine at the conditions used in the test system with PM-1 cells and PBMC's.

### **2.3.3. Pharmacokinetics**

#### Methods of analysis

Analyses of dapivirine in pivotal toxicokinetic and pharmacokinetic studies were performed by adequately validated LC-MS/MS methods.

#### Absorption

In female sheep with a dapivirine-containing ring inserted for 28 days (containing the same amount of dapivirine as the clinical amount), plasma concentrations were low but quantifiable. After removal of the ring, plasma concentrations were below quantifiable levels within 24 h. Concentrations in vaginal fluid were fairly consistent throughout the period of exposure, but the variation in the levels was very high, ranging approximately 10 – 10,000 ng/g. Rectal fluid levels were low. After oral administration of dapivirine to rats, dogs and monkeys, exposure was much higher than after use of the intravaginal ring in sheep (approximately 1000 – 10,000 times higher) and approximately 400 – 3000 times the human exposure after intravaginal exposure, based on AUC<sub>24</sub>. The plasma elimination half-life (T<sub>1/2</sub>) ranged from 3.5 – 7.4 h in rat, dog and monkey.



### Distribution

Protein binding of dapivirine in plasma was high, with unbound fractions of 0.15 – 0.39% in rats, dogs and humans. Unbound fraction in human cervicovaginal fluid was approximately 85%. Blood to plasma distribution indicated no preferential uptake into red blood cells. After intravaginal administration of <sup>14</sup>C-dapivirine-containing gel to female albino rats, the highest concentrations of drug-related material were found in the vagina wall, the wall of the gastrointestinal tract, the liver and abdominal fat. Concentrations in ovary and uterus were low. Low but quantifiable levels were found in the brain. Levels in eye and skin were not quantifiable or very low. In rabbits treated intravaginally with dapivirine-containing gel, only tissue concentrations in vagina and cervix were measured, which showed high variability. In sheep, after treatment with the dapivirine ring for 28 days, concentrations in vaginal tissue were also variable. Concentrations in cervical and rectal tissue were unquantifiable or very low. In vaginal tissue of sheep a sharp decline in concentration from mucosal to serosal surface was found. In pregnant rats, distribution was slower than in non-pregnant female rats. Otherwise, tissue distribution was comparable to non-pregnant female rats. Low but quantifiable concentrations were found in foetuses of rats, with levels comparable to maternal whole blood. No data are available regarding the excretion of dapivirine in milk. Considering the low systemic bioavailability with the use of the dapivirine ring, the amount of dapivirine in mother's milk is expected to be very low or negligible.

### Metabolism

Following oral administration, metabolism of dapivirine is extensive, but dapivirine seems the largest component in plasma of rats, dogs, monkeys and humans. Based on the metabolite profile in plasma, human metabolism seems more similar to monkey and rat than to dog. These data indicate no unique human metabolites. Dapivirine is excreted into urine of monkeys and humans for a substantial part as direct conjugates of dapivirine, whereas in dogs, a substantial part is excreted as conjugated metabolites in bile. Also, in rats a substantial part was excreted as conjugated metabolites in bile. Metabolism in the liver was shown to occur by oxidation, of both the trimethylphenylaminopyrimidinyl and the pyrimidinylaminobenzonitrile moiety in rat, dogs and humans and by glucuronidation, of dapivirine itself and of metabolites formed by oxidation. Dapivirine is metabolized primarily by CYP3A4/5, with contributions from CYP2B6 and CYP2C19. In addition, a large number of UGT enzymes are involved in the formation of glucuronides. Expression (mRNA and protein) and activity of CYP enzymes were found in both vaginal and colorectal human tissue. It is not certain whether UGT enzymes are only expressed in colorectal tissue and not in vaginal tissue, as one publication suggests, or whether UGT enzymes are expressed in both colorectal and vaginal tissue as another publication suggests. In the clinical AR, another concern is formulated regarding this issue. No metabolites unique to vaginal and colorectal tissue were found, which were not also formed by liver fractions or hepatocytes. Data in monkeys indicate no significant metabolism of dapivirine in vaginal and cervical tissue. In rabbits, evidence of metabolism in vaginal and cervical tissues was observed in three out of four rabbits.

### Excretion

No studies to investigate the excretion of dapivirine have been performed in nonclinical species. This is consistent with recommendations provided during a joint Scientific Advice consultation with the European Medicines Agency, US Food and Drug Administration and World Health Organisation in October 2010 (EMA/CHMP/SAWP/686625/2010, 18 November 2010).



## **2.3.4. Toxicology**

### ***Single dose toxicity***

Oral and subcutaneous administration of single doses of dapivirine to mice and rats at doses up to 900 mg/kg was well tolerated. There were no treatment-related deaths and clinical signs were limited to transient ataxia in some animals at oral dose of 640 mg/kg and wet urogenital area in female rats.

### ***Repeat dose toxicity***

The toxicity of repeated oral gavage doses of dapivirine has been assessed in rats and dogs in studies of up to 6-months duration. Dapivirine was administered as a solution in polyethylene glycol 400 (PEG 400). In rats, an increase in liver weight and centrilobular hypertrophy accompanied by related alterations in clinical chemistry parameters were seen in all studies. In addition, effects were also seen in the thyroid and pituitary. The adaptive response of the liver to treatment leads to an increase in the activity of hepatic xenobiotic metabolism, leading to stimulation of the pituitary and subsequently proliferation of thyroid follicular cells. These changes are regarded as an adaptive, rather than an adverse response of the liver to treatment. In dogs, severe liver abnormalities were observed. Panlobular changes consisting of vacuolation, necrosis, hemorrhage, inflammation and bile duct hyperplasia were noted in animals treated at 40 and 120 mg/kg/day who died or were killed in extremis. When animals were allowed to recover after clinical signs of hepatotoxicity were observed, ultimately only partial recovery was observed.

Toxicity associated with intravaginal administration has been evaluated in a 3-month study in rats, in studies of up to 9-months duration in rabbits, and in a 3-month study in sheep. For the studies in rats and rabbits, various gel formulations of dapivirine were used, and in the sheep study dapivirine was administered as a gel and via Dapivirine Vaginal Ring-004. In most rabbit studies, vaginal irritation was assessed according to the Eckstein criteria. There were no treatment-related local findings associated with the intravaginal administration of dapivirine gel or following the insertion of vaginal ring. Although vaginal fluid exposure in sheep did not reach the exposure level observed in woman using the Dapivirine Vaginal Ring-004, sufficient exposure levels were reached when using the dapivirine gel.

In conclusion, evidence of systemic toxicity was only observed in rats and dogs in studies conducted via the oral route, at exposures considerably in excess of those seen in women using Dapivirine Vaginal Ring-004. There were no significant findings indicating local toxicity after intravaginal administration of dapivirine.

### ***Genotoxicity***

A number of genotoxicity tests showed sufficiently that dapivirine will not be a genotoxic risk systemically in humans, but the genotoxic risk at the vaginal tissue is inconclusive, because the used concentrations were too low. However, a 2-year carcinogenicity study (JTC0013) did not reveal toxic, neoplastic or carcinogenic activity of dapivirine at relevant vaginal fluid concentrations, and thus no further genotoxic studies have to be performed.

### ***Carcinogenicity***

A two-year intravaginal carcinogenicity study in rats did not reveal a statistically significant increase in tumour incidence for dapivirine at concentrations 6 to 60 times higher than the maximal observed concentration in vaginal fluid in women using Dapivirine Vaginal Ring-004.

## **Reproduction Toxicity**

In an oral fertility and early embryonic development study in rats, 80 mg/kg/day dapivirine caused post-implantation loss and embryonic resorptions. At 320 mg/kg/day maternal toxicity was observed, and fertility and conception indices were reduced. Male rats treated with 320 mg/kg/day dapivirine caused a non-significant decrease in fertility and conception indices. Systemic exposures in animals were well above the expected systemic exposure in humans, therefore, an effect on fertility because of systemic exposure is not to be expected.

At local exposure in rats, up to a concentration of gel of 3.3 mg/ml did not affect maternal toxicity and embryo-foetal development. This concentration is much higher than the expected maximal concentration of dapivirine in human vaginal fluid (about 100 µg/ml). Oral doses of  $\geq 80$  mg/kg/day in rats caused maternal toxicity, embryo toxicity and malformations at systemic exposures of more than 1000 times the expected human systemic exposure.

Intravaginal administration of up to 3.3 mg/ml did not affect maternal toxicity and embryo-foetal development in rabbits. This is well above the expected maximal concentration of dapivirine in human vaginal fluid. Oral administration of dapivirine in PEG400 or propylene glycol caused maternal and embryo-foetal toxicity at all doses, including controls. However, oral administration of dapivirine in 1% carboxymethyl cellulose containing 0.2% Tween 80 did not affect maternal toxicity and embryo-foetal development in rabbits up to 90 mg/kg/day.

At an oral dose of 20 mg/kg/day of dapivirine in rats, no maternal effects and effects on pre- and postnatal development were seen. At 80 mg/kg/day, only transient reductions in maternal body weight gain and food consumption, along with slight reductions in the body weight and weight gain of offspring were seen. These effects are not considered adverse. The systemic exposures are well above the expected exposures in women using the Dapivirine Vaginal Ring-004.

Given the proposed indication for Dapivirine Vaginal Ring-004, studies in juvenile animals are not considered to be relevant and have not been performed.

## **Toxicokinetic data**

### **Local Tolerance**

In female mice treated vaginally with gels containing 0.5 mg/ml dapivirine for 2 weeks did not show significant differences in concentrations of a number of cytokines and chemokines compared to controls. Also, no significant impact on expression of proteins involved in maintaining the epithelial barrier was shown.

Intravaginal administration of a number of formulations in female rabbits with up to 33 mg/ml dapivirine were generally well tolerated and no dose-dependent irritation of dapivirine is shown.

A 2-week study in rabbits with intravaginal administration of dapivirine at concentrations up to 20 mg/ml did not cause vaginal irritation or provide any evidence of systemic toxicity.

In a Herpes Simplex virus (HSV-2) susceptibility assay of a 7-day study in mice administered vaginally gels of 0.5 mg/ml dapivirine, no increased susceptibility to HSV-2 was seen. Topical application of 2 and 5 mg/ml dapivirine gel on the penis of rabbits did not cause relevant irritation. Rectal application of 0.5, 2 or 5 mg/ml dapivirine gel in rabbits did not show relevant irritation or other harmful effects.

## **Other toxicity studies**

Dapivirine was evaluated in the Magnusson-Kligman guinea pig maximization model of delayed hypersensitivity. Intradermal and topical inductions of 0.2% dapivirine followed by a topical challenge at 0.2% to guinea pigs did not elicit any dermal sensitization response at 24 and 48 hours. No dermal responses were seen in either the vehicle control animals or the test article treated animals at challenge.

No specific immunotoxicological studies have been performed on dapivirine. However, an evaluation of the data from the extensive toxicology program did not identify any effects on leukocytes, plasma globulins, immune system organ weights or histology, incidence of infections, or on the occurrence of tumours that might be indicative of an immunotoxicological effect.

### Other studies

According to the ISO 10993 guideline for the biological evaluation of medical devices, the Dapivirine Vaginal Ring-004 (25 mg) was tested for cytotoxicity, sensitization, vaginal irritation and genotoxicity. All these tests were performed adequately and turned out to be negative for the ring.

Cytotoxicity of dapivirine was tested in rat and dog primary hepatocytes and in a number of human cell lines, among others the human Hela (cervix, adenocarcinoma, epithelial). The cytotoxic response of 50% (CC50) varied between 0.89 to 65.5 µg/ml, which is well below to just below the mean maximum dapivirine concentration measured in the vaginal fluid of women using Dapivirine Vaginal Ring-004 (ca. 100 µg/ml). This indicates that dapivirine may have a cytotoxic effect at the site of the positioned vaginal ring. However, no signs of irritation were shown in the in vivo local tolerance models at high dapivirine concentrations (see above).

The risk of phototoxicity associated with the use of Dapivirine Vaginal Ring is considered to be negligible.

The Dapivirine Vaginal Ring contains two excipients, the silicone oil DDU-360 and the silicone elastomer DDU-4870. The liquid polymer DDU-360 is also known as dimeticone and is used in many medical device and pharmaceutical applications. The safety of DDU-360 has been established by conducting a range of biocompatibility assessments in accordance with the ISO 10993 and US Pharmacopeia (USP) guidelines. DDU-360 turned out to be non-cytotoxic, does not cause sensitization in guinea pigs, local skin irritation in rabbits and systemic toxicity in mice, is non-pyrogenic, non-genotoxic and non-haemolytic. DDU-4870 turned out to be non-cytotoxic, does not cause sensitization in guinea pigs, local skin irritation in rabbits and systemic toxicity in mice, is non-pyrogenic, non-genotoxic and non-haemolytic.

### **2.3.5. Ecotoxicity/environmental risk assessment**

An environmental risk assessment was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

### **2.3.6. Discussion on non-clinical aspects**

The CHMP noted that the antiviral activity of DPV on other viruses has been analysed on a panel of viruses, not including any hepatitis viruses. The CHMP requested the applicant to justify, why Hepatitis B and C virus have not been included in the panel of viruses analysed as requested by EMEA/CPMP/EWP/633/02 Rev. 3.

The applicant has provided a justification for the omission of in vitro data concerning a potential interaction of DPV with hepatitis viruses (HBV and HCV). It is argued, that on the one hand the studies

on DPV interaction with other viruses was performed before the relevant guideline was published and on the other hand the interaction of DPV with HBV and HCV is not considered relevant by the applicant as HIV-NNRTIs in general target highly specifically the HIV-1 reverse transcriptase. Further it is argued, that the site with the highest concentration of DPV (lower female reproductive tract) differs greatly from the site of infection of HBV and HCV and thereby no potential of DPV to exert selective pressure against HBV and HCV is foreseen.

The argumentation of the applicant is acknowledged but not shared by the CHMP. As DPV is a new compound, a thorough analysis regarding the potential antiviral activity of this new NNRTI with viruses other than HIV-1, including HBV and HCV, should be provided as also requested by the respective guideline. For hepatitis E virus (HEV) extrahepatic replication has been demonstrated in human placental tissue (Knegendorf et al., *Hepatol. Commun.*, 2018) and in ovarian tissue of animal models (An et al., *Oncotarget*, 2017). As HEV infection is a major public health concern especially in sub-Saharan Africa (Ifeorah, 2017), the CHMP considers that the antiviral activity of DPV on HEV should also be included in an in vitro analysis. Studies analysing the activity of DPV on hepatitis viruses should be performed (including hepatitis E virus as a relevant pathogen in the proposed patient group).

The CHMP requested in vitro studies analysing the activity of DPV on hepatitis viruses (HBV, HCV, and HEV) to be performed and results provided. The evaluation of dapivirine activity against HBV and HCV in vitro was provided by the applicant accordingly, demonstrating DPV to be not active against both viruses ( $IC_{50} > 1.000 \text{ nM}$  in vitro). A slight antiviral effect can be seen for the highest concentration of DP (1  $\mu\text{M}$ ) on HBV demonstrating decrease of HBV DNA to 70% (mean value,  $n=3$ ) while cell viability is stable (no cytotoxic effect). This finding was discussed in the final report on the interaction study DPV on HCV/HBV.

The applicant provided the final report including raw data of the evaluation of DPV antiviral activity on HBV and HCV. The finding of a potential antiviral effect of DPV on HBV replication was discussed. Data from a previous experiment has been provided which support the applicant's argument, that the finding might be mostly reliant on a cytotoxic effect of DPV on the cell system rather than on HBV replication. The different analytical methods used (qPCR and MTS-assay) to determine virus replication and cell cytotoxicity might further blur the image as they might not confer the same level of sensitivity.

Although the cause of the effect remains somewhat unclear, the applicant's argumentation can be followed that the effect seen rather reflects cytotoxicity than antiviral activity. Further to this, the DPV-concentration at which the effect occurs is very high (1  $\mu\text{M}$ ) and is not reach in plasma levels of women wearing the DPV-containing vaginal ring. This was considered solved by CHMP.

As regards determination of DPV activity on HEV, the challenges associated with the HEV assay are acknowledged. The CHMP is of the view that the results of this analysis should be provided as soon as possible as a post-authorisation measure.

In this light, data on antiviral activity of Dapivirine on HEV should be provided as a post-authorisation measure (PAM).

### **2.3.7. Conclusion on the non-clinical aspects**

The CHMP is of the view that there are no objections to a positive scientific opinion of Dapivirine vaginal ring from a non-clinical point of view.

The CHMP considers the following measure necessary to address the non-clinical issues:

- Data on antiviral activity of Dapivirine on HEV should be provided as a post-authorisation measure.

## **2.4. Clinical aspects**

### **2.4.1. Introduction**

#### **GCP**

A request for a GCP inspection was adopted for the following clinical studies: Study MTN-020 and IPM-027.

The applicant declared that all clinical trials were performed in accordance with GCP and also provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

However, the GCP inspection identified several major and critical findings in relation to one of the pivotal trials included in the application, trial MTN 020, which revealed violations of fundamental principles of ICH GCP, rendering it as GCP non-compliant.

The overall conclusions of the inspectors regarding the inspections of the pivotal clinical trials IPM 027 and MTN-020 are summarised below:

- Study IPM 027:

The data collected and the results reported in IPM 027 are generally considered acceptable based on the knowledge gained during the inspections.

- Study MTN-020:

In study MTN-020 the pattern of deficiencies which occurred on study management level is critical and based on the major and critical key findings inspectors do not consider the results of the efficacy evaluation, as reported in the CSR, reliable. However, the primary endpoint data collected at the clinical research sites are considered credible and supplemental analyses may be acceptable for consideration of the risk-benefit evaluation.

**Table 2 Tabular overview of clinical studies**

<b>Trial Number</b>	<b>Description</b>	<b>Participant Age</b>	<b>Duration</b>	<b># Participants Receiving the Dapivirine Vaginal Ring-004</b>	<b>Countries</b>	<b>Status</b>
IPM 013	Phase I, randomized, double-blind, placebo-controlled trial; safety and pharmacokinetics (systemic and local) of multiple vaginal rings containing dapivirine in healthy, HIV-negative, sexually active women	18 - 40	56/57 days	36	Belgium	Completed

<b>Trial Number</b>	<b>Description</b>	<b>Participant Age</b>	<b>Duration</b>	<b># Participants Receiving the Dapivirine Vaginal Ring-004</b>	<b>Countries</b>	<b>Status</b>
IPM 015	Phase I/II, randomized, double-blind, placebo-controlled trial; safety and pharmacokinetics of 28-day use of Dapivirine Vaginal Ring-004 (inserted at 28-day intervals) in HIV-negative, sexually active women	18 - 40	3 x 28 days	140	Kenya, Malawi, South Africa, Tanzania	Completed

<b>Trial Number</b>	<b>Description</b>	<b>Participant Age</b>	<b>Duration</b>	<b># Participants Receiving the Dapivirine Vaginal Ring-004</b>	<b>Countries</b>	<b>Status</b>
IPM 024	Phase I, randomized, double-blind, placebo-controlled trial; safety and pharmacokinetics in HIV-negative, sexually abstinent women	18 - 40	28 days	8	Belgium	Completed



<b>Trial Number</b>	<b>Description</b>	<b>Participant Age</b>	<b>Duration</b>	<b># Participants Receiving the Dapivirine Vaginal Ring-004</b>	<b>Countries</b>	<b>Status</b>
IPM 028	Phase I, open-label, randomized, 3-period crossover trial; safety and pharmacokinetics; drug-drug interaction between Dapivirine Vaginal Ring-004 and vaginally administered miconazole nitrate in healthy HIV-negative women	18 - 40	2 x 28 days	36	Belgium	Completed
IPM 034	Phase I, open-label, parallel group pharmacokinetic trial in healthy, HIV-negative women to characterize the release profile of dapivirine delivered by a silicone matrix ring (Ring-004), containing 25 mg of dapivirine, over various ring use periods	18 - 40	5 groups of women using Ring-004 continuously for 7, 14, 28, 56 and 84 days, respectively	40	Belgium	Completed

<b>Trial Number</b>	<b>Description</b>	<b>Participant Age</b>	<b>Duration</b>	<b># Participants Receiving the Dapivirine Vaginal Ring-004</b>	<b>Countries</b>	<b>Status</b>
IPM 035	Phase I, open-label, randomized, 3-period, 2-sequence, crossover trial in two cohorts; pharmacokinetics (local and systemic) and safety of Dapivirine Vaginal Ring-004 during menses, with and without tampon use (Cohort I), and evaluation of the impact on (local and systemic) pharmacokinetics when the ring is removed at onset of menses and the same or a new ring (re-)inserted upon completion of menses (Cohort II) in healthy, HIV-negative women	18 - 40	3 x 28 days	38	Belgium	Completed
MTN-024/IPM 031	Phase IIa, 2-arm, placebo-controlled, double-blind, multi-center, randomized trial; safety and pharmacokinetics of Dapivirine Vaginal Ring-004 when inserted once every 4 weeks for a 12-week period in HIV-negative postmenopausal females	45 - 65	12 weeks	72	United States of America	Completed
IPM 027	Phase III, multi-center, randomized, double-blind, placebo-controlled; safety and efficacy of Dapivirine Vaginal Ring-004 when inserted once every 4 weeks over a period of approximately 24 months (104 weeks) in healthy, HIV-negative women	18 - 45	24 months	1307	South Africa, Uganda	Completed
MTN-020	Phase III, multi-center, randomized, double-blind, placebo-controlled; safety and effectiveness of Dapivirine Vaginal Ring-004 when inserted once every 4 weeks in HIV-negative women	18 - 45	> 12 months	1313	Malawi, South Africa, Uganda, Zimbabwe	Completed
IPM 032	Phase IIb, multi-center follow-on open-label trial to evaluate the continued adherence to and safety of the Dapivirine Vaginal Ring-004 inserted at monthly intervals in healthy, HIV-negative women who have participated in IPM 027, and two cohorts of ring-naïve young women	≥ 18	12 months	≈1520	South Africa, Uganda	Ongoing

<b>Trial Number</b>	<b>Description</b>	<b>Participant Age</b>	<b>Duration</b>	<b># Participants Receiving the Dapivirine Vaginal Ring-004</b>	<b>Countries</b>	<b>Status</b>
MTN-025	Phase IIIb, multi-center follow-on open-label trial to evaluate the continued adherence to and safety of the Dapivirine Vaginal Ring-004 inserted at monthly intervals in healthy, HIV-negative women who have participated in MTN-020	≥ 18	12 months	1000 to 2500	Malawi, South Africa, Uganda, Zimbabwe	Ongoing
MTN-023/IPM 030	Phase IIa, 2-arm, placebo-controlled, double-blind, multi-center, randomized trial; safety and pharmacokinetics of Dapivirine Vaginal Ring-004 when inserted once every 4 weeks for a 24-week period in HIV-negative adolescent females	15 - 17	24 weeks	72	United States of America	Completed
IPM 036	Phase I, open-label, randomized trial, with a three-period crossover part in healthy, HIV-negative women to assess drug-drug interaction potential between Dapivirine Vaginal Ring-004, and clotrimazole 10 mg/g (1%) administered as vaginal cream, with a follow-on period to assess the effect of multiple ring removals and re-insertions during the 28-day period of the Dapivirine Vaginal Ring-004 use on the systemic and local exposure and dapivirine residual levels in used rings	18 - 45	2 x 28 days (Part 1) 28 days (Part 2)	36	Belgium	Completed
MTN-029/IPM 039	Phase I, open-label trial; pharmacokinetics and safety of 14-day use of Dapivirine Vaginal Ring-004 in HIV-negative, lactating women, at least 6 weeks postpartum, who are able to produce breast milk but who are not breastfeeding	≥ 18	14 days	16	United States of America	Completed

### 2.4.2. Pharmacokinetics

The clinical trials involving the Dapivirine Vaginal Ring 004 and contributing to the understanding of its clinical pharmacology are listed in Table 3.

All of the trials were conducted in healthy, HIV negative women, which is the target population for the Dapivirine Vaginal Ring. Participants were 18 to 40 years of age (Phase I and Phase I/II trials) or 18 to 45 years of age (Phase III trials), with the exception of MTN 024/IPM 031, which enrolled postmenopausal women 45 to 65 years of age.

The Phase I and Phase IIa trials were conducted either in Belgium or the United States of America (USA) and the majority of participants enrolled were White. One Phase I/II (IPM 015) and the Phase III trials were conducted in sub Saharan Africa and the majority of participants were Black. Albeit it would have been preferable if rich PK sampling was also done in black/coloured women, as these are anticipated to represent the main target population, cross study comparisons provide some reassurance that race has no meaningful effect on the PK characteristics of the dapivirine vaginal ring.

In the Phase I clinical trials all vaginal rings (active or placebo) were placed in the upper vagina by the investigator, in the Phase II trials the rings were either self-inserted or inserted by the investigator, and in the Phase III trials all vaginal rings were self-inserted by the participants.

Throughout the development of the Dapivirine Vaginal Ring, dapivirine concentrations have been assessed in vaginal fluid and plasma. In most Phase I trials, vaginal fluid samples were collected at three locations: near the cervix, near to where the ring was placed and near the introitus; in the Phase III trial IPM 027 vaginal fluid samples were collected at the cervix. The vaginal fluid concentrations provide information on the local distribution and exposure to dapivirine, whilst the plasma samples provide information on the systemic exposure to dapivirine during ring use. The concentrations in plasma are not directly relevant to the efficacy of dapivirine, but these provide an indication that dapivirine was absorbed into the vaginal/cervical tissues. This is important for efficacy as the primary site of action of dapivirine is believed to be within CD4 cells in the tissues of the female lower reproductive tract. The concentration of dapivirine in cervical tissue biopsies was also assessed in two trials, although there is uncertainty as to where measured drug concentrations were actually located (e.g. on the tissue surface, in the dead keratinized cell layers, or in interstitial fluid and living target cells).

**Table 3 Listing of Clinical Trials Contributing to Clinical Pharmacology**

Phase	Trial No. / Year*	Country	Production site / batch numbers	Key Clinical Pharmacology Objective(s)
I	<a href="#">IPM 024</a> 2009 (N=8)	Belgium	CTM 09A02R	Characterize local and systemic dapivirine PK when a single Dapivirine Vaginal Ring-004 was used continuously for 28 days.
	<a href="#">IPM 013</a> 2010 (N=35)	Belgium	CTM 09A02R	Characterize local and systemic dapivirine PK from up to three rings used for different ring use periods (21-35 days) and to assess impact of a ring-free interval.  Characterize dapivirine PD (capacity of ring to protect cervical tissue from infection upon ex vivo challenge with HIV 1; capacity of vaginal fluids collected by cervicovaginal lavage to inhibit HIV 1 infection in vitro).  Effect of menses and tampon use on PK.
	<a href="#">IPM 028</a> 2013 (N=35)	Belgium	QPharma OE525	Drug-drug interaction trial to investigate the effect of dapivirine on the PK of vaginally administered miconazole nitrate (and vice versa).
	<a href="#">IPM 034</a> 2014 (N=40)	Belgium	QPharma OB518	Characterize local and systemic PK when a single Dapivirine Vaginal Ring-004 was used for different ring use periods (seven to 84 days).
	<a href="#">IPM 035</a> 2015-2016 (N=38)	Belgium	QPharma PA540	Characterize the effect of menses and tampon use on local and systemic dapivirine PK.  Characterize the effect of removing the ring during menses on local and systemic dapivirine PK.
	<a href="#">IPM 036</a> 2015-2016 (N=36)	Belgium	QPharma QA576A	Assess drug-drug interaction potential between Dapivirine Vaginal Ring-004, and clotrimazole 10 mg/g (1%) administered as vaginal cream.  Assess the effect of multiple ring removals and re-insertions during the 28-day period of the ring use on the systemic and local exposure and dapivirine residual levels in used rings.
	<a href="#">MTN-029/IPM 039</a> 2016-2017) (N=16)	United States of America	QPharma QA577A	Characterize pharmacokinetics of 14-day use of Dapivirine Vaginal Ring-004 in HIV negative, lactating women, at least 6 weeks postpartum, who are able to produce breast milk but who are not breastfeeding.
I/II	<a href="#">IPM 015</a> 2010-2011 (N=140)	South Africa, Kenya, Malawi, Tanzania	CTM 09A02R+09A03R	Dapivirine trough plasma concentrations following three rings used consecutively for 28 ( $\pm$ 4) days each.
IIa	<a href="#">MTN-024/IPM 031</a> 2014-2015 (N=71)	United States of America	QPharma OK537	Characterize local and systemic dapivirine PK (based on trough values) in postmenopausal women following three rings used consecutively for 28 days each.
	<a href="#">MTN-023/IPM 030</a> 2014-2016 (N=72)	United States of America	QPharma PB542A+QA576A	Characterize pharmacokinetics of Dapivirine Vaginal Ring-004 in HIV-negative adolescent females (between 15 and 17 years of age).
III	<a href="#">IPM 027</a> 2013-2016 (N=1307)	South Africa, Uganda	QPharma NK513+OB517+ OC519+OF528+ OK537+PA540+ PB543+PK574+ PL575	Dapivirine trough plasma and vaginal fluid concentrations following rings used consecutively for 28 days each for 24 months.

	MTN-020 2013-2016 (N=1313)	South Afr, Malawi, Uganda, Zimbabwe	QPharma OB518+OE525+OF52 7+OK538+OK539+ PB541+PB542	Dapivirine trough plasma concentrations following rings used consecutively for 28 days each for a minimum of 12 months.
* number of subjects with PK (dapivirine measured in at least one of the matrices)				

### Bioanalytics

During clinical trials with the Dapivirine Vaginal Ring-004, dapivirine concentrations were analysed in three biological matrices: plasma, vaginal fluid and vaginal or cervical tissue. Dapivirine concentrations in all of the aforementioned matrices were determined using validated high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) by each of the laboratories that provided analytical support. As an internal standard, deuterated dapivirine (dapivirine-d4) was used.

In general, bioanalytical methods were acceptable, properly validated and had acceptable precision and accuracy. However, the long-term stability experiments for the plasma and vaginal fluid samples of study IPM 027 and vaginal fluid samples of study IPM 035 are still on-going, and the bioanalytical (sub) reports will have to be submitted as a Post-Authorisation Measure by Q3 2020. PK data from these studies will be formally referred to as *preliminary* data until this Post-Authorisation Measure has been fulfilled.

### Formulation development

In an effort to create an optimal drug delivery system, IPM developed four different dapivirine vaginal ring formulations. The first three rings (Ring-001, Ring-002 and Ring-003), as well as several gel formulations, were tested in Phase I clinical trials and Phase I/II clinical trials (for two gel formulations only); all were found to be generally safe and well tolerated. Ring-004 containing 25 mg of dapivirine is the product intended to be registered and marketed that delivers approximately 4 mg dapivirine over a period of one month (28 days) in vivo. The Dapivirine Vaginal Ring-004 had the most favorable continuous release profile, with good stability and manufacturing feasibility, and demonstrated pharmacokinetic profiles suitable for use as a microbicide over a 1-month period. This formulation was therefore taken into full clinical development and has been evaluated in Phase I to III clinical trials and is the proposed to be marketed formulation. The Dapivirine Vaginal Ring-004 utilizes a matrix ring delivery system and contains 25 mg of dapivirine dispersed throughout a cured silicone matrix. A platinum catalyzed hydrosilylation reaction is employed for the silicone curing. All relevant clinical studies were done with Dapivirine Vaginal Ring-004.

During the course of development, the production of the Dapivirine Vaginal Ring-004 was transferred from the IPM Clinical Trial Manufacturing (CTM) site (Bethlehem, PA, US) to QPharma (Malmö, Sweden). Drug product used for three of the Phase I/II clinical trials (IPM 013, 015, and 024) was manufactured at the IPM CTM site, whereas drug product used in further clinical development of Ring-004, including the two pivotal Phase III clinical trials, was produced at QPharma. The formulation used in the two pivotal Phase III clinical trials and the formulation proposed to be marketed are the same. Minor optimization of processing conditions and manufacturing scale, consistent with a typical product development lifecycle, occurred during the transfer. The rings from the two production sites were identical with respect to the quantitative and qualitative aspects of the drug product. For these reasons, no dedicated comparative bioavailability or bioequivalence clinical trials comparing the rings from both production facilities were performed. The similarity in dapivirine release characteristics for both rings is highlighted by in vitro dissolution evaluations using the QC method. F2 similarity was demonstrated at all time points for two batches (from 25 lots from both manufacturing sites), that differed most with respect to dapivirine release (of which one happened to be produced by the IPM CTM facility and the other by QPharma). The transfer of the production site for Ring-004 from CTM Bethlehem to QPharma Malmö is considered a minor change and is not anticipated to impact the drug product quality. No major or obvious

changes in pharmacokinetics have been observed between clinical trials IPM 024 and IPM 013 on one side and IPM 028, IPM 034 and IPM 035 on the other side.

#### Population PK analysis

Population PK modeling was performed on vaginal fluid data from trials IPM 024, IPM 013, IPM 028, IPM 027 (preliminary data), MTN-024/IPM 031, and IPM 034. The PK of dapivirine administered as Dapivirine Vaginal Ring-004 were optimally described by a one-compartmental model for vaginal fluids collected at the cervix and near the introitus, following a first-order release from the Dapivirine Vaginal Ring corresponding with an initial release rate of 0.267 mg per day. The half-life of dapivirine in vaginal fluids was 0.89 day (21 hours) while dapivirine distributed with a V/F of 11.1 g fluid. Absorption and elimination rate constants, and the relative bioavailability of introitus relative to cervix compartments, were associated with considerable inter-individual variability, with for example a CV of 83% for absorption rate.

The following statistically significant covariates were found: WGT, age, BIL, and HGT on elimination rate and WGT, age, and HGT on V. The impact of these covariates did not exceed the clinical significance criterion. The relationships of site ID and vaginal fluid pH with V were retained. V differed significantly for two South African research centers (in IPM 027), specifically those of IPM Research Center 02 (ZAF, Edendale) (22%) and IPM Research Center 03 (ZAF, Pinetown) (40% reduction in exposure). V appeared to correlate with pH of vaginal fluid. A trial participant with an extreme vaginal fluid pH of 5.6 would have a 15% reduction in exposure, where extreme is defined as the 90th percentile of the population and the reduction is relative to a participant with a median pH 4.5 of vaginal fluid. It is currently not known how stable the vaginal pH is, however a reduction of 15% in vaginal exposure to dapivirine is not expected to impact efficacy of the dapivirine vaginal ring (via PK only), given the fact that concentrations of dapivirine in vaginal fluid exceed the in vitro HIV-1 IC99 by 1000-fold.

The built vaginal fluid population PK model for the dapivirine vaginal ring seems fit-for-purpose. However, clear over- and under predictions were still observed with the final model in the Visual Predictive Checks (VPCs), next to large log-normal SD values (exceeding 0.5) and high shrinkage values. The difficulties seem to lie in adherence issues in the clinical trials, leading to large and unexplainable variations in the data set, questioning whether further model improvement would be achievable at all. In line with this, no significant covariates were found in explaining the large variabilities in the exposure data as observed in the clinical studies, apart from potential site differences related to adherence differences.

A vaginal fluid-plasma link model was developed with many simplifications and limitations and did not perform optimally, which means this model should not be used for regulatory purposes.

#### In vivo release and residual levels

The Applicant claims an average in vivo release of 4 mg over 28 days continuous use.

The amount of dapivirine released increased with extended use (approximately 10 mg during 84 days of continuous use [IPM 034]). Menses and tampon use as well as co-administration of vaginal miconazole or clotrimazole did not appear to affect the amount of dapivirine released from the ring over a 28-day period.

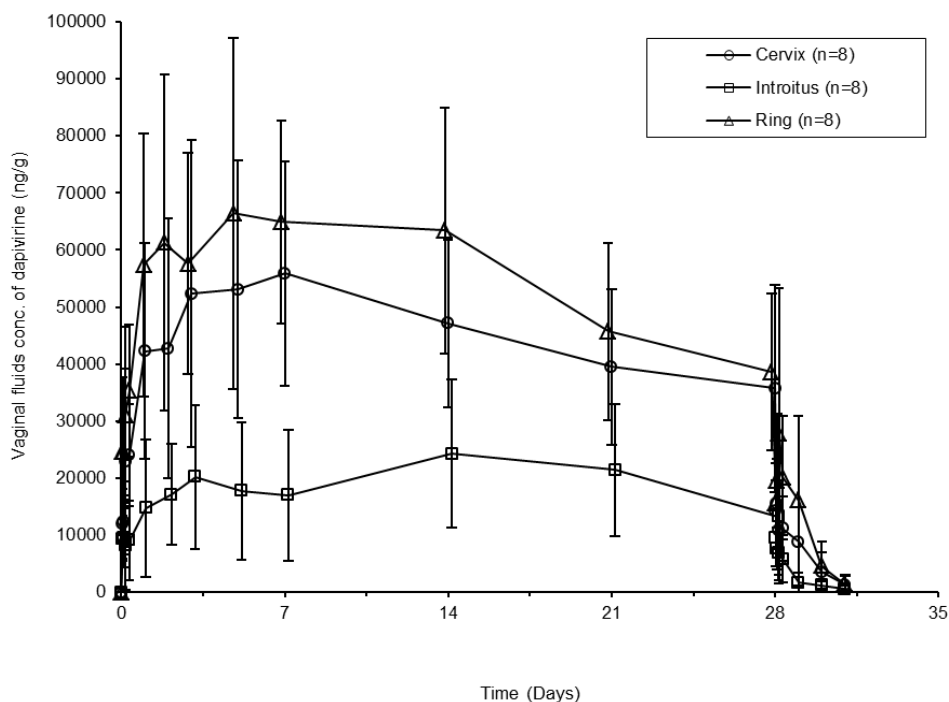
Mean dapivirine ring residual levels were approx. 1 mg higher in the Phase II/III trials compared to the more controlled Phase I trials. Variation in ring residual levels was approx. 9% in the Phase II/III trials and was higher than in the Phase I trials (approx. 4%). For comparison, variation in initial drug load levels, as tested during batch release of the product, was found to be 1.9%. This might be a strong indication that there were adherence problems to ring use in the Phase (II-)III trials.

No clear correlation between plasma DPV concentrations and ring residual DPV levels could be observed in any of the conducted clinical trials or in the pooled data analyses. With regard to the intention to develop potential methods for monitoring adherence in larger trials by means of measuring the residual levels in used rings and correlating them to plasma levels, the measurement of residual ring levels is not a very sensitive measure for adherence, as only a small proportion of the drug load is released during 28 days of ring use, even with full adherence. As a consequence, residual ring levels provide very limited discriminative power to detect short periods of non-adherence.

No formal in vitro-in vivo correlation (IVIVC) has been demonstrated for the dapivirine vaginal ring. It is agreed that IVIVC development in this case might not be a straightforward case, due to the local-acting nature of the drug and predominant local absorption. However, data from residual ring analysis as a function of time worn provides in vivo dissolution for the drug product. Comparison of these data to the corresponding in vitro dissolution results for the clinical batch show that drug release in the body occurs via a diffusion-controlled mechanism, in a similar manner to what is observed in vitro with the QC dissolution method (only developed as a QC test and not to support IVIVC). The Applicant is encouraged to explore further options for IVIVC development as it would help assessing impact of potential future product manufacturing changes.

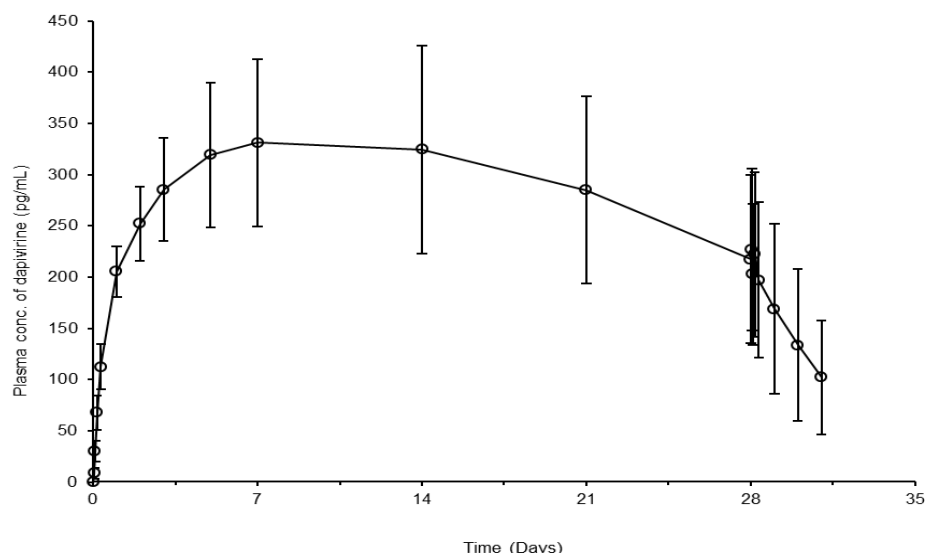
### Absorption

Based on study IPM 024, dapivirine is released from the ring in a sustained manner, distributes into vaginal fluid, and is absorbed into surrounding tissues and plasma. Measurable dapivirine concentrations were detected in vaginal fluid and plasma within 1 to 4 hours after ring insertion. (Figure 2 and Figure 3)



**Figure 2: Mean (SD) Vaginal Fluid Concentration-time Profiles of Dapivirine at the Different Locations During 28 Days of Continuous Use of the Dapivirine Vaginal Ring-004 (IPM 024)**





**Figure 3: Mean (SD) Plasma Concentration-time Profile of Dapivirine (IPM 024)**

Concentrations of dapivirine in vaginal fluid exceeding the in vitro HIV-1 IC<sub>99</sub> (as stated by the applicant) by 1000-fold are achieved within 24 hours of ring insertion. At 4 to 24 hours after ring insertion, vaginal fluid concentrations (at all 3 sampling locations: cervix, ring area and introitus) are similar to those on Day 28 after continuous ring use. Dapivirine plasma concentrations at 24 hours after ring insertion are also similar to those at 28 days after continuous ring use, suggesting tissue concentrations should also be similar. Pharmacokinetic parameters in vaginal fluid (cervix) and plasma are summarized in Table 4 and Table 5. Systemic concentrations of dapivirine observed in plasma with the use of the Dapivirine Vaginal Ring were low (< 2 ng/mL). Dapivirine plasma concentrations stayed well below the MTD after multiple oral administrations: plasma concentrations of dapivirine seen in trials of oral dapivirine (approximately 200 to 4000 ng/mL) are up to 2000-fold higher than plasma concentrations seen in trials using the vaginal route of administration.

**Table 4: Pharmacokinetic Parameters of Dapivirine in Vaginal Fluids (Collected at the Cervix, Near the Introitus, and Near to Where the Ring was Located) (IPM 024)**

Dapivirine in Vaginal Fluid – Cervix, mean (SD)	Dapivirine Vaginal Ring-004 (n = 8)
C <sub>max</sub> (µg/g)	66.61 (20.12)
t <sub>max</sub> (h) <sup>a</sup>	96.60 (4.67 – 336.47)
AUC <sub>0-24h</sub> (µg·h/g)	687.1 (214.1)
AUC <sub>last</sub> (µg·h/g)	30710 (9669)
C <sub>prior to ring removal</sub> (µg/g)	35.78 (18.17)
t <sub>1/2,term</sub> (h)	13.76 (6.92) <sup>b</sup>
Dapivirine in Vaginal Fluid – Introitus, mean (SD)	
C <sub>max</sub> (µg/g)	31.38 (10.95)
t <sub>max</sub> (h) <sup>a</sup>	336.39 (48.45 – 671.40)
AUC <sub>0-24h</sub> (µg·h/g)	259.1 (156.9)
AUC <sub>last</sub> (µg·h/g)	13230 (5704)
C <sub>prior to ring removal</sub> (µg/g)	13.26 (11.14)
t <sub>1/2,term</sub> (h)	– <sup>c</sup>
Dapivirine in Vaginal Fluid – Ring, mean (SD)	
C <sub>max</sub> (µg/g)	79.90 (23.20)
t <sub>max</sub> (h) <sup>a</sup>	84.68 (24.32 – 676.70)
AUC <sub>0-24h</sub> (µg·h/g)	973.2 (270.2)
AUC <sub>last</sub> (µg·h/g)	37750 (9789)
C <sub>prior to ring removal</sub> (µg/g)	38.59 (13.70)
t <sub>1/2,term</sub> (h)	11.82 (4.90)
<sup>a</sup> Median (range)	<sup>b</sup> n = 7 <sup>c</sup> Accurate determination not possible (in CSR: 13.31 (6.04) h)

**Table 5: Pharmacokinetic Parameters of Dapivirine in Plasma (IPM 024)**

Dapivirine in Plasma, mean (SD)	Dapivirine Vaginal Ring-004 (n = 8)
C <sub>max</sub> (pg/mL)	355.0 (87.96)
t <sub>max</sub> (h) <sup>a</sup>	168.54 (120.30 – 336.43)
AUC <sub>0-24h</sub> (pg·h/mL)	3022 (389.1)
AUC <sub>last</sub> (pg·h/mL)	212000 (73900)
C <sub>prior to-ring removal</sub> (pg/mL)	217.5 (82.38)
<sup>a</sup> Median (range)	

The primary site of action of dapivirine is believed to be within CD4 cells in the tissues of the female lower reproductive tract. The precise concentrations of dapivirine in the target cells achieved using the Dapivirine Vaginal Ring 004 are unknown, and even determining dapivirine concentrations within the target tissues has proven to be difficult because of the uncertainty of where drug concentrations were actually measured (e.g. on the tissue surface, in the dead keratinized cell layers, or actually in interstitial fluid and living target cells).

Cervical tissue biopsies were collected in two trials. In study IPM 013, dapivirine concentrations were quantifiable in all participants and the median dapivirine concentration after 28-day use was 0.85 ng/mg, whereas the mean value was 1.91 ng/mg (Arm A). The cervical tissue concentrations in this trial with women of reproductive age were similar to those observed in study MTN-024/IPM 031 with

postmenopausal women. In the latter trial, dapivirine concentrations were only detectable in five of the ten participants (undetectable concentrations probably due to small biopsy samples). The median concentration in the samples with detectable concentrations was 0.60 ng/mg, the mean value was 2.49 ng/mg and individual values ranged from 0.33 to 10.10 ng/mg. Based on the small numbers, and the uncertainty concerning where in the tissue the measured concentrations were located, the data should be interpreted with caution. Furthermore, there were also notable differences in procedural steps and sample processing between the two assays used in both clinical studies.

In general a correlation between dapivirine levels in cervical tissue and the concentration levels in vaginal fluids is missing. According to the Applicant the dapivirine activity in cervical tissue is considered the most relevant for the risk reduction of HIV-1 infection via the genital route. Thus, establishing a correlation study between dapivirine cervical tissue and vaginal fluid levels would have been critical. This, however, has not been presented.

### Distribution

In cervicovaginal fluid, the in vitro protein binding of dapivirine is 15%. Dapivirine is highly bound to plasma proteins (> 99.6%) in vitro.

After vaginal administration of <sup>14</sup>C-dapivirine to non-pregnant rats, concentrations of drug-related material were highest in the vaginal wall, followed by small intestine wall, stomach wall and liver.

In two clinical trials where biopsies were evaluated, the median dapivirine concentrations in cervical tissue after 28 days of using the Dapivirine Vaginal Ring were 850 and 600 ng/g or at least 200 times the stated in vitro IC<sub>99</sub>.

### Metabolism

Given the low systemic exposure seen when dapivirine is administered vaginally as a microbicide, the metabolic fate of dapivirine has not been investigated extensively, based on recommendations provided during a joint Scientific Advice consultation with the European Medicines Agency, US Food and Drug Administration and World Health Organisation in October 2010. A limited number of in vitro and in vivo studies have been performed to investigate the metabolism of dapivirine.

Following oral administration, dapivirine is mainly excreted as metabolite. However, dapivirine seems the largest component in plasma of humans. This indicates that metabolism of dapivirine is extensive, but metabolites are excreted directly where these are formed.

Metabolism in the liver was shown to occur by oxidation and by glucuronidation, of dapivirine itself and of metabolites formed by oxidation. Considering the in vivo pre-clinical and clinical data, glucuronidated dapivirine is expected to be the most important metabolite in humans.

Dapivirine is metabolized primarily by CYP3A4/5 in human liver, with contributions from CYP2B6 and CYP2C19. In addition, a large number of UGT enzymes (UGT1A1, -1A3, -1A4, -1A6, -1A7, -1A8, -1A9, -1A10, -2B4, -2B7 and -2B15, according to To et al., 2013) are involved in the formation of dapivirine glucuronide metabolites.

Studies with vaginal tissue samples from three healthy human donors indicate that expression and activity of CYP enzymes were found in vaginal tissue. Expression and activity of UGT enzymes were not found in vaginal tissue, according to the Applicant based on To et al., 2013.

No metabolites unique to vaginal tissue (i.e. not formed by liver fractions or hepatocytes) were found, indicating that human liver microsomes and hepatocytes may be used to predict the local metabolism after vaginal administration. The studies performed by To et al (2013) indicate that metabolism is expected to occur in human vaginal tissue and this may be a source of variation (for example because of CYP3A5 polymorphism) in the local exposure to dapivirine.

No transporters studies with dapivirine have been performed. However, based on the outcome of study IPM 028 the Applicant has indicated that transporter studies would be initiated in order to better understand the unexpected results of this study. The results of the transporter studies are requested to be submitted as a Post-Authorisation Measure by Q3 2020. The paper of Zhou et al., 2013 indicates that six efflux transporters and six uptake transporters were found to be highly expressed in human ectocervix and vagina.

### Elimination

In the overall clinical trial population, the terminal elimination half-life ( $t_{1/2}$ ) of dapivirine was approximately 13 hours in vaginal fluid (cervix) and approximately 82 hours in plasma. 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.

In trials IPM 035 (preliminary data) and IPM 036, temporary ring removal for various periods and subsequent re-insertion resulted in a marked drop in dapivirine vaginal fluid concentrations. After re-insertion of the same ring, vaginal fluid concentrations started to increase again immediately and returned to levels similar as observed prior to ring removal.

## ***Dose proportionality and time dependencies***

### Time dependency

Median trough vaginal fluid concentrations of dapivirine were steady over time in study IPM 027 (preliminary data) over a period of 2 years continuous use of the dapivirine ring. No systematic trends over time could be observed either for dapivirine measured in plasma, in studies IPM 027 (preliminary data), IPM 015 (over 12 weeks) and MTN 020 (over 3 years). Therefore, no signs of time dependency of dapivirine pharmacokinetics upon chronic use seem to be present.

### Inter- and intra-individual variability

Inter-subject variability in vaginal fluid PK parameters ranged from 30-50% across the Phase I studies and tended to be somewhat higher for the introitus site as compared to the ring and cervix collection sites. This variability can be considered moderate and is lower as compared to variability caused by oral formulations. Inter-subject variability in plasma PK parameters was even lower with %CV ranging from 20 to 30% across the Phase I studies.

Inter-subject variability in vaginal fluid (cervix) trough dapivirine concentrations in Phase II/III studies MTN-024/IPM 031 and IPM 027 was in the order of 100%, considerably larger than the variability in the more controlled Phase I studies and might question the explanatory power of these parameters. Additionally, these results reveal that subjects in the Phase II/III trials seemed to be less adherent to the 28-day regimen than Phase I trial subjects.

For example, for study IPM 015 (performed in Africa), the intra- and inter-individual coefficients of variation (CVs) of trough dapivirine plasma concentrations were 74% and 109%, respectively. For MTN-024/IPM 031 (performed in USA), the intra- and inter-individual CVs of trough dapivirine plasma concentrations were 25% and 48%, respectively. For trough dapivirine vaginal fluid concentrations, the corresponding CVs were 109% and 147%. The more flexible visit window periods in study IPM 015 as compared to study MTN-024/IPM 031 are a possible explanation for the higher variability observed in trough dapivirine plasma concentrations in study IPM 015, as well as potential different adherence in the African sites as compared to the US sites.

From the population PK analysis it was concluded that inter-individual variabilities were large, with CV values up to 85%, indicating a large spread in exposure among women using the Dapivirine Vaginal Ring.

### ***Special populations***

In trial MTN-024/IPM 031 dapivirine vaginal fluid concentrations (at the cervix) and in plasma were evaluated in postmenopausal women (45 to 65 years of age) at ring removal (Week 4, 8 and 12). Median dapivirine vaginal fluid and plasma concentrations were similar for the three visits. However, the mean dapivirine plasma concentrations tended to increase over the 12 weeks follow-up and a performed F-test indicated a trend over time. Compared to the other clinical pharmacology trials with mostly premenopausal women, the mean vaginal fluid concentrations appeared to be two-fold higher (mean 64 to 79 µg/g) compared to mean values of 20 to 36 µg/g in other clinical pharmacology trials; median concentrations tended to be lower, at 34-45 µg/g, while no differences in plasma concentrations were observed. Additionally, a high inter-individual variability was observed. The covariate analysis performed in the population pharmacokinetic analysis also did not show a clinically relevant effect of age on dapivirine vaginal fluid pharmacokinetics (menopausal state was not evaluated as covariate). Trial MTN-024/IPM 031 is considered to be representative for the elderly population. The most likely reason for the apparent difference in dapivirine vaginal fluid concentrations may be that postmenopausal women have lower vaginal fluid volumes compared to premenopausal women.

A potential impact of race on the pharmacokinetics of dapivirine cannot be directly deduced from the available data, as the performed clinical pharmacology trials generally enrolled Caucasian participants, while in the Phase III trials most participants were Black. As such, the Caucasian race coincides with trials under controlled settings with frequent sampling, while the Black race coincides with trials performed in the clinical setting, with sparse sampling. For this reason, race was not evaluated as covariate in the population PK model development. In pivotal Phase III study IPM 027 (preliminary data), the overall trough median dapivirine vaginal fluid concentration (after approx. 28 days of ring use) was 13.2 µg/g. In the clinical pharmacology trials, mean values ranged between 20 to 36 µg/g. Median dapivirine plasma concentrations prior to ring removal were 264 pg/mL in IPM 027 and 199 pg/mL in MTN-020, compared to mean values of 218 to 329 pg/mL in the clinical pharmacology trials. Considering the different setting of the Phase III and clinical pharmacology trials the above data suggest that dapivirine vaginal fluid and plasma concentrations were at least within the same range in Black and Caucasian participants. The lower median trough dapivirine vaginal fluid concentration from study IPM 027 is likely caused by the reported adherence issues in the Phase III trials rather than being a race effect. However, a more extensive PK sampling in the target population would have been helpful.

Body weight was also tested as a covariate in the population PK analysis and was found to be a statistically significant covariate on elimination rate and on V. The impact of this covariate did not exceed the clinical significance criterion.

In view of the low systemic exposure of dapivirine when using Dapivirine Vaginal Ring, hepatic impairment is not expected to affect dapivirine exposure. In view of the low systemic exposure of dapivirine when using Dapivirine Vaginal Ring and the fact that oral dapivirine was shown to undergo negligible renal clearance, renal impairment is neither expected to affect dapivirine exposure.

A pharmacokinetic trial in healthy HIV-negative lactating women at least 6 weeks postpartum, who were able to produce breast milk but were not breastfeeding (study MTN-029/IPM 039) showed that dapivirine concentrations were approximately 2-fold (based on  $C_{max}$ ) and 1.7-fold (based on  $AUC_{0-14days}$ ) higher in breast milk compared to plasma. The median ratio of dapivirine in cervicovaginal fluid (CVF) to plasma was approximately 118 based on  $C_{max}$  and 62 based on  $AUC_{0-14days}$ , confirming that systemic exposure is very low compared to local vaginal exposure. Estimated potential daily levels of infant exposure to

dapivirine were low (~75 ng/kg/day) compared to the MTD for multiple oral dapivirine doses in adults of 300 mg twice daily (equivalent to 12 mg/kg/day for a 50 kg woman). The estimated daily dapivirine intake by an 8-kg breastfed infant was calculated at 594 ng/day based on the daily consumption of 150 mL/kg/day breast milk and a mean dapivirine intake of 74 ng/kg/day. However, it must be noted that these data may be different for women who are actually breastfeeding as they will likely have a different amount of milk production, different blood flow in breast tissue etc.

Study MTN-023/IPM 030 was a Phase IIa study for a 24-week ring use period in healthy, HIV-negative, sexually experienced adolescent females between 15 and 17 years of age. The dapivirine concentrations in plasma at ring removal remained comparatively constant over the test period of 24 weeks and were more or less similar those observed in other trials in adult women between 18-65 years of age.

## ***Pharmacokinetic interaction studies***

### Drug-drug interactions

Considering the low plasma concentrations of dapivirine, no effect of dapivirine on the exposure of systemically co-administered drugs, that are either a substrate for CYP enzymes or transporters, is expected. Furthermore, no clinically relevant effects of other systemically co-administered drugs are expected on plasma concentrations of dapivirine.

Studies with vaginal tissue samples from three healthy human donors indicate that expression and activity of CYP enzymes were found in vaginal tissue. Expression and activity of UGT enzymes were not found in vaginal tissue, according to the Applicant based on To et al., 2013. Additional UGT and transporter inhibition studies using clinically relevant concentrations reached locally for the relevant UGTs and transporters, for which test systems are available, will be performed and submitted as a Post-Authorisation Measure by Q3 2020.

### *Drug-drug interaction between miconazole and dapivirine*

A drug-drug interaction study (IPM 028) with vaginally administered miconazole nitrate, as an oil-based formulation in a vaginal capsule, was conducted.

Co-administration of the Dapivirine Vaginal Ring with a single vaginal dose of 1200 mg miconazole nitrate resulted in temporarily lower vaginal fluid concentrations and a modest increase in systemic exposure of dapivirine. During the first days after insertion the dapivirine vaginal fluid levels were approx. 2 to 3-fold lower in presence of miconazole nitrate, and from Day 14 onwards dapivirine vaginal fluid levels were higher in presence of miconazole nitrate, as compared to treatment with the ring alone. Systemic (plasma) exposure to dapivirine was increased 1.2-fold from three days on after ring insertion.

The Applicant argued that this might partially be explained by inhibition of hepatic CYP3A4 by miconazole, however the miconazole plasma concentrations decline too fast to explain the long-lasting increase seen in plasma concentration of dapivirine (up to ring removal). Furthermore, the decrease in dapivirine concentrations in vaginal fluid cannot be explained by hepatic CYP3A4 inhibition. Both effects on dapivirine concentrations, i.e. a decrease in vaginal fluid concentrations and increase in dapivirine plasma concentrations might be explained by inhibition of efflux transporters in the vaginal wall. Although in vitro experiments have shown that dapivirine is not a substrate for P-glycoprotein, many other (efflux) transporters (BCRP, MRP1, MRP4, MRP5, and MRP7) were identified in the vaginal wall. However, the exact mechanism behind the observed interaction remains to be elucidated and more extensive in vitro transporter studies for both dapivirine and miconazole will need to be performed to understand the underlying mechanism of the interaction (this is part of the above-mentioned Post-Authorisation Measure).

Local and systemic miconazole exposure was increased after co-administration of a single dose of vaginal miconazole nitrate with the Dapivirine Vaginal Ring compared to miconazole nitrate alone; miconazole concentrations in vaginal fluids were 6-fold higher and miconazole concentrations in plasma were 4-fold higher. As both vaginal fluid and plasma concentrations of miconazole increased, it is not expected that miconazole nitrate would be less efficacious if co-administered with the Dapivirine Vaginal Ring. With regard to safety, the mean plasma  $C_{max}$  for miconazole after treatment with 1200 mg miconazole nitrate in the presence of the Dapivirine Vaginal Ring was 11.7 ng/mL, whereas the mean plasma  $C_{max}$  after 60 mg miconazole nitrate oral gel formulation was approximately 4-fold higher (31-49 ng/mL). As no major safety concerns or (severe) AEs were reported after oral gel exposure, this is also not expected when vaginally applied miconazole nitrate at a dose of 1200 mg is used in the presence of the Dapivirine Vaginal Ring.

Due to the presence of capsule remnants in the vaginal fluid, there were some methodological difficulties/uncertainties related to the measurements of the vaginal concentrations of both drugs. Therefore, it must be concluded that the results of this interaction study cannot be considered reliable. Moreover, the clinical relevance of the reduced vaginal dapivirine levels upon co-administration with vaginal miconazole is unclear. Therefore, women should be advised to use additional preventive measures against HIV, when co-treated with vaginal miconazole.

#### *Drug-drug interaction between clotrimazole and dapivirine*

A further trial (IPM 036) to investigate the potential for interactions with another clinically relevant vaginally co-administered drug (clotrimazole, which is the most commonly used antifungal azole in South Africa) was performed. In this study daily 5 g dose of clotrimazole 10 mg/g (1%), a water-based vaginal cream (antifungal), was administered for 7 consecutive days. Clotrimazole is a CYP3A4 inhibitor (next to 1A2, 2C9, 2D6, 2C19 inhibitor). Local levels (in vaginal fluid collected at the cervix) of dapivirine and clotrimazole were similar to slightly higher during co-administration, which is not considered to be clinically relevant. However, there are some methodological caveats to this study. Vaginal sampling for measurement of both dapivirine and clotrimazole was only done at the cervix and it is not clear how much of the clotrimazole cream got into the cervix, since it can be assumed that most of the cream was attached to the vaginal walls. This may have led to a temporary dilution of the vaginal fluid and hence also of the dapivirine concentrations. Thus these study results can also not be considered representative. Therefore, concurrent use of both products should be undertaken with caution.

The Applicant's plan to conduct in-vitro transporter studies to better understand the mechanism of the observed interaction is appropriate. This information can be used to make predictions for co-administration of dapivirine (formulated as vaginal ring) with other intra-vaginally applied (azole) antifungals and may result in recommendations for drug use in the intended SmPC/PIL. The transporter studies will be submitted as a Post-Authorisation Measure by Q3 2020. It is advised that if in vitro data indicate that dapivirine is a substrate or inhibitor of drug transporters, that the Applicant will investigate the in vitro substrate and or inhibition potential for the same transporters.

#### *Effects of menses and tampon use*

The effects of menses and tampon use on dapivirine vaginal fluid and plasma concentrations were evaluated in a dedicated trial where oral contraceptives were used to regulate the timing of menses relative to the ring use period (IPM 035, preliminary data). It is assumed that oral contraceptives had no influence on the vaginal fluid PK of dapivirine, which seems reasonable.

When the Dapivirine Vaginal Ring was used continuously for 28 days, dapivirine vaginal fluid concentrations at all locations decreased during menses but increased again thereafter and typically achieved concentrations consistent with the control (no menses) group after completion of menses. The use of tampons generally resulted in slightly more pronounced decreases in vaginal fluid concentrations



during menses, which were most apparent at the introitus. Dapivirine plasma concentrations were not notably affected.

From the mean concentration-time profile it may be concluded that on Day 15 dapivirine concentrations in vaginal fluid are decreased approximately 6-fold as compared to Day 11, regardless of tampon use. As the clinical relevance of the reduced vaginal dapivirine levels during menses and potential tampon use is unclear, women should be advised to use additional preventive measures against HIV during menses.

Studies IPM 035 and IPM 036 also evaluated the impact on dapivirine exposure when the ring was removed during menses and re-inserted afterwards. Ring removal resulted in marked reductions in dapivirine concentrations in vaginal fluid and plasma, in vaginal fluid to undetectable levels two days after ring removal, and therefore continued use of the ring during menses is recommended.

### 2.4.3. Pharmacodynamics

Dapivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTIs bind to and block HIV reverse transcriptase (RT) intracellularly, thereby preventing HIV from replicating. The primary site of action for the Dapivirine Vaginal Ring-004 therefore is considered to be within CD4 cells in the tissues of the lower female reproductive tract.

During male-to-female sexual transmission, HIV is transferred from semen to an uninfected female partner. HIV can be present in semen as free viral particles or cell-associated HIV-1, both forms are thought to be infectious (reviewed in Anderson et al., AIDS. 2010; 24:163–187). Several natural barriers exist that protect the female genital tract, including the presence of mucus. Viral particles or virus-infected cells that defy the cervical mucus can reach the epithelial layer, which constitutes another barrier to efficient transmission of HIV and other pathogens. This barrier can however be significantly weakened through lesions that commonly occur as a result of various infections or coital/sexual abrasion. Moreover, the cervix (especially the endocervix and the transitional zone), thought to be the main site for HIV transmission in the female genital tract, is covered by only a single-layer columnar epithelium. Once the epithelial barrier has been overcome, migrant free HIV-1 or HIV-1-infected cells reach the submucosal tissue, wherein they can interact with HIV-1 target cells (i.e. activated CD4 T cells and macrophages). Uptake of HIV by host dendritic cells (DCs), and subsequent transfer to local lymph nodes by these DCs, is also thought to significantly contribute to viral dissemination (see also Barreto-de-Souza et al., *Am J Reprod Immunol.* 2014).

The precise concentrations of dapivirine in the target cells achieved upon use of the Dapivirine Vaginal Ring-004 are unknown, and determining concentrations within the target tissues has proved difficult because of the uncertainty of where measured drug levels are actually located (eg, on the tissue surface, in the dead keratinized cell layers, or actually in the living cells). As there is no surrogate marker or model for risk reduction in HIV-1 infection acquired via vaginal intercourse, no *in vitro-in vivo* correlation studies or pharmacodynamic trials were performed. Using *in vitro* assays, the applicant determined the 99% inhibitory concentrations (IC<sub>99</sub>) for dapivirine in vaginal tissue to be 3.3 ng/ml.

Results of Study IPM 013, where vaginal fluid samples collected by cervicovaginal lavage of women treated with dapivirine-containing vaginal rings were challenged *in vitro* with HIV-1, suggest that the dapivirine levels present in vaginal fluid have some kind of inhibitory effect. HIV-infection was inhibited by a mean of 89% when the samples were used undiluted, and by 71% when diluted 10-fold. Whether this corresponds to a similar *in vivo* inhibitory effect is however unknown.



## ***Mechanism of action***

Dapivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI), and the primary site of action for the Dapivirine Vaginal Ring-004 is believed to be within CD4 cells in the tissues of the lower female reproductive tract. The precise concentrations of dapivirine in the target cells achieved using the Dapivirine Vaginal Ring-004 are unknown, and even determining concentrations within the target tissues has proved difficult because of the uncertainty of where measured drug levels are actually located (eg, on the tissue surface, in the dead keratinized cell layers, or actually in the living cells).

A study in sheep was performed in which dapivirine levels in tissues of the reproductive tract were evaluated by taking transverse sections from the mucosal to the serosal surfaces with stringent measures to limit the potential for drug contamination.

Analysis of tissue samples demonstrated the presence of dapivirine throughout the vaginal wall, ranging from 8.59 to 738 ng/g (equivalent to approximately 8.59 to 738 ng/mL), and generally showing a decreasing concentration gradient from the mucosal to the serosal surface. In human ectocervical tissue explants challenged in vitro with HIV-1, dapivirine achieved greater than 99% inhibitory concentrations (IC<sub>99</sub>) at concentrations  $\geq 10$  nM (3.3 ng/mL).

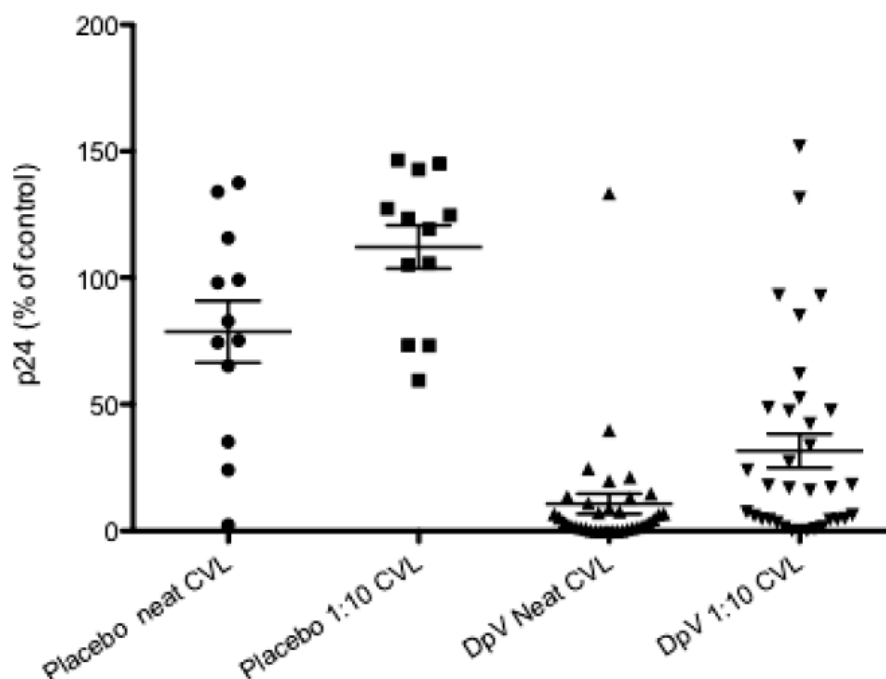
Further evidence of the likely efficacy of the Dapivirine Vaginal Ring-004 was seen in ex vivo PK assessments performed using vaginal fluid samples collected by cervicovaginal lavage in a Phase I trial (IPM 013) using an HIV replication assay in T cell cultures. The analyses demonstrated that, despite the significant dilution (approximately 50-fold) of drug associated with the lavage sample collection method, there remained sufficient bioactive drug within the samples to inhibit HIV-infection by a mean of 89%, and samples retained 71% inhibitory activity even when diluted a further 10-fold. In another Phase I trial (MTN-013/IPM 026), a very similar ring made of the same silicone and containing 25 mg dapivirine alone or in combination with the C-C chemokine receptor type 5 antagonist maraviroc, demonstrated a dapivirine concentration-related inhibition of HIV-1 in cervical tissue biopsies challenged ex vivo.

## ***Primary and Secondary pharmacology***

### **Primary pharmacology**

#### ***From study IPM 013- Vaginal Fluid Samples Collected by Cervicovaginal Lavage:***

Samples from participants in study IPM 013 (a double-blind, randomized, placebo-controlled trial, conducted over three months at one research center in Belgium among 48 healthy, human immunodeficiency virus (HIV)-negative, sexually active women) treated with vaginal rings containing dapivirine, inhibited HIV-infection by a mean of 89% when used neat, and retained 71% inhibitory activity even when diluted 10-fold. The variability in antiviral activity was higher among participants exposed to placebo rings, resulting in interquartile range (IQR) values of 68.93 and 57.69 for neat and diluted samples, respectively. IQR values corresponding to participants exposed to dapivirine rings were 10.55 and 43.49 for neat and diluted samples, respectively (Figure 4).



**Figure 4 Antiviral activity of neat or 1:10 dilution of each cervicovaginal lavage sample collected post-application of placebo or dapivirine vaginal ring. Each symbol represents the mean p24 from triplicate wells as a % of virus control obtained for each sample.**

Results of the antiviral assay demonstrated that there was sufficient bioactive drug within the cervicovaginal lavage fluids collected from women using the dapivirine vaginal ring to provide significant anti-HIV activity in neat cervicovaginal lavage fluid. Mean dapivirine concentrations measured in the neat lavage fluids were  $197.3 \pm 137.5$  ng/mL for Group A and  $189.2 \pm 113.6$  ng/mL for Group B, and these are approximately 50 to 170 times lower than the concentrations (10 to 32  $\mu\text{g/g}$ ) measured in samples collected using tear test strips at the same time points. These differences are likely due to dilution effects associated with the use of saline during the lavage collection procedure, the possible precipitation of dapivirine following the addition of saline, and adsorption of dapivirine to the collection equipment. Consequently, the pharmacodynamic assay results can be considered to represent considerable underestimations of the in vivo bioactivity of dapivirine in cervicovaginal fluids.

#### Cervical Tissue – Ex Vivo Challenge with Human Immunodeficiency Virus

Cervical tissue samples, obtained by biopsy on Day 28 (Arm A) or Day 35 (Arm B), were collected for ex vivo challenge with HIV to assess whether they were protected from HIV infection. However, similar studies performed during IPM 020 failed to produce reliable results. Further investigations suggested that samples needed to be fresh in order for the assay to work; however, the samples collected in this trial and IPM 020 were frozen prior to testing. Consequently, the samples from this trial were not evaluated.

#### **Secondary pharmacology**

Based on the low systemic concentrations of dapivirine observed in trial participants receiving vaginal formulations of dapivirine and the absence of a nonclinical QTc signal at clinically relevant concentrations, as well as the absence of any clinically relevant abnormalities in electrocardiograms (ECGs) in any clinical trial with oral dapivirine, no thorough QTc trial was conducted in support of the Dapivirine Vaginal Ring-004. Scientific Advice from the Committee for Medicinal Products for Human Use (CHMP) and the United States (US) Food and Drug Administration (FDA) confirmed that a thorough QTc trial was not required.

## 2.4.4. Discussion on clinical pharmacology

No *in vitro-in vivo* correlation studies or pharmacodynamic trials were performed.

Although the mechanism of action of dapivirine vaginal ring as PrEP is understood (blocking HIV-1 infection by inhibiting the process of HIV-1 reverse transcription), the precise dapivirine concentration in the target cells needed to reach this goal is unknown. As mentioned by the applicant, determining dapivirine concentrations within the target tissues is difficult and was unsuccessful at several occasions. As such, the applicant determined the 99% inhibitory concentrations (IC<sub>99</sub>) for dapivirine in vaginal tissue using *in vitro* assays, and aims to induce dapivirine levels well in excess of this IC<sub>99</sub> concentration (determined to be 3.3 ng/ml in vaginal tissue) in clinical practice. Results of an *in vitro* HIV model suggest that the dapivirine levels present in vaginal fluid have some kind of inhibitory effect, but whether this corresponds to a similar *in vivo* inhibitory effect is unknown.

## 2.4.5. Conclusions on clinical pharmacology

While the chosen strategy and the difficulties around the analysis of dapivirine concentrations in the target cells can be understood, there are uncertainties regarding the applicability of the *in vitro* observed IC<sub>99</sub> concentration for the real-life clinical situation. These uncertainties are unlikely to be solved with the currently available data. Given that there is efficacy data on which the eventual benefit/risk assessment will be based, this is accepted by the CHMP.

## 2.5. Clinical efficacy

The evaluation of the efficacy profile of the Dapivirine Vaginal Ring-004 in reducing the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-1 negative women in combination with safer sex practices is based on the results from the two Phase III trials IPM 027 and MTN-020 conducted in sub-Saharan Africa (cf. Table 6).

**Table 6 Phase III trials and main additional studies**

Study	Study Design	Numbers by Treatment Regimen	Primary endpoint
<i>Pivotal Efficacy and Safety Studies</i>			
<b>IPM 027 (Ring Study)</b> Healthy, HIV-negative women in South Africa and Uganda	104-week, Phase III, multi-center, randomized, double-blind, placebo-controlled study	m-ITT Population: Dapivirine: 1300 Placebo: 650	Incidence rate of HIV-1 seroconversion
<b>MTN-020 (Aspire)</b> Healthy, HIV-negative women in Malawi, South Africa, Uganda, and Zimbabwe	Endpoint driven, Phase III, multi-center, randomized, double-blind, placebo-controlled study	m-ITT Population: Dapivirine: 1313 Placebo: 1313	Incidence rate of HIV-1 seroconversion
<i>Main additional Studies</i>			
<b>TMC120-C105</b> Antiretroviral naïve, HIV-1 positive subjects	Double-blind, randomized, Placebo-controlled, dose-finding, multi-center trial	50 mg b.i.d.: 13 100 mg b.i.d.: 15 Placebo: 15	Viral load decay rates during 7-day treatment with dapivirine
<b>IPM 032 (Dream)</b> Ongoing study, final CSR expected Q4 2019	Open-label extension trial to IPM 027	Estimated enrollment 1700	Safety and adherence, Incidence rate of HIV-1 seroconversion
<b>MTN-025 (Hope)</b> Ongoing study, final CSR expected Q4 2019	Open-label extension trial to MTN-020	Estimated enrollment 2500	Safety and adherence, Incidence rate of HIV-1 seroconversion

### 2.5.1. Dose response studies

No clinical dose-finding Phase IIb trial was conducted. The dapivirine molecule was originally developed as an oral ARV drug (TMC120) in the late 1990s. A dose response study (**TMC120-C105**) was conducted with the oral drug. Study TMC120-C105 (TIBO-0001-105) was a phase IIa randomized, double-blind, placebo-controlled single drug therapy dose-finding trial in antiretroviral naive HIV-1 positive subjects. Subjects received either placebo or 50 mg TMC120 b.i.d. or 100 mg TMC120 b.i.d. for a 7-day treatment period. In total, 43 subjects were enrolled in the trial, 15 in the placebo group, 13 in the 50 mg TMC120 treatment group and 15 in the 100 mg TMC120 treatment group. All subjects, except 1 in the 50 mg TMC120 treatment group completed the trial. The main conclusion drawn from this trial was that TMC120 administered as 50 mg or 100 mg b.i.d. for 7 days was well tolerated and safe. Both doses were effective in reducing the viral load, mean viral load decay in the 50 mg b.i.d. group was -0.21 RNA copies/ml/day and -0.24 RNA copies/ml/day in the 100 mg b.i.d. group.

No formal dose-finding study has been performed with the dapivirine vaginal ring. In an effort to create an optimal drug delivery system, IPM developed four different dapivirine vaginal ring formulations. The first three rings (Ring-001, Ring-002 and Ring-003), as well as several gel formulations, were tested in Phase I clinical trials and Phase I/II clinical trials (for two gel formulations only); all were found to be generally safe and well tolerated. The first three rings (Ring-001, Ring-002, and Ring-003) were however not developed further due to stability issues and/or suboptimal *in vivo* drug release characteristics. Ring-004 containing 25 mg of dapivirine is the product intended to be registered and marketed that delivers approximately 4 mg dapivirine over a period of one month (28 days) *in vivo*.

As also mentioned in the pharmacokinetics and pharmacodynamics sections of this report, the applicant considers the *in vitro* dapivirine activity in cervical tissue (99% inhibitory concentration [IC<sub>99</sub>] against HIV-1BaL = 3.3 ng/ml) relevant for the risk reduction of HIV-1 infection via the genital route and therefore targets concentrations well in excess of 3.3 ng/ml to be induced by the vaginal ring. Use of the Dapivirine Vaginal Ring-004 results in vaginal fluid concentrations of dapivirine that are more than 3000-fold higher than the above mentioned IC<sub>99</sub> within 24 hours after ring insertion. Vaginal fluid concentrations do however not necessarily correlate with the concentration within the CD4 cells in the tissues of the lower female reproductive tract. The evidence that Dapivirine Vaginal Ring-004, containing 25 mg dapivirine, provides the dapivirine exposure in the vaginal tissue required to effectively protect a woman from contracting HIV-1, is therefore considered to be limited.

### 2.5.2. Main studies

#### Title of the studies

**IPM 027 (Ring Study) - A 104-week, Phase III, Multi-Center, Randomised, Double-Blind, Placebo-Controlled Safety and Efficacy Trial of a Dapivirine Vaginal Matrix Ring in Healthy HIV Negative Women.**

**MTN-020 (Aspire) - An endpoint driven, Phase III, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Safety and Effectiveness Trial of a Dapivirine Vaginal Matrix Ring in Healthy HIV Negative Women.**

Both **IPM 027** and **MTN-020** are Phase III, multi-center, randomized, double-blind, placebo-controlled studies, conducted to assess the safety and efficacy (IPM 027) or effectiveness (MTN-020) of Dapivirine Vaginal Ring-004 when inserted once every 4 weeks in healthy, HIV-negative women.

Study MTN-020 can however no longer be regarded as confirmatory for the efficacy of the Dapivirine Vaginal Ring, due to the serious and manifold uncertainties surrounding the data quality and reliability

that became evident during the GCP inspection and due to the possible bias on the estimated effect by stopping the recruitment of two centers.

### **Study participants, sample size and randomisation**

Both studies included sites in South Africa and Uganda, and study MTN-020 additionally had sites located in Malawi (n=272 subjects enrolled (10% of total population for study MTN-020)) and Zimbabwe (n=678 subjects enrolled (25.8% of total population)).

The population eligible for participation in either IPM 027 or MTN-020 was roughly similar, and corresponds to a population that is considered relevant for the sought indication. The studies differed in several aspects in their design, including:

- Sample size (IPM 027: ~1950 participants, MTN-020: ~2600 participants)
- Assumed annual HIV incidence rate within the population (IPM 027: 4%, MTN-020: 5%)
- Expected detectable reduction in HIV infection rate (IPM 027: 50%, MTN-020: 40%)
- Randomization (IPM 027: 2:1 ratio, MTN-020: 1:1 ratio)
- Duration (IPM 027: 104 weeks, MTN-020: until 120 HIV seroconversions were observed (endpoint driven trial))
- Interim analysis (IPM 027: one reported interim efficacy analysis was performed when approximately 50% of the targeted events had occurred and the significance level of the primary analysis was adjusted for this interim look, MTN-020: three interim DSMB efficacy analyses were performed when approximately 25%, 50% and 75% of targeted events had occurred, but without adjustment of the significance level of the primary analysis).

### **Statistical methods and endpoints**

The primary efficacy endpoint (HIV-1 seroconversion rate) and important secondary efficacy endpoints (including HIV-1 drug resistance mutations among participants who acquired HIV-1, and adherence to and acceptability of ring use) were generally comparable between the trials and considered relevant. Of note, monthly (28 days) samples were collected for HIV RNA testing in IPM 027, while these were collected 3-monthly (84 days) in MTN-020.

The efficacy analyses were performed for the modified intent-to-treat (m-ITT) population, which included all participants who were randomized to one of the two treatment groups, Dapivirine Vaginal Ring-004 or Placebo Ring and were never determined to be HIV-seropositive at the enrolment Visit.

In general, the applied statistical methods appear appropriate and it is accepted although not pre-specified that in the MTN-020 study the Cox Proportional Hazards model stratified for center was used in the primary efficacy analysis. In IPM 027 the same model was pre-specified and used in the primary efficacy analysis.

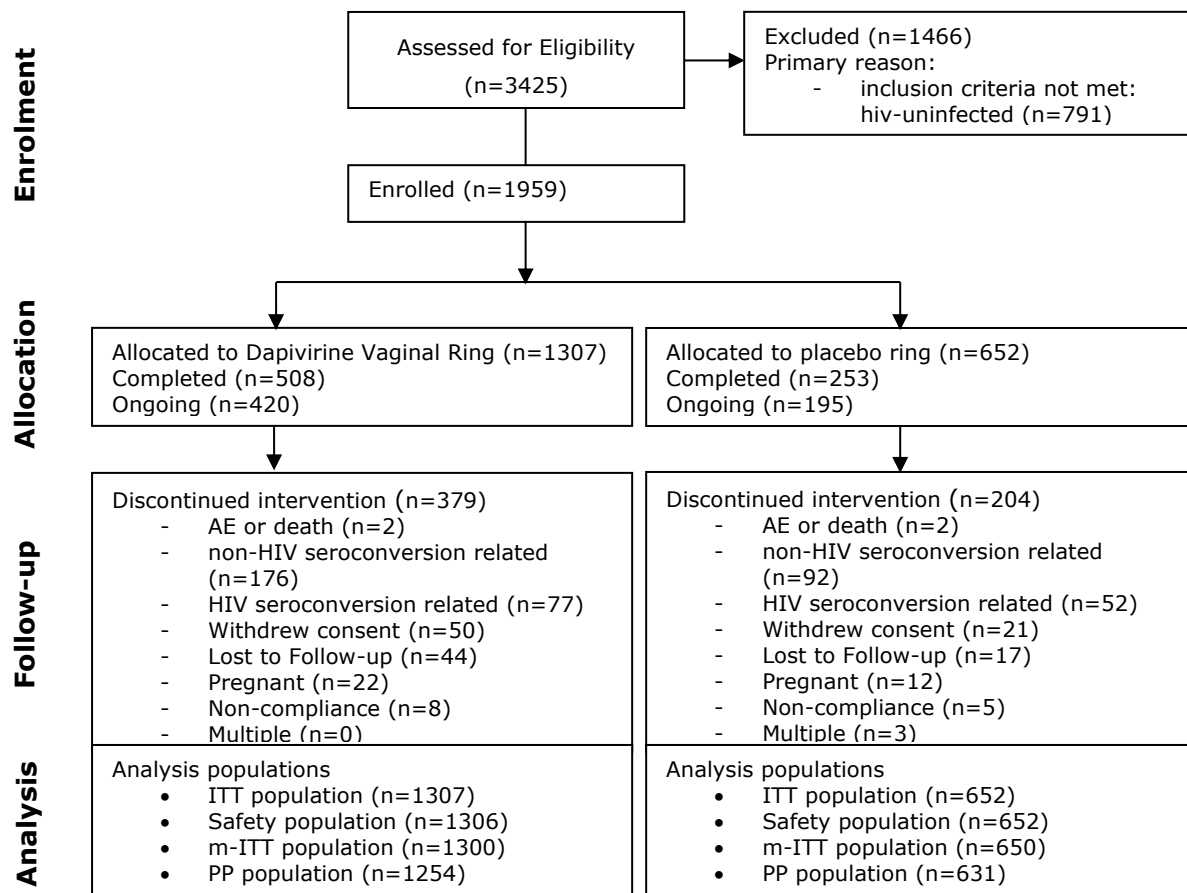
In the CSR of the MTN-020 study, the alpha level of the primary analysis was not adjusted for multiplicity upon performing the interim analyses. Two adjustments were proposed by the applicant: an O'Brien-Flemming adjusted alpha level and a simulated adjusted alpha level. The applicant mentioned that the O'Brien-Flemming adjusted level cannot be used in the MTN-020 as this method can only be applied in case the same null hypothesis was used in the interim analyses as well as in the primary analysis. This is acknowledged, because the null hypothesis of 25% was used in the interim analyses, while the primary analysis was tested against the null hypothesis of 0%. The simulated adjusted alpha level was determined by the applicant based on a simulation program. In this program, for each interim analysis,

the number of trials for which the null hypothesis of 25% is rejected is based on all 2626 subjects. This is not correct, because not all 2626 participants were already enrolled at time of first interim analysis. In fact the number of participants at first interim were 1678. It is not clear whether the performed simulation program gives an expected smaller alpha level than the real alpha level and thus may lead to an overestimation of the adjusted alpha level. Therefore, the true adjusted alpha level will be between 0.0446 (OB method) and 0.0499 (an over-estimated alpha adjustment based on not correctly performed simulation method).

The main post-hoc/sensitivity analyses for the IPM 027 were the primary analysis excluding all participants enrolled at Center 03, primary analysis with placebo imputation of missing data, and a primary analysis before and after adherence counselling (cut-off date of 31 May 2013) and for the MTN-020 study these were the primary analysis excluding all participants enrolled at Centers 320 and 321, the protocol sensitivity analysis with the original protocol primary endpoint, and a primary analysis before and after adherence counselling (cut-off date of 31 May 2013).

- **Participant flow**

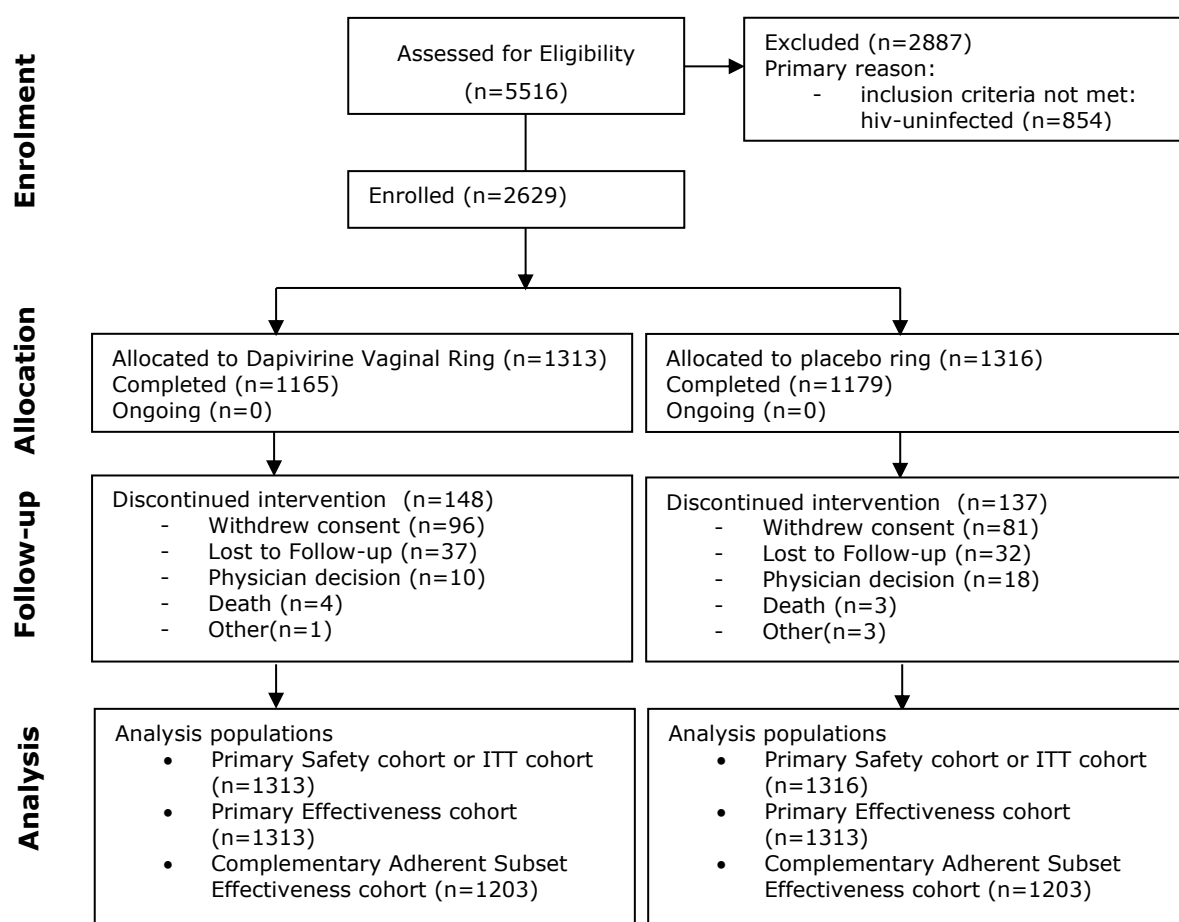
### Study IPM 027 (Ring Study)



**IPM 027 (Ring study): First Subject First Visit: 27 March 2012, 13 December 2016 (date of last contact).**

The data cut-off for the final analysis of primary endpoints: 16 October 2015.

## Study MTN-020 (Aspire)



### MTN-020 (Aspire): First Subject First Visit: 24 July 2012.

Last Subject Last Visit: 03 July 2015.

## Results

### Baseline data

For both studies, the two treatment groups were well matched with respect to demographic characteristics.

In IPM 027, the majority of participants were Black (1941/1959; 99.1%). The overall mean (SD) age was 26.0 (5.87) years. The overall mean (SD) height, weight, and BMI were 158.8 (7.14) cm, 70.9 (17.89) kg, and 28.1 (7.01) kg/m<sup>2</sup>, respectively. The participants' marital and relationship status revealed that the majority of the women were never married (1747/1959; 89.2%), 9.2% (181/1959) were married, 1.0% (20/1959) were legally separated, eight (8/1959; 0.4%) were widowed, and three (3/1959; 0.2%) were divorced. The majority of the women had children (1791/1959; 91.4%) and reported to have a main sex partner (1924/1959; 98.2%). Approximately 54% of the participants reported that their partners knew they were using the ring.

In MTN-020, the majority of participants were Black (2454/2629; 93.3%). Half of them were South African (1426/2629; 54.2%). The overall mean (SD) age was 27.2 (6.18) years. The overall mean (SD) height, weight, and body mass index (BMI) were 159.1 (6.63) cm, 68.3 (15.90) kg, and 27.0 (6.68) kg/m<sup>2</sup>, respectively. The participants' marital and relationship status revealed that more than half of the



women were not married (1553/2629; 59.1%). The majority of the women had a main sex partner (2616/2629; 99.5%); 63.9% (1680/2629) of the participants reported that their partners knew that they were using the ring. The number of sex partners was two or more for 16.7% (439/2629) of the participants.

STIs were frequently present at enrolment in participants of both studies (27.5% (540/1959) of participants in IPM-027, 21.0% (551/2629) of participants in MTN-020). As per inclusion criteria, STIs were not a reason for exclusion, but participants had to be asymptomatic for genital infections at the time of enrolment.

## **Randomisation and number analysed**

### ***Study IPM 027 (Ring study)***

In total, 1959 participants were enrolled in the trial, of whom 1307 in the Dapivirine Vaginal Ring-004 group and 652 in the placebo ring group.

The **ITT population** included all participants who were randomized to one of the two treatment groups, Dapivirine Vaginal Ring-004 or placebo ring, and analysed as members of that treatment group, regardless of adherence to the planned course of treatment. All 1959 participants randomized in the trial were included in the ITT population.

The **m-ITT population** included all participants who were included in the ITT population but who were never determined to be HIV-seropositive at the Enrolment Visit. Participants who had seroconverted after enrolment were excluded from the m-ITT population on the basis of baseline information indicating presence of HIV-1 infection collected prior to randomization, but which only became available after randomization. The m-ITT population included 1950 participants: 1300 participants in the Dapivirine Vaginal Ring-004 group and 650 participants in the placebo ring group.

The **PP population** was a subset of the m-ITT population, i.e. all participants who were HIV-1 negative at the Enrolment Visit, with no major protocol deviations. The PP population included 1885 participants: 1254 participants in the Dapivirine Vaginal Ring-004 group and 631 participants in the placebo ring group.

### ***Study MTN-020 (Aspire)***

In total, 2629 participants were enrolled in the trial, of whom 1313 in the Dapivirine Vaginal Ring-004 group and 1316 in the placebo ring group.

The Primary Safety Cohort (or **ITT Cohort**) included all 2629 eligible participants who were randomized to one of the two treatment groups, Dapivirine Vaginal Ring-004 group (1313 participants) or placebo ring group (1316 participants), and analysed as members of the treatment group to which they were randomized, regardless of adherence to the planned course of treatment.

The Primary Effectiveness Cohort was the **m-ITT Cohort**, which differed from the Primary Safety Cohort only in the exclusion of participants deemed to be HIV RNA positive at the time of randomization, based on retrospective PCR testing of archived blood samples taken at enrolment. Some participants could have already been infected with HIV-1 but not yet had detectable levels of HIV antibodies at the Enrolment Visit and were therefore assumed to be HIV-negative. Retrospective PCR testing was performed on the archived blood samples for all participants who seroconverted during the trial to identify participants who had been infected at the time of enrolment but had undetectable levels of HIV antibodies. The Primary Effectiveness Cohort included 2626 participants: 1313 in the Dapivirine Vaginal Ring-004 group and 1313 in the placebo ring group (cf. Table 7).



**Table 7 Participants in the Dapivirine Vaginal Ring-004 and in the placebo ring group.**

	<b>ITT</b>		<b>m-ITT</b>		<b>PP</b>	
	<b>Dapivirine</b>	<b>Placebo</b>	<b>Dapivirine</b>	<b>Placebo</b>	<b>Dapivirine</b>	<b>Placebo</b>
<b>IMP 027</b>	1307	652	1300	650	1254	631
<b>MTN-020</b>	1313	1316	1313	1313		
<b>Pooled</b>	2620	1968	2613	1963		

**Primary Endpoint: HIV-1 Seroconversion**

In **IPM 027**, based on the primary analysis, the estimated proportion of participants with confirmed seroconversions was 5.9% (77/1300) of participants in the Dapivirine Vaginal Ring-004 group, and 8.6% (56/650) of participants in the placebo ring group. The estimated rate of HIV-1 seroconversion per 100 person-years was 4.08 (95% CI: 3.17 to 4.99) in the Dapivirine Vaginal Ring-004 group, and 6.10 (95% CI: 4.51 to 7.70) in the placebo ring group. The estimated risk reduction of HIV-1 infection for the Dapivirine Vaginal Ring-004 relative to the placebo ring, adjusted for center, was 30.67% (95% CI: 0.90 to 51.50%;  $P = 0.0414 < 0.0466$ , the adjusted alpha level) and was found statistically significant (Table 8, Figure 5). Despite the advice by CHMP the Applicant decided to stop the study early. Additional analyses based on the remaining blinded period have been provided by the Applicant.

During the procedure major inconsistencies in the data and analyses have been identified, e.g. seroconversions were erroneously not counted as trial endpoints, follow-up times were not correctly calculated, and figures within and between several tables provided in the same or different rounds of assessment were not matching. Additionally, the rapid test logs, provided upon request, have not resolved the uncertainties concerning the correct handling, processing and interpretation of the HIV-1 rapid tests used in study IPM 027.

As per CHMP request a comprehensive and thorough quality control (QC) review for all clinical data was conducted in order to, if possible, provide a reliable estimate of the primary efficacy measure of Study IPM 027.

Although the data clean-up showed some discrepancies with the latest reported data, there is no relevant change in the point-estimate, as the discrepancies did not result in identification of additional seroconversions. The final updated analyses suggest a statistically significant HIV 1 risk reduction of 35% (95% CI: 9% to 54%;  $P = 0.01$ ) for the DVR relative to placebo. This outcome is supported by various sensitivity analyses requested during the procedure (see also section "Additional analyses IPM 027" below). Moreover, the Applicant provided a worst case analysis counting all samples with discordant rapid test results at the last study visit, for which PCR-back testing was not possible as failures with 30 samples in the DVR- and 10 samples in the placebo group. Based on this analysis, the proportion of participants with confirmed seroconversions was 8.6% (112/1,302) of participants in the DVR group, and 10.9% (71/650) of participants in the placebo ring group. The DVR reduced the risk of HIV-1 infection by 24.96% (95% CI: -1.05% to 44.27%;  $P = 0.0586$  based on the Cox PH model) relative to the placebo ring. Based on a two-sided log-rank test, the P-value was 0.0577. While the difference between the two groups is not statistically significant, even this extremely unlikely worst case scenario (all missing samples = failures) still shows a trend in favour of DVR. Moreover, the tipping point analysis, provided by the applicant upon request of CHMP, showed that an additional 11 seroconverters would be needed in the DVR-group to change the study outcome to non-significant, a figure very unlikely to be achieved with the number of missing samples.

In **MTN-020**, based on the primary analysis, the estimated proportion of participants with HIV-1 seroconversions was 5.4% (71/1313) in the Dapivirine Vaginal Ring-004 group and 7.4% (97/1313) in the placebo ring group. The estimated rate of HIV-1 seroconversion per 100 person-years was 3.31 (95% CI: 2.54 to 4.08) in the Dapivirine Vaginal Ring-004 group and 4.55 (95% CI: 3.64 to 5.45) in the placebo ring group. The estimated risk reduction of HIV-1 infection for Dapivirine Vaginal Ring-004 relative to the placebo ring, adjusted for center, was 26.75% (95% CI: 0.490 to 46.080%;  $P = 0.046$ ) (Table 9, Figure 6). Due to the performed interim analyses, the alpha level for the primary analysis needs to be adjusted. The true adjusted alpha level is unknown, but will be between 0.0446 (O'Brien Fleming estimation, which is not correct because the interim analyses and the primary analysis used different null hypotheses) and 0.0499 (based on simulation performed by the applicant, for which the simulated alpha level may be smaller than the real alpha level and thus leading to an overestimation of the adjusted alpha level).

As mentioned, the conduct of MTN 020 was not considered GCP compliant and the study results as reported in the clinical study report are not regarded as reliable. This means that this application is based on a single pivotal trial, IPM-027, which should be in line with defined thresholds with respect to internal and external validity, clinical relevance, data quality, internal consistency and statistical significance (POINTS TO CONSIDER ON APPLICATION WITH 1. META-ANALYSES; 2. ONE PIVOTAL STUDY, CPMP/EWP/2330/99).

**Table 8 Summary of HIV-1 Seroconversion Rates: Primary Analysis – Modified Intent-to-Treat Population (IPM 027)**

	Dapivirine	Placebo	Dapivirine Versus Placebo
Number of participants in m-ITT population	1300	650	-
Number of confirmed trial endpoints <sup>a</sup>	77 (5.9%)	56 (8.6%)	-
Number of censored values <sup>a,b</sup>	1223 (94.1%)	594 (91.4%)	-
Total person years of follow-up (years)	1888	917	-
HIV-1 seroconversion rate <sup>c</sup> (per 100 person-years <sup>d</sup> ) (95% CI)	4.08 (3.17; 4.99)	6.10 (4.51; 7.70)	0.69 (0.49; 0.99)
Percentage reduction in HIV-1 seroconversion (95% CI)	-	-	30.67 (0.90; 51.50)
P-value based on Cox Proportional Hazards model: Treatment effect <sup>e</sup>	-	-	0.0414

CI = confidence interval, HIV = human immunodeficiency virus, m-ITT = modified intent-to-treat

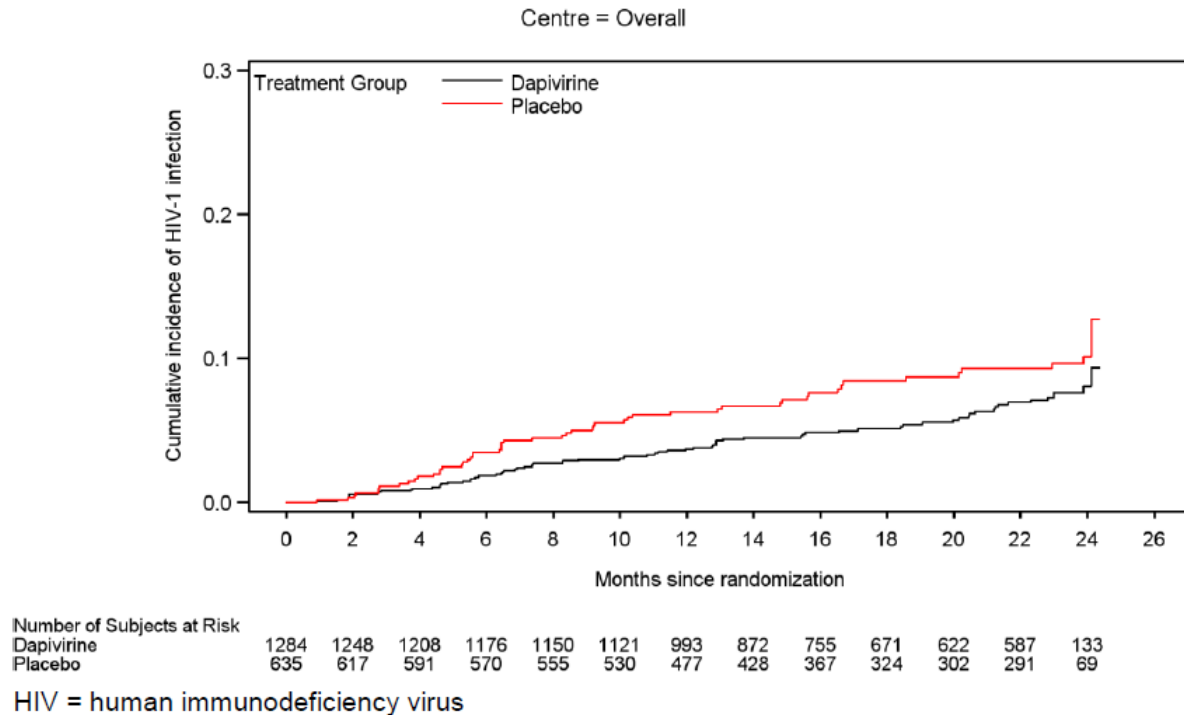
a. The number of participants in the m-ITT population is the denominator for the calculation of the percentages.

b. Participants that did not demonstrate HIV-1 seroconversion were censored at the date of the last negative HIV-1 test result.

c. Hazard ratio and the unadjusted CI for the hazard ratio were estimated based on a Cox Proportional Hazards model stratified for research center.

d. Person-years were based on the cumulative follow-up time (ie, time to HIV-1 seroconversion or time to censoring).

e. The P-value is evaluated at the 0.0466 significance level to account for the superiority evaluation at the interim analysis.



**Figure 5 Time to Seroconversion Based on Confirmed Trial Endpoints: Kaplan-Meier Plot (IPM 027)**

**Table 9 Summary of HIV-1 Seroconversion Rates: Primary Analysis – Primary Effectiveness Cohort (MTN-020)**

	Treatment Group		
	Dapivirine Vaginal Ring-004	Placebo Ring	Dapivirine Vaginal Ring-004 Versus Placebo Ring
Number of participants in the Primary Effectiveness Cohort	1313	1313	-
Number of events	71	97	-
Number of censored values <sup>a</sup>	1242	1216	-
Follow-up time (person-years) <sup>b</sup>	2141	2130	-
HIV-1 infection rate (per 100 person-years <sup>c</sup> ) (95% CI)	3.32 (2.54; 4.09)	4.55 (3.65; 5.46)	-
Hazard ratio <sup>d</sup> (95% CI)	-	-	0.73 (0.54; 1.00)
Percentage reduction in HIV-1 infection rate (95% CI)	-	-	26.73 (0.47; 46.07)
P-value based on Cox Proportional Hazards model: Treatment effect	-	-	0.0466

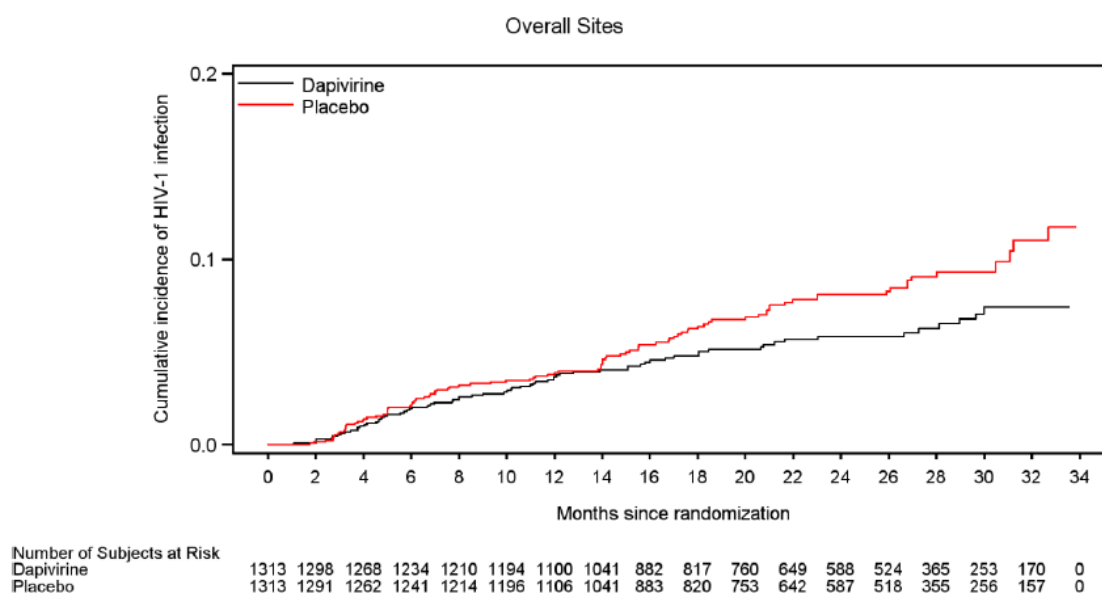
CI = confidence interval, HIV = human immunodeficiency virus

<sup>a</sup> Participants who did not demonstrate HIV-1 infection were censored at the date of the last negative HIV-1 test result.

<sup>b</sup> Follow-up time is from date of Enrollment Visit to the date of the first confirmed positive HIV test result, or to the date of last negative HIV test result received.

<sup>c</sup> Person-years were based on the cumulative follow-up time (ie, time to HIV-1 infection or time to censoring).

<sup>d</sup> Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazards model stratified for research center.



HIV = human immunodeficiency virus

**Figure 6 Time to HIV-1 Seroconversion: Kaplan-Meier Plot: Primary Analysis (MTN-020)**

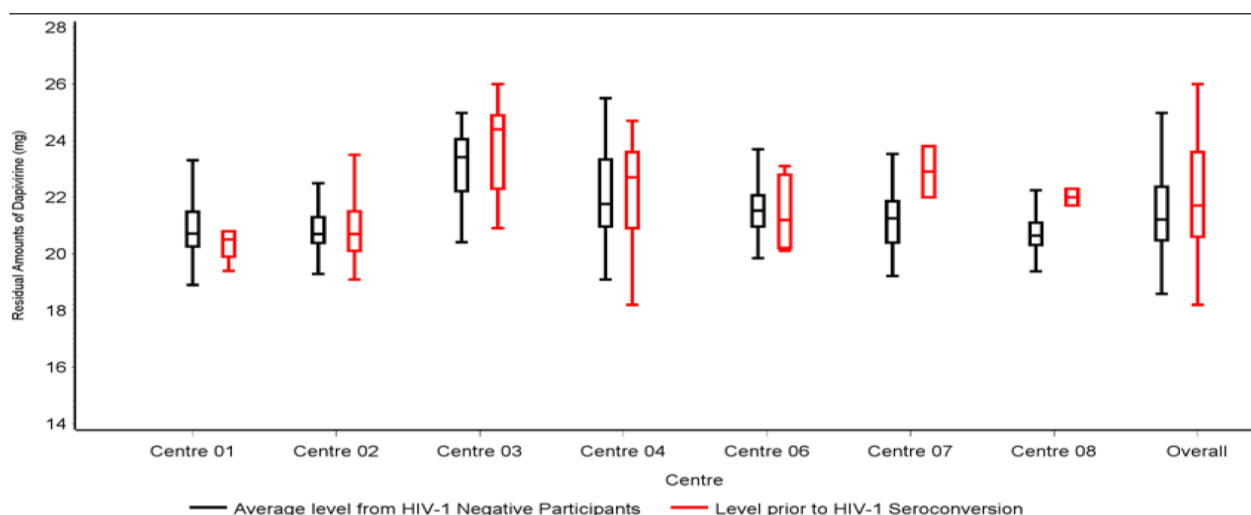
The estimated level of risk reduction evoked by the Dapivirine Vaginal Ring-004 vs placebo was statistically significant in the IPM-027, but the statistical significance is unknown in the MTN-020. The observed efficacy is considered to be very low. The confidence interval associated with the Hazard Ratio is wide, ranging from a 2 times lower risk for HIV-1 seroconversion when using the dapivirine vaginal ring, to hardly any protective effect at all. (It should be noted that a comprehensive and thorough quality control (QC) review for all clinical data was requested in order to provide a reliable estimate of the primary efficacy measure of Study IPM 027. This is being discussed later on in the report.)

It was noted that differential effects were seen for individual research centers, in both trials. In IPM 027 there are 4 research centers where no effect of dapivirine vaginal ring in reducing the risk of HIV-1 seroconversion was observed (Center 02, 06, 07 and 08), and 3 research centers where some level of effect could be seen (Center 01, 03 and 04, see Table 10).

**Table 10 IPM 027 -HIV-1 seroconversion rates per 100 p-y according to the centers**

	Dapivirine HIV-1 sc rate per 100 p-y (95% CI)	Placebo HIV-1 sc rate per 100 p-y (95% CI)	Dapivirine vs Placebo HIV-1 sc rate per 100 p-y (95% CI)	N (number of seroconversions)	
				Dapivirine	Placebo
Center 01	1.16 (0.23 to 2.09)	4.14 (1.69 to 6.58)	0.29 (0.10 to 0.79)	319 (6)	162 (11)
Center 03	9.82 (4.68 to 14.96)	15.28 (5.81 to 24.75)	0.64 (0.28 to 1.46)	150 (14)	73 (10)
Center 04	4.69 (2.68 to 6.69)	8.16 (4.28 to 12.04)	0.73 (0.37 to 1.44)	302 (21)	152 (17)
Center 02	6.05 (3.72 to 8.37)	6.73 (3.20 to 10.25)	0.90 (0.47 to 1.75)	254 (26)	126 (14)
Center 08	2.24 (-0.87 to 5.36)	2.47 (-2.37 to 7.31)	0.90 (0.08 to 10.35)	78 (2)	40 (1)
Center 06	3.17 (0.63 to 5.70)	3.21 (-0.42 to 6.85)	1.27 (0.31 to 5.29)	132 (6)	65 (3)
Center 07	2.78 (-1.07 to 6.63)	0.00 (0.00 to 0.00)	144562 (0.00 to -145E5)	65 (2)	32 (0)

The applicant was requested to further explain this observation. It was thereby noted that the average ring residual level (considered to be a measure of adherence to ring use: the lower the residual level, the more adherent the subject is considered to have been, see also further below for more details regarding this analysis) does not seem to be any different in subjects who seroconverted compared to participants who remained HIV-1 negative throughout the study, neither overall nor in individual centers (see Figure 7).

**Figure 7 IPM-027: Ring Residual Levels Prior to HIV-1 Seroconversion vs Residual Levels of Participants who remained HIV-1-Negative (mITT Population)**

The two exceptions, Center 07 and 08, for which a difference in residual levels could be seen between participants who seroconverted and those who remained HIV-1 negative, actually showed no overall risk reduction in the dapivirine vs placebo group. Of note, similar conclusions can be drawn when dapivirine

plasma concentrations are used as measure of adherence. As the difference in outcome between research centers cannot be explained by differences in adherence (as measured by ring residual levels or plasma concentrations), the applicant was requested to explore potential reasons for this divergence between centers, e.g. if there are differences in baseline characteristics or sexual behaviour between the trial participants enrolled in the centers with vs without a reduced risk in the dapivirine group. The applicant argued that there is no statistically significant difference in the treatment effect across research centers. It is acknowledged that the small number of HIV-1 infections at some of the centers makes it difficult to draw firm conclusions and hence the issue is not further pursued.

All above comments are also applicable to study MTN-020. See Table 11 for the results per individual research center for study MTN-020.

**Table 11 MTN-020- HIV-1 seroconversion rates per 100 p-y according to the centers**

	Dapivirine HIV-1 sc rate per 100 p-y (95% CI)	Placebo HIV-1 sc rate per 100 p-y (95% CI)	Dapivirine vs Placebo HIV-1 sc rate per 100 p-y (95% CI)	N (number of seroconversions)	
				Dapivirine	Placebo
Harare: Spilhaus	0.00 ( 0.00 ; 0.00)	4.48 ( 1.38 ; 7.59)	0.00 ( 0.000; )	115 (0)	115 (1)
Johannesburg: WRHI CRS	1.19 (-0.46 ; 2.84)	4.94 ( 1.52 ; 8.37)	0.24 ( 0.051;1.136)	105 (2)	108 (8)
Blantyre: Queen Elizabeth Hospital	1.25 (-1.20 ; 3.70)	3.68 (-0.48 ; 7.84)	0.34 ( 0.035;3.272)	64 (1)	66 (3)
Durban: CAPRISA eThekweni CRS	3.10 ( 0.62 ; 5.58)	7.83 ( 3.73 ; 11.93)	0.40 ( 0.152;1.030)	123 (6)	121 (14)
Durban: RK Khan Hospital	5.12 ( 1.33 ; 8.91)	8.01 ( 3.05 ; 12.98)	0.64 ( 0.245;1.693)	76 (7)	73 (10)
Durban: Umkomaas	4.40 ( 0.09 ; 8.72)	6.02 ( 1.20 ;10.84)	0.73 ( 0.205;2.570)	52 (4)	51 (6)
Durban: Verulam CRS	5.39 ( 1.40 ; 9.38)	7.19 ( 2.49 ; 11.89)	0.75 ( 0.280;2.017)	75 (7)	75 (9)
Durban: Valley Trust/Botha's Hill	4.55 ( 1.18 ; 7.91)	5.36 ( 1.65 ; 9.08)	0.85 ( 0.308;2.339)	90 (7)	89 (8)
Kampala: Makerere University	2.17 ( 0.27 ; 4.07)	2.21 ( 0.27 ; 4.15)	0.98 ( 0.284;3.385)	127 (5)	126 (5)
Chitungwiza: Seke South	1.71 (-0.22 ; 3.64)	1.65 (-0.22 ; 3.52)	1.04 ( 0.209; 5.138)	111 (3)	113 (3)
Cape Town: Emavundleni Centre	4.23 ( 0.84 ; 7.61)	4.03 ( 0.81 ; 7.26)	1.05 ( 0.338;3.253)	82 (6)	84 (6)
Lilongwe: Lilongwe Central Hospital	3.68 (-0.48 ; 7.84)	3.43 (-0.45 ; 7.32)	1.08 ( 0.218;5.342)	71 (3)	70 (3)
Durban: Tongaat CRS	7.41 ( 1.92 ; 12.90)	5.88 ( 1.17 ; 10.58)	1.25 ( 0.422;3.735)	52 (7)	51 (6)
Chitungwiza: Zengeza	1.79 (-0.24 ; 3.81)	1.17 (-0.45 ; 2.79)	1.51 ( 0.253;9.053)	112 (3)	112 (2)
Durban: Isipingo CRS	9.33 ( 3.55 ; 15.11)	5.13 ( 1.02 ; 9.23)	1.82 ( 0.660;5.000)	58 (10)	59 (6)

- **Complementary Analyses**

#### IPM 027: Excluding Research Center 03

Because of a high level of protocol non-compliance observed within the first six months of initiation of the trial at Research Center 03, the applicant discontinued Research Center 03 after discussion with the

South African MCC and the FDA. Scientific Advice was also requested from CHMP, who advised against this early discontinuation.

The primary analysis was also performed excluding Research Center 03. The estimated proportion of participants with confirmed seroconversions was 5.5% (63/1150) of participants in the Dapivirine Vaginal Ring-004 group and 8% (46/577) of participants in the placebo ring group. The estimated rate of HIV-1 seroconversion per 100 person-years was 3.61 (95% CI: 2.72 to 4.50) in the Dapivirine Vaginal Ring-004 group and 5.40 (95% CI: 3.84 to 6.96) in the placebo ring group. The estimated risk reduction of HIV-1 infection for Dapivirine Vaginal Ring-004 relative to the placebo ring, adjusted for center, was 29.68% (95% CI: -4.53 to 52.70%;  $P = 0.0772$ ). Exclusion of Center 03 from the analysis did not result in a noteworthy other predicted risk reduction compared to the original analysis. This fits with the Center 03-specific analysis showing an estimated HIV-1 seroconversion rate of 9.82 (CI 4.68 to 14.96) per 100 py in the dapivirine group vs 15.28 (CI 5.81 to 24.75) per 100 py in the placebo group (Dapivirine vs Placebo: estimated % risk reduction 36%, 95% CI: -46 to 72% see also table showing outcomes per center above, see Table 10). Although the confidence intervals are wide and overlap between dapivirine and placebo groups, the trend of a ~30% estimated risk reduction after exclusion of Center 03 from the analysis, is similar as for the original analysis. Noteworthy, however, the difference was no longer statistically significant when excluding center 03, although the remaining number of participants was the same as initially planned.

#### MTN-020: Excluding Research Center 320 and 321

In this analysis, only the 13 research centers whose early performance metrics were determined to have achieved an acceptable level were included (adherent subset analysis). Research Centers 320 and 321 (both located in Durban, KwaZulu-Natal, South Africa) were excluded from this analysis. Both excluded research centers showed no protective effect in the dapivirine vs placebo groups. According to this analysis, the estimated proportion of participants with HIV-1 seroconversions was 4.5% (54/1203) in the Dapivirine Vaginal Ring-004 group and 7.1% (85/1203) in the placebo ring group. The estimated rate of HIV-1 seroconversions per 100 person-years was 2.78 (95% CI: 2.04 to 3.52) in the Dapivirine Vaginal Ring-004 group and 4.44 (95% CI: 3.50 to 5.38) in the placebo ring group. The estimated risk reduction of HIV-1 infection for Dapivirine Vaginal Ring-004 relative to the placebo ring, adjusted for center, was 37.44% (95% CI: 11.99 to 55.53%;  $P = 0.007$ ). Although it can be concluded from this analysis that adherence to some extent drives the level of HIV-1 infection risk reduction, the estimated risk reduction compared to placebo was still only 10% more than what was observed in the primary analysis (estimated % risk reduction 26.75% (95% CI: 0.490 to 46.080%).

#### IPM 027 and MTN-020: Analyses Before and After Enhanced Adherence Counseling

Measures were taken to enhance adherence because of suspected non-adherence to ring use in both trials. These measures were not completely similar between the two studies but largely overlapped. Measures included, but were not limited to, additional adherence workshops, male engagement activities, group discussions with participants, and collection of used rings for residual drug analysis (for MTN-020, in IPM 027 this was already done from the start).

In both studies, adherence to ring use increased after implementation of these measures. This was determined by comparing residual drug levels in used rings before and after 31 May 2013 (IPM 027), or by comparing dapivirine plasma concentrations before and after 31 May 2013 (MTN-020). In neither of the two studies, the enhanced adherence measures resulted in an increase of the estimated HIV-1 risk reduction rate (conclusion further elaborated later on in the report, following the QC review of all clinical data in order to provide a reliable estimate of the primary efficacy measure of Study IPM 027).



#### IPM 027: Placebo imputation for subjects who discontinued not for seroconversion

The seroconversion rate based on confirmed trial endpoints with placebo imputation for participants who discontinued (not for seroconversion) showed similar results compared to the primary analysis including this subset of participants.

#### MTN-020: By-protocol Sensitivity Analysis

In the primary analysis, the participant was treated as seroconverting at the time of the product use end visit (PUEV) if HIV-1 antibodies were detected at the Trial Exit/Termination Visit and further RNA PCR testing showed detectable HIV RNA levels at PUEV. In the by-protocol sensitivity analysis, the follow-up time during the planned four weeks off product at the end of the study up to and including the Trial Exit/Termination Visit was not included. The by-protocol sensitivity analysis results were identical to the primary analysis results.

#### **Additional analyses IPM 027**

During the assessment procedure, several additional analyses were provided by the Applicant. The following updated or additional efficacy analyses were performed:

##### **Primary Efficacy Analysis (data cut-off date 16 October 2015):**

- A. Repeat of the primary efficacy analysis based on the corrected m-ITT population, including as endpoints all observed HIV-1 seroconversions (based on positive RNA PCR tests or positive Western Blot tests, and irrespective of HSMC decision), based on data as of the cut-off date of 16 October 2015.
- B. Repeat of the primary efficacy analysis based on the corrected m-ITT population (and including participant 04-00307), including as endpoints all observed and HSMC-confirmed seroconversions, based on data as of the cut-off date of 16 October 2015.

##### **Complete Double-blind Treatment Period:**

- C. Repeat of the primary efficacy analysis based on the corrected m-ITT population (and including participant 04-00307), including as endpoints all observed HIV-1 seroconversions (based on positive RNA PCR tests or positive Western Blot tests, and irrespective of HSMC decision) during the complete double-blind trial period.
- D. Repeat of the primary efficacy analysis based on the corrected m-ITT population (and including participant 04-00307), including as endpoints all observed and HSMC-confirmed seroconversions during the complete double-blind trial period.

##### **Sensitivity Analyses:**

- E. Efficacy analyses A and C above, with the addition to consider a participant to have had a seroconversion in case this participant had a positive or discordant test without a confirmed RNA PCR test or Western Blot test at the last visit of the considered treatment period, independent of the reason.

**Note:** only one participant (PID 04-00307) was identified for whom no follow-up testing was performed after discordant rapid test results were observed, and who was subsequently confirmed to have been HIV infected. This participant was conservatively included in all additional efficacy analyses performed (analyses A to D, F and G). No analysis E was therefore performed.

- F. Sensitivity analysis on the corrected m-ITT population (including participant 04-00307), and including all HIV seroconversions (irrespective of HSMC ruling as trial endpoints), excluding those (seven) participants who were already HIV infected at enrolment, but conservatively also



including seroconverters who were HIV RNA positive at the first visit after the double-blind on-treatment period, but who were HIV RNA negative at the last visit on blinded IP.

- G. Sensitivity analysis on the corrected m-ITT population (including participant 04-00307), and including all HSMC-confirmed HIV-1 seroconversions during the complete trial period, irrespective of HSMC ruling as trial endpoints, ie, only excluding the seven participants who were already HIV infected at enrolment.

It was however noted that not all seroconversions had been included and not all follow-up times had been correctly determined. Hence adjustment of (some of) the above analyses was considered required.

Unfortunately, when reviewing the updated analyses, inconsistencies e.g. in the used follow-up times were again identified, which severely questions the reliability of the provided clinical data. Therefore, upon request, an independent third party was contracted by the Applicant to conduct a quality control (QC) of the efficacy data of this trial.

The results of the above-mentioned efficacy analyses, based on the QC reviewed data, are as follows (Table 12):

**Table 12 Results of the additional efficacy analyses.**

Efficacy Analysis (DPV versus placebo) <sup>a</sup>		Number of Endpoints		Percentage reduction in HIV-1 seroconversion (95% CI)	P-value Cox Proportional Hazards model	P-value Log-rank test
		DPV	PBO			
A	Updated analysis	81	59	34.38 (8.17; 53.11)	0.0140	0.0133
B	Updated analysis	80	59	35.07 (9.05; 53.64)	0.0120	0.0114
C	Updated analysis	84	62	36.60 (11.95; 54.35)	0.0065	0.0061
D	Updated analysis	82	61	36.81 (11.95; 54.65)	0.0067	0.0062
F	Updated analysis	87	62	34.48 (9.22; 52.71)	0.0110	0.0105
G	Updated analysis	88	63	34.77 (9.83; 52.81)	0.0097	0.0092

## Secondary endpoints

### HIV-1 Drug Resistance Mutations in Participants who seroconverted

A resistance assessment was available for 298 of the 301 participants who seroconverted in the Phase III trials IPM 027 and MTN-020, resulting in a virology analysis population of 146 and 152 participants in the dapivirine and placebo groups, respectively.

In order to identify HIV variants that may be associated with a change in susceptibility to dapivirine, collected plasma samples of participants who were identified as seroconverters, were analysed for the presence of resistance mutations, if HIV-1 RNA levels were >200 copies/ml. Based on the provided information, NNRTI resistance mutations were observed in 16/79 (20.03%) and 8/58 (13.8%) of participants in the dapivirine vs placebo ring group in IPM 027, respectively, and in 8/68 (11.8%) and 9/96 (9.4%) of participants in the dapivirine vs placebo ring group in MTN-020, respectively. PI resistance mutations were present in the viruses of 3 participants in IPM 027 (3 in the dapivirine group and 0 in the placebo group) and in none in MTN-020. NRTI resistance mutations were detected in the viruses of 2 participants in IPM 027 (both in the dapivirine group) and of 2 participants in MTN-020 (one each in the dapivirine and placebo group), respectively.

Among participants who had more than one resistance assessment, changes over time were observed in 3/72 participants in the dapivirine vaginal ring group, compared to 0/48 participants in the placebo ring group. All of the changes were identified after the dapivirine vaginal ring was discontinued, and include the K103 K/N and V106M variant in 1 participant, the G190A/G substitution in another participant, and the E138A and V108V/I variants in the third participant. The Applicant stated that both subjects of IPM 027 did not receive ART prior to sequence analysis, while one subject of MTN-020 had received EFV plus 2 NRTIs for approximately 6 months, followed by 5 months of treatment discontinuation before the re-initiation of therapy. The resistance testing was performed during treatment interruption. NGS sequencing of these viruses demonstrated that the resistance-associated mutations were present at the time of seroconversion and it cannot be excluded that these developed under dapivirine treatment. Therefore, these subjects were included in the final virology assessment.

According to the Applicant reduced *in vitro* susceptibility to DPV typically required more than one substitution in reverse transcriptase (site-directed mutants). However, the following single mutations were found in phenotyped NNRTI resistant recombinant clinical and *in vitro* isolates each leading to significant fold changes and loss in sensitivity to DPV: L100I, K103N, Y181C/I, Y188L, G190E and F227C (max FCs: 39, 33, 63, 1859, 1127, 1644, 46, respectively).

*In vitro* substitutions were not observed more frequently in viruses from dapivirine-exposed vs placebo-exposed subjects who seroconverted. On the other hand, resistance-associated mutations that were not detected *in vitro* were detected *in vivo* (i.e. K103N, G190A).

The E138A substitution was found more frequently in dapivirine-exposed vs placebo-exposed subjects in study IPM 027. E138A is a common polymorphism found in HIV-1 subtype C isolates, and is associated with reduced susceptibility to rilpivirine and etravirine, two close analogues of dapivirine, but not with nevirapine and efavirenz, which are the more widely used NNRTIs in sub-Saharan Africa. However, if due to the epidemiological situation, E138A should be equally distributed among study groups and therefore treatment-emergence of this resistance mutation cannot be excluded. Data from the open-label extension studies and PAMs may help to understand whether this observation is a chance finding or real signal.

Preliminary data from the open-label extension studies showed a higher tendency for development of resistance compared to the pivotal trials, IPM 032 (29.4% (5/17)) and MTN-025 (18.2% (6/33)) vs. IPM 027 trial: Dapivirine Vaginal Ring: 13/82 (15.9%); placebo ring: 8/57 (14.0%) and MTN-020 trial: Dapivirine Vaginal Ring: 8/68 (11.8%); placebo ring: 9/96 (9.0%). Potential reasons for this trend need to be cautiously evaluated; also considering the Applicant's assumption, that adherence will be higher in a real-world scenario. The identified resistance pattern (A98G, E138A, K101E and K103N), even if numbers are small, might have an impact on susceptibility to currently recommended first-line treatments, if they will be confirmed in clinical practice. In IPM 032 only participants that were assigned to the DPV-ring group in the parent trial, encoded viruses with NNRTI resistance associated mutations, while none of the former participants of the placebo group of IPM 027 encoded viruses with NNRTI RAMs. Thus, participants with longer dapivirine treatment may be at higher risk of development of NNRTI RAMs.

In conclusion, based on the submitted data, no definitive conclusions on the potential to develop resistance associated with DPV treatment can be drawn. However, the possibility that resistance-associated mutations develop upon dapivirine selective pressure cannot be excluded, even if it is acknowledged that the incidence of transmitted resistance has been shown to increase in the last years. The development of resistance under dapivirine treatment with special focus on E138A, G190A, A98G, K103N, K101E, V106M, V179D and V179I and their combinations should remain under supervision to provide a more accurate picture of the resistance profile of dapivirine.

### Acceptability of the Vaginal Ring

The vaginal ring was considered acceptable by >95% of all participants at the end of the ring use period in both IPM 027 and MTN-020. At the end of follow-up, over 92% of participants in both studies found it not difficult at all to insert the vaginal ring, >85% reported that she did not feel the ring during normal daily activities, and >94% in IPM 027 and >70% in MTN-020 reported that her partner did not feel the ring during vaginal sex. The outcome of this kind of questionnaires should however be interpreted with caution, as the reliability of the self-reported answers could be questionable.

### Time-varying Product-adherence Analyses

The Applicant's pre-defined definition of adherence is based on the cut-offs of 23.5 mg for the ring residual level and 95 pg/ml for plasma concentration. Results of the post hoc analysis of time-varying product-adherence comparing Dapivirine Vaginal Ring-004 adherent periods to placebo ring using pre-defined cut-off values are presented in Table 13 for study IPM 027 and Table 15 for study MTN-020. To determine a Dapivirine Vaginal Ring-004 adherent period, both the dapivirine residual level and dapivirine plasma concentration were considered if they were both available; otherwise it was based on the available assessment.

Results of the post hoc analysis of time-varying product-adherence comparing Dapivirine Vaginal Ring-004 non-adherent periods to placebo ring using pre-defined cut-off values are presented in Table 14 for study IPM 027 and Table 15 for study MTN-020.

**Table 13 Summary of HIV-1 Infection Rates: Time-varying Product-adherence Analysis Based on Pre-defined Cut-offs for Dapivirine Plasma Concentrations and Ring Residual Levels With Placebo Included as Comparator – Modified Intent-to-Treat Population (IPM 027)**

Adherence Definition <sup>a</sup>		Dapivirine Adherence Versus Placebo		
Dapivirine Ring Residual Level (mg)	Dapivirine Plasma Concentration (pg/mL)	Percentage Reduction in HIV-1 Infection	95% CI for Percentage Reduction in HIV-1 Infection	P-value Based on Cox Proportional Hazards Model: Adherence Effect
≤ 23.5	≥ 95	38.31	9.51; 57.94	0.0135

CI = confidence interval, HIV = human immunodeficiency virus

<sup>a</sup> If both the dapivirine residual level in the used ring and dapivirine plasma concentration were available; otherwise, categorization was based on the available measurement.

**Table 14 Summary of HIV-1 Infection Rates: Time-varying Product-adherence Analysis Based on Pre-defined Cut-offs for Dapivirine Plasma Concentrations and Ring Residual Levels With Placebo Included as Comparator: Dapivirine Vaginal Ring-004 Non-adherent Periods Versus Placebo Ring – Modified Intent-to-Treat Population (IPM 027)**

Adherence Definition		Dapivirine Vaginal Ring-004 Non-adherent Periods Versus Placebo Ring		
Dapivirine Ring Residual Level (mg)	Dapivirine Plasma Concentration (pg/mL)	Percentage Reduction in HIV-1 Infection	95% CI for Percentage Reduction in HIV-1 Infection	P-value Based on Cox Proportional Hazards Model: Adherence Effect
≤ 23.5	≥ 95	23.30	-24.28; 52.66	0.2814

CI = confidence interval, HIV = human immunodeficiency virus

**Table 15 Summary of HIV-1 Infection Rates: Time-varying Adherence Analysis – Primary Effectiveness Cohort, Based on Time to Detection of HIV RNA (MTN-020)**

	Dapivirine Vaginal Ring-004 Adherent Periods	Dapivirine Vaginal Ring-004 Non- Adherent Periods	Placebo Ring	Dapivirine Vaginal Ring-004 Adherent Periods Versus Placebo Ring	Dapivirine Vaginal Ring-004 Non-Adherent Periods Versus Placebo Ring
Number of events	44	23	97	-	-
Number of censored values <sup>a</sup>	967	256	1216	-	-
Follow-up time (person-years) <sup>b</sup>	1738	401	2128	-	-
Hazard ratio <sup>c</sup> (95% CI)	-	-	-	0.59 (0.41; 0.85)	1.16 (0.73; 1.84)
Percentage reduction in HIV-1 infection rate (95% CI)	-	-	-	40.61 (14.96; 58.52)	-16.23 (-84.46; 26.76)
<i>P</i> -value based on Cox Proportional Hazards model: Adherence effect	-	-	-	0.0044	0.5232

CI = confidence interval, HIV = human immunodeficiency virus, RNA = ribonucleic acid

<sup>a</sup> Participants who did not demonstrate HIV-1 infection were censored at the date of the last negative HIV-1 test result.

<sup>b</sup> Follow-up time over all participants during adherent and non-adherent time intervals, respectively. A participant could switch between the adherent and non-adherent risk set over time and thus contribute data to both the adherence and non-adherence time.

<sup>c</sup> Hazard ratio and 95% CI were estimated based on a Cox Proportional Hazards model stratified for research center and including adherence as a time-varying covariate.

Adherence = Dapivirine plasma concentration  $\geq$  95 pg/mL.

The applicant performed several additional analyses for both studies using different cut-off values to define adherence. It becomes clear from these analyses that the estimated risk reduction of contracting HIV-1 infection vs placebo was higher in the adherent periods (regardless of the exact definition), but not obvious in the non-adherent periods (regardless of the exact definition). However, the maximal estimated risk reduction, with 95% confidence interval, found for the dapivirine vaginal ring was 48.25% (4.68%, 71.90%) based upon a residue cut off level of  $\leq$ 20 mg in the adherent period in study IPM 027. Although 48% is substantially higher than the approximately 30% risk reduction estimated for the primary analysis of study IPM 027, the confidence interval is wide and it is still considered to be relatively small for a maximal effect (conclusion further elaborated later on in the report, following the QC review of all clinical data in order to provide a reliable estimate of the primary efficacy measure of Study IPM 027).

## Summary of main efficacy studies

The following table (Table 16) summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

## Summary of efficacy for trial IPM 027 (Ring study)

Of note, the numbers provided in this table are those based on the QC reviewed data, analysis B (based on the corrected m-ITT population (and including participant 04-00307), including as endpoints all observed and HSMC-confirmed seroconversions during the trial period with cut-off date 16 Oct 2015).

**Table 16 Summary of efficacy for trial IPM 027 (Ring study)**

<b>Title:</b> A multicenter, randomized, double-blind, placebo-controlled safety and efficacy trial of a dapivirine vaginal matrix ring in healthy HIV-negative women			
Study identifier	IPM 027 (Ring study)		
Design	Randomized, multicenter, parallel group, placebo-controlled study		
	Duration of main phase:	104 weeks	
	Ring-free follow-up phase:	6 weeks	
Hypothesis	Superiority		
Treatments groups	Dapivirine Vaginal Ring-004	Dapivirine Vaginal Ring containing 25 mg dapivirine, 104 weeks, 1307 subjects	
	Placebo Vaginal Ring	Placebo Vaginal Ring containing no active ingredient, 104 weeks, 652 subjects	
Endpoints definitions and	Primary endpoint	HIV-1 infection rate	Incidence rate of HIV-1 seroconversion
	Secondary endpoint	Adherence	The proportion of participants who reported adherence to the use of the vaginal ring inserted once every four weeks over the trial period (defined as ≤23.5 mg ring residual level and/or ≥95 pg/ml plasma concentration)
	Secondary endpoint	HIV-1 Drug resistance mutations	The proportion of participants with HIV-1 drug resistance mutations among participants who acquired HIV-1
Data cut-off	16 October 2015		
<b>Results and Analysis</b>			
<b>Analysis description</b>	<b>Primary Analysis</b>		
Analysis population and time point description	Modified-Intent to treat (m-ITT) population Either Week 104 or early discontinuation (Last Product Use) or cut-off date 16 October 2015		
Descriptive statistics and estimate variability	Treatment group	Dapivirine Vaginal Ring-004	Placebo Vaginal Ring
	Number of subjects	1302	650
	<b>HIV-1 seroconversion rate (per 100 person-years) (95% CI)</b>	<b>4.23 (3.31; 5.16)</b>	<b>6.43 (4.79; 8.08)</b>
Effect estimate per comparison	Primary endpoint	Comparison groups	Dapivirine vs Placebo
		Hazard ratio for HIV-1 seroconversion per 100 person-years(95% CI)	0.65 (0.46; 0.91)
		Percentage reduction in HIV-1 sc (95% CI)	35.07% (9.05 to 53.64%)
		p-value based on treatment effect based on the Cox PH model	0.012 < 0.0466

Analysis description	Secondary Analyses (Please note that the secondary analyses are still based on the initially submitted data)			
Analysis population and time point description	m-ITT Either Week 104 or early discontinuation (Last Product Use) or cut-off date 16 October 2015			
Descriptive statistics and estimate variability	Treatment group	Dapivirine Vaginal Ring-004 adherent period	Dapivirine Vaginal Ring-004 non-adherent period	Placebo Vaginal Ring
	Total person years of follow-up (years)	1449	433	914
	Number of seroconversions	51	26	56
Effect estimate per comparison	Secondary endpoint	Comparison groups	Adherent vs placebo	Non-adherent vs placebo
		<b>Hazard ratio for HIV-1 infection (95% CI)</b>	<b>0.62 (0.42; 0.90)</b>	<b>0.77 (0.47; 1.24)</b>
		% reduction in HIV-1 sc (95% CI)	38.31% (9.51 to 57.94%)	23.30% (-24.28 to 52.66%)
Descriptive statistics and estimate variability	Treatment group	Dapivirine Vaginal Ring-004		Placebo Vaginal Ring
	Virology analysis population (n)	79		58
	Number of NNRTI resistance mutations (n (%))	16 (20.0%)		8 (13.8%)
	Number of NRTI resistance mutations (n (%))	2 (2.5%)		0 (0%)
	Number of PI resistance mutations (n (%))	3 (3.8%)		0 (0%)

### ***Clinical studies in special populations***

Clinical studies in special populations were, apart from a small trial in 96 postmenopausal women (MTN-024/IPM 031), a trial in 16 healthy lactating, but not breastfeeding women at least 6 weeks postpartum (study MTN-029/IPM 039) and a trial in 96 female adolescents (MTN-023/IPM 030), not performed. This is acceptable. Both studies are considered supportive studies for this application.

### ***Analysis performed across trials (pooled-analyses AND meta-analysis)***

Pooling of data was performed for the Phase III trials IPM 027 and MTN-020. However, given the serious and manifold uncertainties surrounding the data quality and reliability that became evident during the GCP inspection for Study MTN-020, and given that the data of Study IPM 027 has been updated since these results were initially submitted, this pooled-analyses is no longer considered appropriate.

### ***Supportive studies***

**IPM 015**, a Phase I/II, randomized, double-blind, placebo-controlled trial conducted in Kenya, Malawi, South Africa and Tanzania, investigated the safety and pharmacokinetics of 28-day use of Dapivirine Vaginal Ring-004 (inserted at 28-day intervals) in a total of 140 HIV-negative, sexually active women. A total of three participants, who were all assigned to the placebo ring group, HIV seroconverted during the trial. No efficacy analyses were performed.

## **Ongoing trials**

### Open-label extension trials

**IPM 032 (DREAM)** and **MTN-025 (HOPE)** are Phase IIIb open-label extension trials that offer the extended use of the Dapivirine Vaginal Ring-004 to former IPM 027 and MTN-020 participants, respectively, who are healthy, HIV-negative and not pregnant or breastfeeding. Trials IPM 032 and MTN-025 initiated in July 2016 and are being conducted in the same countries as IPM 027 and MTN-020, respectively.

IPM 032 was initiated shortly before all of the IPM 027 participants had completed the protocol-specified two-year follow-up. MTN-025 was initiated approximately one year after completion of MTN-020.

The open-label extension trials are designed to collect additional safety data, further assess acceptability and adherence to Dapivirine Vaginal Ring-004 use, as well as the incidence of HIV-1 seroconversion. Originally it was planned to include two additional cohorts of healthy women  $\geq 18$  to  $\leq 21$  and  $> 21$  to  $< 25$  years of age, who have not used the Dapivirine Vaginal Ring 004 previously (Dapivirine Vaginal Ring-naïve cohorts), but these cohorts were unfortunately not initiated. Of note, since the 312 women between 18 to 21 years of age originally enrolled in IPM 027 are now older than 21 years, no additional data in younger women will be generated in these studies.

The applicant provided the CSRs for both studies during the procedure. In IPM 032, 26 (26/941; 2.8%) participants were confirmed to have seroconverted, 18 (18/941; 1.9%) of which were determined to have been HIV-1 infected while on IP. Of the remaining eight confirmed HIV-1 seroconverters, three (3/26; 11.5%) were already infected at enrollment before commencing DVR use, and three (3/26; 11.5%) became HIV-1 infected after the LPUV. For the remaining two (2/26; 7.7%) participants, it was unclear if HIV-1 infection (based on the detection of HIV-1 RNA) occurred during IP use. The incidence rates resulting from the four analyses that have been performed ranged from 1.8 to 2.3 per 100 person-years. HIV-1 incidence was compared descriptively to the rate estimated by bootstrap sampling, using adjusted estimates of incidence from the placebo ring group in IPM 027. For the number of participants included in the m-ITT analysis in IPM 032, matching placebo participants were resampled with replacement from IPM 027 based on research center, age and presence of STIs at screening. Based on observations in IPM 027, these factors were selected because of their strong association with HIV incidence. The bootstrap sampling resulted in an estimated HIV-1 incidence of 4.7 per 100 person-years in the absence of DVR use, a confidence interval was not provided. The calculated rates resulting from the four HIV-1 incidence analyses of IPM 032 data were between 51% and 62% lower than the estimated rate in the absence of access to the DVR.

In MTN-025, there were 38 participants with confirmed HIV-1 seroconversion. In total, 33 (33/38; 86.8%) of these participants had seroconversion determined to have occurred after they had been provided at least one ring. Three (3/38; 7.9%) other participants were already infected at enrollment, and the remaining two (2/38; 5.3%) had a confirmed post-enrollment seroconversion but were never provided a ring. The calculated incidence rates resulting from each of these analyses were similar: 2.7 (95% CI, 1.9 to 3.7) per 100 person-years. HIV-1 incidence was compared descriptively to the rate expected by bootstrap sampling, using adjusted estimates of incidence from the placebo ring group in MTN-020. For the number of participants included in the Exposed HIV Incidence and Adherence Cohort in MTN-025, matching placebo participants were resampled with replacement from the MTN-020 trial based on RC, age and presence of STIs at screening. The bootstrap sampling resulted in an estimated HIV-1 incidence of 3.9 (95% CI, 3.1 to 4.8) per 100 person-years in the absence of DVR use. The calculated rates resulting from the HIV-1 incidence analyses for this trial were approximately 31% lower than the estimated rate in the absence of access to the DVR.



Based on the above results, both OLE studies may suggest some positive impact of the DVR on HIV-1 incidence. However, this conclusion is fully dependent on the estimated incidence that is used as a comparison, given that these studies did not include a placebo arm.

#### Seroconverter Studies

Participants who HIV seroconverted during the IPM 027 and MTN-020 trials were offered enrolment in the long-term follow-up observational cohort studies **IPM 007** and **MTN-015**, respectively. These studies will assess the impact, if any, of ARV exposure at the time of HIV-1 infection, i.e., evaluate disease progression and monitor drug resistance in participants previously exposed to the Dapivirine Vaginal Ring-004. In addition, participants who seroconvert during the open-label extension trials will also be offered enrolment in the IPM 007 and MTN-015 studies. The Applicant provided the CSR for IPM 007 and a summary report for MTN-015.

#### Planned Trial With the Dapivirine Vaginal Ring-004

**MTN-034 (previously known as MTN-034/IPM 045) (REACH)** is a Phase IIa trial at five research centers in Kenya, South Africa, Uganda and Zimbabwe. Intended to further characterize the safety, tolerability, and adherence in a population of younger women, this crossover trial is due to directly compare the safety of and adherence to the Dapivirine Vaginal Ring (25 mg dapivirine) with oral PrEP (TDF/FTC) in a healthy, HIV-negative, sexually-active adolescent and young African adult female population 16 to 21 years of age was initiated on 29 January 2019. This trial, MTN-034 (REACH), will be conducted by MTN under the regulatory sponsorship of NIH/NIAID/DAIDS. Approximately 250 participants are now expected to be enrolled, instead of 300 originally planned, due to challenges of continuing study enrolment during the COVID-19 pandemic. This trial will collect information on the safety and acceptability of, and adherence to the Dapivirine Vaginal Ring (25 mg dapivirine) and oral PrEP (TDF/FTC), as well as the preference for either trial product over a 12-month period. The trial will also explore whether biological or physiological factors affect product efficacy or HIV susceptibility in this age group. IPM will have full access to the data (and CSR), and this information will be used to address the missing information about Dapivirine Vaginal Ring use in sexually-active females under 18 years of age. Trial conduct is expected to be concluded during Q4 2021.

In addition, a future trial in pregnant women is planned to address the safety of the Dapivirine Vaginal Ring-004 during pregnancy.

Furthermore, it was noted that several studies with additional ring formulations containing higher amounts of dapivirine compared to the 25 mg containing dapivirine vaginal ring-004 have been performed or are ongoing. These include a 200 mg dapivirine containing vaginal ring with or without a contraceptive (see MTN website at [www.mtnstopshiv.org](http://www.mtnstopshiv.org)) and a microbicide vaginal ring containing dapivirine 100 mg with or without darunavir 300 mg (Murphy et al, J Antimicrob Chemother 2014; 69: 2477–2488). The applicant explained that further development of a vaginal ring containing dapivirine in combination with the protease inhibitor darunavir, and a vaginal ring containing dapivirine in combination with DS003, a potent, novel gp120 binding entry inhibitor have been paused due to resource constraints. These rings are in the early stages of development, with pre-formulation experiments having recently been completed. Regarding the development of vaginal rings combining dapivirine with contraception, the applicant explained that a 14-day Phase I trial has been completed. Preparation for the next clinical trial that will evaluate the combination ring over a 90-day follow-up period is in progress. Based on results, further formulation optimization will be undertaken.



### 2.5.3. Discussion on clinical efficacy

No dose response studies have been performed with the Dapivirine vaginal ring formulation. The present substantiation of the 25mg dose largely relies on the in vitro results indicating an IC99 of 3.3 ng/ml, this is however considered a questionable measure for the in vivo inhibitory effect on HIV-1 replication. As a consequence, it is unclear whether the 25 mg dapivirine contained in the vaginal ring-004, results in the most optimal intracellular concentration of dapivirine in the target cells to prevent HIV-1 from replicating.

#### ***Design and conduct of clinical studies***

The two main studies, IPM 027 and MTN-020, were randomised, double-blind, placebo controlled studies. Study MTN-020 can however no longer be regarded as confirmatory for the efficacy of the Dapivirine Vaginal Ring, due to the serious and manifold uncertainties surrounding the data quality and reliability that became evident during the GCP inspection and due to the possible bias on the estimated effect by stopping the recruitment of two centers. This means that this application is now based on a single pivotal trial, IPM-027. During the procedure, inconsistencies concerning the data and analyses for Study IPM 027 were identified, e.g. seroconversions were erroneously not counted as trial endpoints, used follow-up times were not correct, and inconsistencies were noted in several provided tables. Additionally, the provided rapid test logs did not resolve the uncertainties concerning the correct handling, processing and interpretation of the used HIV-1 rapid tests as defined in the study report of IPM 027. As per CHMP request, the Applicant contracted an independent third party to conduct a quality control (QC) review of the efficacy data of this trial. It is notable that in this single pivotal trial scenario, the registrational study needs to be particularly compelling with respect to internal and external validity, clinical relevance, data quality, internal consistency and statistical significance (POINTS TO CONSIDER ON APPLICATION WITH 1. META-ANALYSES; 2. ONE PIVOTAL STUDY, CPMP/EWP/2330/99).

Both studies were performed in healthy adult women (18 to 45 years of age), living in sub-Saharan Africa. The population was selected in part from settings where the product is intended to be used. In total, four countries in sub-Saharan Africa, apart from Uganda all from the Southeast, i.e. Malawi, South Africa and Zimbabwe were involved in the pivotal trials. The majority of study participants were from South Africa, mainly from KwaZulu Natal, the province with the highest HIV prevalence of the country. Women from other countries, also heavily affected by the HIV epidemic, have not participated in the efficacy studies of the dapivirine vaginal ring. At each monthly visit, a new vaginal ring (containing either dapivirine 25 mg or no active ingredient) was dispensed with instructions to continuously use it for the next 28 days. HIV-1 serology testing was performed and women received counselling and male condoms. As an indicator of adherence to the investigational product, dapivirine levels in plasma, as well as residual dapivirine levels in used rings were determined (from the start of study IPM 027, and in study MTN-020 from August 2013 onwards (i.e. approximately 1 year after the study started)).

The selection of a placebo vaginal ring as comparator may be regarded as disputable, since oral pre-exposure prophylaxis with tenofovir disoproxil/emtricitabine (TDF/FTC) has been approved for adults at high risk of HIV-infection by major regulatory authorities, such as US FDA by June 2012, i.e. just before MTN-020 started. However, PrEP with TDF/FTC was not regarded as "standard of care", was not recommended by WHO at that time and got approved in South Africa (as the first African country) only late in 2015, i.e. when the DPV-VR trials had ended or were close to termination. Therefore, HIV-/STI-counselling with provision of male/female condoms, as done in the two DPV vaginal ring efficacy studies, can be regarded as adequate control. In addition, use of oral PrEP as comparator would have complicated the conduct of the study in a blinded fashion, necessitating a double dummy design and thereby potentially impacting on participants' compliance.

With respect to the selection of the endpoints there is some ambiguity in the wording of the study protocols and study reports: "Time to HIV-1 seroconversion", "incidence rate of HIV-1 seroconversion"

and “% reduction in HIV-1 seroconversion” are used. While, in principle, the endpoint should be “time to HIV-1 seroconversion” and the remainder is a matter of calculation, the confusion is indeed unfortunate. In addition, “efficacy” and “effectiveness” are not clearly distinguished. While MTN-020 was aiming at demonstration of effectiveness, i.e. efficacy on the population level, “incidence rate of HIV-1 seroconversion” would be the correct measure, while for demonstration of efficacy on the individual level (IPM 027) “% reduction in HIV-1 seroconversion” would be better suitable. For demonstration of effectiveness a reduction of HIV-1 seroconversion rate by at least 25% was included in the assumptions for sample size/power calculation. However, the primary analysis was tested against the null hypothesis of 0%.

Complementary analyses, e.g. those excluding certain study centres, were specified during the course of the study. Moreover, several post-hoc analyses were conducted in an attempt to address the challenges observed with respect to participants’ adherence to the protocol in general and specifically to ring use.

For most parts the Applicant adhered to the CHMP Scientific Advice. However, with respect to the early termination of study IPM 027 the Applicant did not. This decision led to several questions with respect to the validity of the study results (cf. below sections).

A single rapid test formed the basis of HIV testing at each visit in IPM 027. If the rapid test was non-reactive, the participant was determined to be HIV-1 negative and could continue the study. If the rapid test was reactive, retesting was done, with a different one. The rapid test results were recorded on rapid test result logs, which served as source documentation and were maintained at the RCs. These rapid test result logs were submitted for review upon request. The rapid test logs did however not resolve the uncertainties concerning the correct handling, processing and interpretation of the used HIV-1 rapid tests as defined in the study report of IPM 027. Therefore, a quality control review by a third party was undertaken.

## Statistical methods and analyses

While the statistical methods applied are, in principle, regarded as appropriate, several deficiencies with respect to data analysis and presentation were noted, some of which were considered critical and have thus been raised as major objections in the first round. These deficiencies pertain to early termination of study IPM 027, missing information for either or both pivotal studies, such as details on the statistical tests (time to event test) applied and how interim analyses were accounted for, the non-provision of interim reports, and details on DSMB meetings. While some of these aspects were clarified with the responses to the D120 LoQ and the GCP-inspection, particularly at the Sponsor sites, there are still outstanding issues remaining in this regard. These residual uncertainties are unlikely to be resolved with additional questions or explanations.

For the IPM 027 study an interim efficacy analysis was performed when approximately 50% of the expected trial endpoints had occurred. The actual number of seroconversion HIV-1 infections at the interim was 52. Therefore the two-sided significance level of the primary analysis was adjusted to **0.0466** instead of 0.05.

In the MTN-020 study three interim DSMB efficacy analyses were performed when approximately 25%, 50%, and 75% of the targeted number of HIV-1 endpoints (HIV-1 seroconversions) were reached. In this case the significance level of the primary analysis should be corrected to maintain the two-sided study error rate of 5%. Based on the Lan and De-Mets/O’Brien-Fleming method the adjusted two-sided significance level for the primary analysis is **0.0446**. According to the applicant this method cannot be used in the MTN-020 because not all tests were performed against the same null hypothesis, which is acknowledged. Therefore, the applicant performed a simulation and this resulted in an adjusted alpha

level of **0.0499**. The applicant was requested to provide the simulation plan, the simulation results and a discussion why the applicant considers the primary analysis to be statistically significant. The simulation plan as described by the applicant may result in a smaller alpha level than the real alpha level and thus will lead to an overestimation of the adjusted alpha level. Therefore, the true adjusted alpha level will be between 0.0446 (O'Brien-Fleming method) and 0.0499 (an over-estimated simulated alpha adjustment).

Due to the uncertainties surrounding the data quality and reliability that became evident during the GCP inspection, and due to the possible bias on the estimated effect by stopping the recruitment of two centers, the study MTN-020 is no longer considered confirmatory for efficacy.

## ***Efficacy data and additional analyses***

### **Primary endpoint**

The estimated risk reduction of HIV-1 infection for Dapivirine Vaginal Ring-004 relative to the placebo ring, based on the initially submitted data, was approximately 30% (IPM 027: 30.67% (unadjusted 95% CI: 0.90%–51.50%;  $p=0.0414 < \mathbf{0.0466}$ ), MTN-020: 26.75% (unadjusted 95% CI: 0.49%–46.80%;  $p=0.046$ ). While both studies suggest that Dapivirine Vaginal Ring-004 reduces the risk of HIV-1 infection), confidence intervals for both studies are wide and the lower bound of the unadjusted 95% confidence intervals barely excludes 0% for each of the two studies.

During the assessment procedure, several additional analyses were provided by the Applicant, based on the cut-off date of 16 October 2015 (analyses A and B), the complete double-blind trial period (analyses C, D, and G), or the first visit after the double-blind on-treatment period (analysis F). However, it seemed that not all seroconverters were correctly taken into account and the time-to follow-up was not properly calculated. Hence, the input for these analyses needed to be adjusted. These adjusted analyses led to new inconsistencies, however. Another issue that was identified during the assessment related to the observed imbalance in the number of participants in the dapivirine arm ( $n=54$ ) vs placebo arm ( $n=20$ ) who were lost to follow-up and hence discontinued the trial early without an exit visit. The applicant was requested to perform PCR analyses on samples of these participants to rule out HIV infection. The applicant notified the Rapporteurs and EMA that the stored samples could not be tested because they were destroyed in 2018 (for more information, see clinical JAR). Only some PK samples anticoagulated in heparin-lithium, were available and subsequently used for PCR analyses. Approximately half of the samples for which PCR testing was requested, could not be tested, and of all samples that could be tested approximately half failed. Eventually, HIV infection status could not be confirmed for **40 participants**: samples for 18 participants had no result, 15 participants had no post-enrollment pharmacokinetic sample, and for 7 participants, no sample was able to be tested due to not being found at FARMOVS.

It cannot be excluded that additional trial participants would be found HIV positive, if the test could have been performed. The exact number of additional seroconverters, as well as the distribution across the dapivirine and placebo arms, remains unknown. This uncertainty renders a reliable estimate of the overall treatment effect impossible. The Applicant performed a worst case scenario; Missing = Failure analysis. Based on this analysis, the Dapivirine Vaginal Ring reduced the risk of HIV-1 infection by 24.96% (95% CI: -1.05% to 44.27%;  $P = 0.0586$  based on the Cox PH model) relative to the placebo ring. Based on a two-sided log-rank test, the  $P$ -value was 0.0577. A tipping point analysis showed that, for the primary analysis method which was based on the time-to-seroconversion and used a log-rank test, significance is maintained in all 1,000 simulated trials when adding up to 11 additional seroconversions (maximum simulated  $P$ -value: 0.0498; 25th and 975th ordered  $P$ -values: 0.0401 and 0.0471).

### Outcome QC review

Concerns were raised regarding the quality of the data in IPM 027. The Applicant contracted an independent third party to conduct a quality control (QC) of the efficacy data of this trial, as requested.

Although the data clean-up revealed some discrepancies with the latest reported data, these discrepancies did not result in identification of additional seroconversions. and thus has no impact on the overall number of trial endpoints, as for all except one already known seroconverter, negative subsequent rapid test results were available up to and including the last trial visit.

### **Additional efficacy considerations**

For the pooled analysis the reduction of the risk of HIV-1 seroconversion by 30% (as initially reported) translates into prevention of 1.3 seroconversions if 100 women used the DPV-VR for one year. This effect is considered rather modest and the applicant was requested to discuss its relevance on a population level (if 10,000 women used it for one year it could prevent 134 seroconversions) as the downside of an efficacy of 30% is that the invention is ineffective in 70% of cases. The applicant argues that a 30% risk reduction is relevant at the population level, a view which was shared by experts consulted in a scientific advisory group meeting held as part of the review process. It was however clearly stated by the experts that the Dapivirine vaginal ring should not be seen as a first-line intervention, but may be used e.g. when oral PrEP is not/cannot be used, and/or is not available.

Moreover, it would need to be shown that the ring use would not impact on subsequent therapeutic options in those seroconverting. Even if the number of identified viruses that confer high and low level resistance to efavirenz and nevirapine was low in IPM 027 there seems to be a trend of more viruses that confer high-level resistance to efavirenz and nevirapine in the Dapivirine group. Interestingly this trend was also observed in the open-label trials MTN-025 and IPM 032. Therefore, the potential development of resistance-associated mutations under DPV treatment that confer high- or intermediate cross-resistance should remain under supervision and should be listed as a PAM in the RMP.

The generalisability of the trial findings is hampered by the stringent in- and exclusion criteria, e.g. with respect to concomitant diseases. The Applicant provided reasoning for the stringent inclusion criteria as related to concomitant conditions, i.e. being consistent with the design of Phase III clinical trials in general, as this not only protects participants from potential harm in the trial, but also allows for a clearer assessment of potential drug-related AEs, which can be endorsed as a matter of prudence.

Noteworthy, the rates of screening failures were very high in both studies, even despite a "pre-screening" approach has been applied. Depending on the study centre more than 50% of the subjects were screening failures because of pre-existing HIV-1 infection. The fact that this was only diagnosed at screening emphasizes the importance of reliable exclusion of HIV-infection prior to ring use (and also at regular/close intervals during its use). Moreover, a considerable proportion of subjects was excluded from the studies based on "soft", non-transparent criteria, being left to the investigator's discretion. The applicant provided an analysis of the "soft" reasons for screening failure and the conclusion that none of the reasons underlying the investigators' discretion not to enrol a woman, would hamper the generalizability of the study results, is endorsed.

While participants underwent regular, four-weekly trial visits with a broad spectrum of examinations/investigations/lab tests and subsequently received therapy for any concurrent condition diagnosed at the respective visit, the feasibility of this approach in clinical practice is questionable. Hence, it is not clear, if the trial results can be applied to a "real world setting". Most importantly, regular HIV-tests would be important, given the modest efficacy of the DPV-VR and that potential cross- resistance with WHO-recommended first-line therapies cannot be excluded. In the studies, pre-existing STIs- a

factor known to facilitate HIV-infection – had to be treated prior to enrolment and participants received therapy at each visit when a respective infection was diagnosed. The percentage of participants presenting with any urogenital condition at screening was high in both studies and hence a considerable proportion of potential users have to be considered at higher risk of HIV-infection. In addition, the conditions of medical care in “real life” are unknown. Moreover, systemic anti-infectives were used for therapy of genital infections in the vast majority, as use of topical (vaginal) therapies was discouraged by protocol. In clinical practice, considering the B/R of topical preparations, topical (vaginal) therapies are first-line treatment options. Drug-drug interactions have been investigated only for miconazole capsules and clotrimazole 10 mg/g vaginal cream. Significant effects on dapivirine and miconazole vaginal fluid levels were observed in the miconazole DDI trial, whereas in the clotrimazole DDI trial only modest effects were observed on dapivirine and clotrimazole vaginal fluid levels. The clinical relevance seems to be low in both cases, and uncertainties remain. In both studies there were methodological issues related to the measurements of the vaginal concentrations of both drugs, making the results unreliable. Moreover, the influence of excipients in the topical formulations remains unknown. No other DDI studies are planned.

The dapivirine molecule was originally developed as an oral ARV drug in the late 1990s, after which it was further developed as a topical microbicide for the prevention of HIV-1 infection. There is no established animal model in place to prove efficacy for an NNRTI as the active compound. Based on *in vitro* studies in cervical tissue, the applicant determined an IC<sub>99</sub> against HIV-1<sub>Bal</sub> of 3.3 ng/ml, and subsequently targets dapivirine concentrations in the genital tract in humans well in excess of this concentration. While this strategy is not unreasonable, vaginal fluid concentrations do not necessarily correlate with the concentration within CD4 cells in the tissues of the lower female reproductive tract, which is assumed to be the primary site of action of dapivirine. According to the applicant, efforts were made to determine dapivirine concentrations within the target tissues, but this has proven difficult because of the uncertainty of where the drug concentration was actually measured (eg, on the tissue surface, in the dead keratinized cell layers, or in interstitial fluid and living target cells).

No dose response studies have been performed with the dapivirine vaginal ring formulation. The present substantiation of the 25mg dose largely relies on the *in vitro* results indicating an IC<sub>99</sub> of 3.3 ng/ml, this is however considered a questionable measure for the *in vivo* inhibitory effect on HIV-1 replication. As a consequence, it is unclear whether the 25 mg dapivirine contained in the vaginal ring-004, results in the most optimal intracellular concentration of dapivirine in the target cells to prevent HIV-1 from replicating. Nevertheless, both pivotal studies suggest that the dapivirine vaginal ring is associated with an approximately 30% lower risk of contracting HIV infection. However, the 95% confidence intervals of each study are wide and barely exclude 0. The impact of adherence as well as of varying sexual practices on the efficacy estimate appears ill defined. The applicant was requested to further discuss the external validity and clinical relevance of the results. The applicant acknowledges the perspective that the point estimates of benefit as observed in the two Phase III trials in relevant geographical areas were lower than anticipated. The applicant also recognizes that there are some remaining uncertainties around the magnitude of the observed benefit and its reflection of the real-life situation, including the clinical relevance for women at risk in sub-Saharan Africa. The applicant argues that the observed 30% risk reduction is relevant both at the individual as well as at the population level, and mentions that the dapivirine vaginal ring should not be seen as a replacement for other preventive modalities, but rather as part of a comprehensive prevention package from which a healthcare professional and participant can choose.

### **Adherence and correct ring use**

The Applicant has made several efforts to break down the efficacy results into subgroups for elucidating influential factors and defining those women, who would profit most from use of the ring. For this, univariate and multivariate analyses in different subgroups were conducted, for most of them the results

were inconclusive, as not consistent between the two pivotal studies. However, women, whose partners were aware of the ring use, had a lower risk of HIV-1 seroconversion as compared to those whose partners were not aware, and ring use led to a more pronounced reduction in risk. Further post hoc analyses indicated that participants with plasma dapivirine levels of 95 pg/ml or more and dapivirine residual levels in the ring of less than 23.5 mg after its removal at day 28 (after insertion) showed a higher risk reduction.

The Applicant considered these PK parameters to be correlates of adherence. While this can be endorsed for “not using the ring at all” versus “any use of the ring”, these measures do not allow for a better degree of granularity of adherence, as none of the PK parameters can be linked to the time of/around the “risk exposure”, and they do neither seem to correlate with self-reported adherence during the studies. Phase 1 studies showed considerable inter-individual variability (depending on the parameter investigated) and no data have been provided on intra-individual variability. Factors, apart from adherence, potentially influencing release/uptake of DPV from the vaginal ring have not been investigated.

Ring residual levels, as a measure of adherence, were compared between subjects who seroconverted and participants who remained HIV-1 negative throughout the study. Neither overall, nor in individual centers, the average ring residual level prior to seroconversion was any different in subjects who seroconverted compared to participants who remained HIV-1 negative throughout the study. As such, it can be concluded that there does not seem to be a direct relation between efficacy and adherence as measured by ring residual levels, which is not unexpected given the uncertainties relating to adherence measures as described above. The difference in outcome between research centers cannot be explained by differences in adherence (as measured by ring residual levels or plasma concentrations). No baseline characteristics or sexual behaviour between the trial participants enrolled in the centers with vs without a reduced risk in the dapivirine group, that may be related to protection against HIV-1 infection, could be defined.

### **Subgroup analyses**

The **subgroup analyses** (all based on the initially submitted dataset) revealed that for several categories, the treatment differences differed among the subgroups within this category. The categories “number of male sex partners (0-1,  $\geq 2$ )” and “presence of STIs (i.e. yes, no)” were identified in both studies. Of interest is that HIV-1 infection risk reduction in the pooled Dapivirine Vaginal Ring-004 groups versus the pooled placebo ring groups was only observed in women older than 21 years of age. In this subgroup, the HIV-1 infection risk reduction was 39.8% (95% CI 20.19; 54.56) while no HIV-1 infection risk reduction was observed in the subgroup of women 18 to 21 years of age (risk reduction -4.81% (95% CI -57.31; 30.17)). There is no apparent biological rationale for this finding. Lower adherence to ring use may have played a role, but this cannot be reliably assessed. Interpretation of subgroup analysis data should be done with caution, due to the fact that several subgroups could be linked to each other (e.g. younger subjects could have more frequent STIs at screening (32% versus 21% (pooled data)) and were probably less frequently married (8% versus 33% (pooled data)) compared to older women). Further reassurance on the efficacy of DVR in the subgroup of young women should be provided (see section 6 and 7). A remarkable higher HIV-1 infection risk reduction was noted between ‘participants whose partners were aware of the ring use’ compared to those whose partners were not aware. The difference was more pronounced in IPM 027, but a similar trend was observed in MTN-020. It is not unreasonable to think that women whose partners are aware of the ring use are less likely to remove the ring before sexual intercourse than women who did not tell their partner they were using a vaginal ring. As it is unknown to what extent the ring can be taken out for any period of time before losing its protective effect, the impact on HIV-1 infection risk reduction cannot be reliably assessed.



In addition, regional differences between the study centres were seen. Only a very limited number of study centres from a total of four countries participated in the studies, with the vast majority of the women recruited in South Africa, specifically in the province KwaZulu Natal. Socio-economic and cultural conditions as well as gender dynamics and community factors showed some degree of variability already across the study sites –as also discussed by the Applicant, these aspects were considered to impact on the participants' motivation to adhere to the DPV-VR. However, a much larger variability with an unknown impact on the efficacy of the DPV-VR can be anticipated with wider spread use of the product, e.g. in other countries. This pertains also to efficacy/safety of the product in women, currently excluded from the studies, e.g. those who underwent genital mutilation or in regions with concomitant conditions, only rarely seen in the population studied, such as HIV-2 infection.

While the *relative* risk reduction would be assumed to be the same irrespective of the HIV-prevalence, a numerical difference in risk reduction was seen for the comparison South African sites versus other African countries in the pooled analysis (3.1% versus 1.1%) with seroconversion rates in both groups being much higher in the South African sites. In addition, the *absolute* risk reduction would have to be taken into account when assessing benefits and risks for the individual user.

### **Dapivirine-associated viral mutations**

It is not unlikely that the dapivirine vaginal ring would have a reduced efficacy against infection with HIV-1 variants harbouring **dapivirine-associated viral mutations**. According to the Applicant reduced *in vitro* susceptibility to DPV typically required more than one substitution in reverse transcriptase (site-directed mutants). However, *in vitro* resistance development has revealed six major DPV resistance associated mutations (L100I, K103N, Y181C/I, Y188L, G190E and F227C) which significantly influence the susceptibility to DPV. Resistance developed fast *in vitro* and conferred cross-resistance to other NNRTIs. These findings are especially of relevance when undiagnosed HIV-positive women use DPV, as resistance development may compromise potential therapeutic treatment options. It still remains unclear, how these findings correlate with the clinical situation and the incompletely characterised risk of drug resistance in case of prophylaxis failure need further consideration. Resistance data from samples obtained soon after HIV-1 infection of participants who seroconverted in the two Phase III trials (IPM 027 and MTN-020) demonstrated little evidence of any increase in mutations associated with reduced susceptibility to NNRTIs in the Dapivirine Vaginal Ring-004 group. However, data from the open-label extension trials IPM 032 and MTN-025 indicate a higher tendency for development of resistance compared to the pivotal trials. In addition, data from IPM 032 indicate that participants with longer dapivirine treatment might be at higher risk of development of NNRTI RAMs. Hence, the possibility that resistance associated mutations develop upon dapivirine selective pressure cannot be excluded. Although data are limited and it cannot be excluded that NNRTI resistance could impact the treatment response to NNRTI based regimens, the recent change in WHO guidelines recommending dolutegravir-based regimens as the preferred initial treatment option for all HIV infected patients and the apparent absence of NRTI RAMs in patients failing DPV PrEP, alleviates somewhat these concerns.

Although efficacy of the vaginal ring may have been shown in comparison to placebo, there has been increasing evidence for use of oral PrEP (tenofovir disoproxil ±emtricitabine) leading to its recommendation for individuals at substantial risk, e.g. per 2016 WHO HIV guideline. This cannot be dismissed and DPV-VR's efficacy and subsequently its place in therapy will have to be seen in light of the other options for prevention.

Although the impact of knowledge of using a product providing incomplete protection on sexual behaviour is not known, there is increasing evidence that people on oral PrEP change their behaviour and use condoms less often, especially now they know oral PrEP is effective in reducing the risk of HIV-1 infection (e.g. Molina et al., Lancet HIV 2017). If the frequency of condomless sex acts would also increase when women use the dapivirine vaginal ring, due to a perception that they are at least to some extent protected

by using the vaginal ring, the 30% risk reduction may not outweigh the increase in risk due to condomless sex and the net effect may even be an increased incidence rather than a decrease in new HIV-1 infections at the population level (see for example also the results of the modelling studies by Smith et al., AIDS 2005, and Grant et al., JIAS 2017). Additionally, the impact of untreated STI on efficacy remains an issue of concern. Although the information provided by the applicant suggests that there is no major impact on efficacy and/or safety when women with STIs use the dapivirine vaginal ring, HCPs will be instructed to identify and treat any urogenital infections which may be present as per local guidelines. Measures to further study the real life effectiveness of the dapivirine ring, including the uncertainties delineated above, have been taken into consideration by the applicant, but in the opinion of the applicant a HIV seroconversion registry is not a feasible option when considering the intended markets for the Dapivirine Vaginal Ring. According to the applicant, routine risk communication and additional risk minimization measures already proposed will adequately address the important identified and potential risks associated with use of the Dapivirine Vaginal Ring.

There are two open-label extension trials ongoing, IPM 032 (DREAM) and MTN-025 (HOPE). However, due to the important uncertainties described earlier, the results from these OLE studies can only be regarded as supportive. In addition, these studies will not be able to provide reassurance regarding the external validity of the results, since they enrolled the same participants in the same sites as the parent studies. It is however reassuring that transmission rates in the OLE studies were at least not higher than what has been seen in the parent studies.

No efficacy data are available for women less than 18 years of age. This is considered a relevant omission in view of the fact that women in the age group 15 to 24 years are those at highest risk for HIV-infection. Furthermore, it is not clear if a threshold, e.g. age/weight/height can be defined for whom the ring may (not) be used due to its size or other formulation-specific aspects.

In addition, efficacy data are not available for pregnant women, not for women immediately post-partum and not nor for women older than 45 years.

#### ***Additional expert consultation***

A SAG expert meeting has been held on 3 December 2018. The main conclusions were that the Dapivirine vaginal ring should not be ruled out as part of a global strategy to reduce HIV transmission in addition to the current available and effective standard approaches for HIV negative women in sub-Saharan Africa. The Dapivirine vaginal ring should not been seen as a first-line intervention, but the SAG members recognised that the Dapivirine vaginal ring has a place in prevention strategy, e.g. when oral PrEP is not/cannot be used, and/or is not available. More data would be welcome, but no specific suggestions were put forward. Presently not much evidence points towards high risk of resistance development, however, more data would be needed in order to have a clearer picture on this matter.

### **2.5.4. Conclusions on the clinical efficacy**

Based on the analyses submitted, both pivotal trials seem to show a reduction in HIV-1 seroconversions in women aged 18 to 45 years. However, Study MTN-020 can no longer be regarded as confirmatory for the efficacy of the Dapivirine Vaginal Ring, due to the serious and manifold uncertainties surrounding the data quality and reliability that became evident during the GCP inspection and due to the possible bias on the estimated effect by stopping the recruitment of two centers. This means that this application is based on a single pivotal trial, IPM-027. Also for this study, major inconsistencies in the data and analyses were identified. A comprehensive and thorough quality control (QC) review for all clinical data was requested in order to provide a reliable estimate of the primary efficacy measure of Study IPM 027. The Applicant contracted an independent third party to conduct this quality control.



Although the QC revealed some discrepancies with the originally reported dataset, no additional HIV-1 infections were identified. From the outset of the assessment the effect size has always been regarded as rather modest, and this was also confirmed by the SAG (December 2018). The CHMP agreed that this could be addressed by phrasing the SmPC accordingly (e.g. the therapeutic indication).

The internal and external validity, data quality and internal consistency have, after several rounds of outstanding issues and their assessment, been adequately addressed, also when contextualising these with other PrEP-studies. The clinical relevance of the findings was confirmed by the SAG and since the reported effect size has not changed since then, the SAG's views should be considered still valid.

Looking at the totality of the evidence, there is supporting evidence for a beneficial effect of the dapivirine vaginal ring of other efficacy and safety studies, i.e. MTN-020 and IPM 032 –despite their limitations. The effect size of MTN-020, the only other randomized controlled study, is in the same range as that of IPM 027. In the open-label study IPM 032 DVR's efficacy compares favourably with the adjusted simulated placebo incidence (and external placebo incidence rates) and also for study MTN-025, when using the (as best as possible) matching (sub)groups as most conservative comparison, the point estimate is still in favour of DVR. None of the study results/sensitivity analyses points in the opposite direction, which is regarded as reassuring by the CHMP.

However, current uncertainties remain on the effect size in younger women. The CHMP therefore imposed a Category 1 Post-Authorisation Efficacy Study (PAES) to address this, to confirm the overall effect size as well as to systematically collect information about NNRTI resistance in seroconverters. (cf. section 2.7).

The CHMP considers the following measures necessary:

- Post-authorisation efficacy study (PAES):  
Phase IV, open label, multicentre efficacy study in healthy HIV-negative young women age 18-25 years (stratified for 18 to 21 years and >21 to 25 years) using the Dapivirine Vaginal Ring over a period of 12 months to address the current uncertainty in the efficacy in younger women and to confirm the overall effect size by establishing an appropriate counterfactual and to systematically collect information about NNRTI resistance in seroconverters.

## **2.6. Clinical safety**

Three (pooled) groups were defined to evaluate the safety profile of Dapivirine:

- Phase I pooled analysis,
- Phase II IPM 015 trial
- Phase III pooled analysis.

All analyses were performed for each (pooling) group separately. Table 17 provides an overview of the clinical trials that were included in the different pooled analyses.

The Phase I pooled analysis included safety results of the trials **IPM 013**, **IPM 024**, **IPM 028**, **IPM 034**, and **IPM 035**, which were conducted in healthy HIV-negative women in Belgium.

The Phase II (**IPM 015**) and III (**IPM 027** and **MTN-020**) clinical trials were conducted in healthy, HIV-negative, sexually active women in sub-Saharan Africa.

The IPM 027 trial is currently ongoing. The final analysis of the primary efficacy and safety endpoints was performed with a data cut-off date of 16 October 2015.

In all trials, AEs of all severity grades were captured in Case Report Forms with the following exception:

- In trial MTN-020, all SAEs and AEs of severity Grade 2 or higher were captured as well as the following Grade 1 (mild) AEs: genital, genitourinary, or reproductive system AEs, laboratory AEs, and AEs that resulted in permanent product discontinuation. Research center staff documented in source documents all AEs reported by or observed in enrolled trial participants regardless of severity and presumed relationship to the IP, in case the other Grade 1 events needed to be captured in the clinical database at some future time point depending on the emerging product safety profile.

The phase III clinical trials, IPM 027 and MTN-020, are the pivotal trials of this MAA, as such, the Phase III pooled analysis set is considered the most important safety analysis set of this application and results of this safety analysis set are presented and discussed in detail. Safety issues of the Phase I pooled analysis and Phase II IPM 0150 set are discussed when relevant.

**Table 17 Overview of trials included in the safety analyses of the Dapivirine Vaginal Ring-004**

Trial Number	Design/Population/ Age range	Primary Objective(s)	Treatment Regimen	N Enrolled	Country
<b>Phase I Trials Included in the Phase I Pooled Analysis</b>					
IPM 013	Double-blind, randomized, placebo-controlled, single-center trial Healthy, HIV-negative, adult women 18 - 40 years old, extremes included	<ul style="list-style-type: none"> <li>To assess the safety of the platinum-catalyzed vaginal matrix ring as compared to the placebo ring when used for 56 days (Group A) or 57 days (Group B) by healthy, sexually active HIV-negative women.</li> <li>To examine local and systemic pharmacokinetics of dapivirine when delivered by the platinum-catalyzed vaginal matrix rings containing 25 mg of dapivirine, measured in plasma, vaginal fluids, and cervical tissue during the trial period.</li> </ul>	<p>Group A (ratio 3:1):</p> <ul style="list-style-type: none"> <li>A1: Dapivirine Vaginal Ring-004 for 28 days + 28 days (N = 18)</li> <li>A2: placebo ring for 28 days + 28 days (N = 6)</li> </ul> <p>Group B (ratio 3:1):</p> <ul style="list-style-type: none"> <li>B1: Dapivirine Vaginal Ring-004 for 35 days + 21 days + 1 day (N = 18)</li> <li>B2: placebo ring for 35 days + 21 days + 1 day (N = 6)</li> </ul>	48	Belgium

Trial Number	Design/Population/ Age range	Primary Objective(s)	Treatment Regimen	N Enrolled	Country
IPM 024	Double-blind, randomized, placebo-controlled, single-center trial Healthy, HIV-negative, adult women 18 - 40 years old, extremes included	<ul style="list-style-type: none"> <li>• To assess the safety and tolerability of the platinum-catalyzed vaginal matrix ring containing dapivirine as compared to the placebo ring when used continuously for 28 days by healthy, HIV-negative women.</li> <li>• To assess dapivirine concentrations in plasma before, during, and after 28-day use of a silicone elastomer vaginal matrix ring containing dapivirine.</li> <li>• To assess dapivirine concentrations in vaginal fluids before, during, and after 28-day use of a silicone elastomer vaginal matrix ring containing dapivirine.</li> </ul>	Two arms (ratio 1:1): Arm A: Dapivirine Vaginal Ring-004 for 28 days (N = 8) Arm B: placebo ring for 28 days (N = 8)	16	Belgium

Trial Number	Design/Population/ Age range	Primary Objective(s)	Treatment Regimen	N Enrolled	Country
IPM 028	Open-label, randomized, three-period crossover, single-center trial Healthy, HIV-negative, adult women 18 - 40 years old, extremes included	<ul style="list-style-type: none"> <li>To determine the effect of vaginally administered <b>miconazole nitrate</b> on the local (vaginal fluid, collected at the cervix) and systemic (plasma) pharmacokinetics of dapivirine, delivered by the Dapivirine Vaginal Ring-004, in healthy, HIV-negative women.</li> <li>To determine the effect of dapivirine, delivered by the Dapivirine Vaginal Ring-004, on the local (vaginal fluid, collected at the cervix) and systemic (plasma) pharmacokinetics of miconazole, administered as a vaginal capsule in healthy, HIV-negative women.</li> </ul>	<p>Two treatment sequences (ratio 1:1) A-B-C (N = 18) and B-A-C (N = 18) consisting of the following treatments:</p> <ul style="list-style-type: none"> <li>A: Dapivirine Vaginal Ring-004 for 28 days</li> <li>B: Dapivirine Vaginal Ring-004 for 28 days + single dose (1200 mg) miconazole nitrate inserted as a vaginal capsule directly after insertion of the Dapivirine Vaginal Ring-004</li> <li>C: single dose (1200 mg) miconazole nitrate vaginal capsule</li> </ul> <p>Each treatment was separated by a washout period of three weeks.</p>	36	Belgium
IPM 034	Open-label, parallel group, single-center trial Healthy, HIV-negative, adult women 18 - 40 years old, extremes included	To describe the local and systemic <b>pharmacokinetics of dapivirine</b> , delivered by Ring-004, measured in plasma and vaginal fluid of healthy, HIV-negative women using the investigational product continuously over periods of 7, 14, 28, 56 or 84 days (1, 2, 4, 8, or 12 weeks, respectively).	<p>Five groups (ratio 1:1:1:1:1)</p> <p>Group A: Dapivirine Vaginal Ring-004 for 7 days (N = 8)</p> <p>Group B: Dapivirine Vaginal Ring-004 for 14 days (N = 8)</p> <p>Group C: Dapivirine Vaginal Ring-004 for 28 days (N = 8)</p> <p>Group D: Dapivirine Vaginal Ring-004 for 56 days (N = 8)</p> <p>Group E: Dapivirine Vaginal Ring-004 for 84 days (N = 8)</p>	40	Belgium

Trial Number	Design/Population/ Age range	Primary Objective(s)	Treatment Regimen	N Enrolled	Country
IPM 035	Open-label, randomized, two-cohort, three-period crossover, single-center trial Healthy, HIV-negative, adult women 18 - 40 years old, extremes included	<ul style="list-style-type: none"> <li>To determine the effect of <b>menses</b> on the local and systemic pharmacokinetics of dapivirine, delivered by the Dapivirine Vaginal Ring-004, in healthy, HIV-negative women.</li> <li>To determine the effect of <b>tampon use</b> during menses on the local and systemic pharmacokinetics of dapivirine, delivered by the Dapivirine Vaginal Ring-004, in healthy, HIV-negative women.</li> </ul>	<p>Two treatment sequences:</p> <ul style="list-style-type: none"> <li>Cohort 1 (N = 22) (ratio 1:1): A-B-E or B-A-E</li> <li>Cohort 2 (N = 16) (ratio 1:1): C-D-E or D-C-E</li> </ul> <p>consisting of the following treatments:</p> <ul style="list-style-type: none"> <li>A: Dapivirine Vaginal Ring-004 for 28 days uninterrupted, no tampon use during menses</li> <li>B: Dapivirine Vaginal Ring-004 for 28 days uninterrupted, tampon use during menses</li> <li>C: Dapivirine Vaginal Ring-004 for 28 days, ring removed during menses (5 days), reinserted five days after start of menses, no tampon use</li> <li>D: Dapivirine Vaginal Ring-004 for 28 days, ring removed at start menses, new ring after 5 days, no tampon use</li> <li>E: Dapivirine Vaginal Ring-004 for 28 days uninterrupted, no menses</li> </ul> <p>Each treatment was separated by a washout period of 28 days.</p>	38	Belgium
<b>Phase II Trial</b>					
IPM 015	Double-blind, randomized, placebo-controlled, multi-center trial Healthy, HIV-negative, adult women 18 - 40 years old, extremes included	To assess and compare the <b>safety</b> of a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine and a placebo ring inserted once every 28 days over a 12-week period among healthy, sexually active, HIV-negative women	<p>Two arms (ratio 1:1):</p> <p>Dapivirine Vaginal Ring-004 for 12 weeks (N = 140)</p> <p>placebo ring for 12 weeks (N = 140)</p> <p>A new ring was inserted once every 28 days.</p>	280	Kenya, Malawi, Tanzania, South Africa

Trial Number	Design/Population/ Age range	Primary Objective(s)	Treatment Regimen	N Enrolled	Country
<b>Phase III Trials Included in the Phase III Pooled Analysis</b>					
IPM 027	Double-blind, randomized, placebo-controlled, multi-center trial Healthy, HIV-negative, adult women 18 - 45 years old, extremes included	<ul style="list-style-type: none"> <li>To determine the <b>efficacy</b> of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every four weeks over a period of approximately 24 months (104 weeks), in preventing HIV-1 infection among healthy, sexually active HIV-negative women</li> <li>To assess the <b>safety</b> of dapivirine administered in a silicone elastomer vaginal matrix ring, when inserted once every four weeks over a period of approximately 24 months (104 weeks).</li> </ul>	Two arms (ratio 2:1): Dapivirine Vaginal Ring-004 for approximately 24 months (104 weeks) (N = 1307) placebo ring for approximately 24 months (104 weeks) (N = 652) A new ring was inserted once every four weeks.	1959	South Africa, Uganda
MTN-020	Double-blind, randomized, placebo-controlled, multi-center trial Healthy, HIV-negative, adult women 18 - 45 years old, extremes included	<ul style="list-style-type: none"> <li>To determine the <b>effectiveness</b> of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every four weeks, in preventing HIV-1 infection among healthy sexually active HIV-uninfected women.</li> <li>To assess the <b>safety</b> of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every four weeks over the investigational product use period.</li> </ul>	Two arms (ratio 1:1): Dapivirine Vaginal Ring-004 for > 12 months (endpoint driven) (N = 1313) placebo ring for > 12 months (endpoint driven) (N = 1316) A new ring was inserted once every four weeks.	2629	Malawi, South Africa, Uganda, Zimbabwe

N = number of participants, CSR = Clinical Study Report, HIV = human immunodeficiency virus

## Patient exposure

In the three (pooled) safety analysis groups, a total of 2917 subjects were exposed to the Dapivirine ring representing 4181 patient years of exposure (Table 18). This was mainly attributable to patients from the Phase III trials. In the Phase III trials, 2091 subjects were exposed to Dapivirine for  $\geq 12$  months and 710 subjects were exposed to Dapivirine for  $\geq 24$  months.

**Table 18 Overall Exposure of Participants Included in the Phase I Pooled Analysis, the Phase II IPM 015 Trial, and the Phase III Pooled Analysis**

Exposure	Dapivirine (Any Duration)	Person Years
	n (%)	(Years)
<i>Safety Population</i>	2917	-
< 1 month	63 (2.2%)	3.16
$\geq 1$ to < 3 months	276 (9.5%)	57.31
$\geq 3$ to < 6 months	113 (3.9%)	42.09
$\geq 6$ to < 12 months	289 (9.9%)	250.21
$\geq 12$ to < 18 months	621 (21.3%)	769.14
$\geq 18$ to < 24 months	760 (26.1%)	1417.82
$\geq 12$ months	2091 (71.7%)	3828.12
$\geq 24$ months	710 (24.3%)	1641.16
Missing <sup>a</sup>	85 (2.9%)	-
Total	2917 (100.0%)	4180.89
n = number of participants with this observation <sup>a</sup> Some participants had a missing investigational product end date and were therefore not included in the descriptive statistics. Note: This table includes all participants who received the Dapivirine Vaginal Ring-004 (any duration) in the trials included in the Phase I pooled analysis (trials IPM 013, IPM 024, IPM 028, IPM 034, and IPM 035), the Phase II IPM 015 trial, and the trials included in the Phase III pooled analysis (trials IPM 027 and MTN-020).		

## Adverse events

### General frequency of adverse events

#### Phase I Pooled Analysis

Of the 171 subjects in the Phase I pooled analysis, a large proportion of patients experienced at least 1 treatment-emergent adverse event (TEAE) with 94 (87.0%) subjects in the Dapivirine (28 days) group and 13 (92.9%) subjects in the placebo group. No clinical relevant differences in incidence in adverse events between the Dapivirine (28 days) and placebo group have been observed, but it has to be taken into account that the number of subjects receiving Dapivirine for 28 days is much higher (n=108) than those who received placebo (n=14). The majority of TEAEs were mild or moderate in severity. Severe (Grade 3) or potentially life-threatening (Grade 4) TEAEs and IP-related TEAEs were reported less frequently in the Dapivirine group compared with the placebo group (1.9% (2/108) versus 7.1% (1/14) and 5.6% (6/108) versus 7.1% (1/14), respectively).



The most common adverse events (*i.e.* in  $\geq 10.0\%$  of subjects in the Dapivirine (28 days) group) were headache (39.8% and 42.9% for the Dapivirine (28 days) and the placebo group, respectively), metrorrhagia (25.0% and 28.6%), nasopharyngitis (21.3% and 7.1%), vaginal haemorrhage (12.0% and 28.6%), abdominal pain lower (12.0% and 14.3%), menometrorrhagia (10.2% and 0%), nausea (10.2% and 0%), and oropharyngeal pain (10.2% and 7.1%). The higher incidence in TEAE menometrorrhagia in the Dapivirine group compared with the placebo group has not been observed in the Phase II and Phase III pooled analysis sets and are probably due to the very limited amount of subjects ( $n=14$ ) included in the placebo group, compared to 108 subjects in the Dapivirine (28 days) group.

### **Phase II IPM 015 trial**

In the Phase II IPM 015 trial, the incidence of at least one TEAE for subjects in the Dapivirine (82.9% (116/140)) was slightly lower compared with the placebo group (88.5% (123/130)). The most commonly reported TEAEs (*i.e.*, in  $\geq 10.0\%$  of the subjects in the Dapivirine group) were metrorrhagia (18.6% and 19.3% for the Dapivirine and the placebo group, respectively), gynaecological chlamydia infection (15.7% and 15.7%), vulvovaginal candidiasis (14.3% and 8.6%), urinary tract infection (12.9% and 10.0%), and upper respiratory tract infection (10.7% and 11.4%).

The incidence in IP-related TEAEs was comparable between both groups (22.9% of the subjects in the Dapivirine group and 22.3% of the subjects in the placebo group). IP-related TEAEs  $> 2\%$  (experienced by  $\geq 3$  subjects) in either group were urinary tract infection (2.1% for both groups), vaginal candidiasis (2.9% and 1.4% in the Dapivirine and placebo group, respectively), vaginitis bacterial (2.1% and 1.8%), vulvovaginal mycotic infection (1.4% and 2.1%), metrorrhagia (6.4% and 2.9%), and vulvovaginal pruritus (3.6% and 2.1%).

### **Phase III pooled analysis**

#### *Demographic and Other Characteristics in the Individual and Pooled Phase III Trials*

The trials included in the Phase III pooled analysis were conducted in Malawi, South Africa, Uganda, and Zimbabwe.

When comparing trials IPM 027 and MTN-020, no differences were observed, except for marital status, baseline method of contraception, and abnormal vaginal flora.

In trial IPM 027, more subjects were not married (91.0% [1188/1306] of subjects in the Dapivirine group and 90.3% [589/652] of subjects in the placebo group) compared to trial MTN-020 (59.9% [786/1313] and 58.3% [767/1316], respectively) (Table 19).

Long-acting injectable progestins were used more often and transdermal contraceptive patches and IUDs were used less frequently in trial IPM 027 than in trial MTN-020. In both trials, the majority of participants used long-acting injectable progestins, followed by oral contraception and subcutaneous implants in trial IPM 027 and transdermal contraceptive patches, oral contraception, and IUDs in trial MTN-020. Other methods of contraception were used in  $\leq 5.0\%$  of subjects in the Dapivirine group in the IPM 027 or MTN-020 trials.

When comparing trials IPM 027 and MTN-020, the proportion of subjects with an abnormal vaginal flora, as indicated by a Nugent score  $\geq 7$ , was lower in trial IPM 027 than in trial MTN 020 at baseline.

Within trials IPM 027 and MTN-020, no differences were observed between the Dapivirine and placebo groups for any of the demographic and baseline parameters.

The majority of subjects were Black (96.5% [2527/2619] in the Dapivirine group and 94.9% [1868/1968] in the placebo group) and older than 21 years (77.7% [2036/2619] and 79.4%

[1563/1968], respectively). Mean (SD) BMI was 27.44 (6.802) kg/m<sup>2</sup> in the Dapivirine group and 27.57 (6.902) kg/m<sup>2</sup> in the placebo group.

At baseline, any sexually transmitted infections (STI) was identified in 24.6% (643/2619) of the subjects in the Dapivirine group and 22.5% (442/1968) of the subjects in the placebo group (Table 20). Positive tests were observed for:

- Chlamydia trachomatis in 15.0% (394/2619) of the subjects in the Dapivirine group and 13.2% (259/1968) of the subjects in the placebo group.
- Trichomonas vaginalis in 8.2% (214/2615) and 7.7% (151/1965), respectively.
- Neisseria gonorrhoeae in 4.7% (122/2619) and 4.1% (80/1968), respectively.
- Syphilis in 1.3% (33/2619) and 1.4% (28/1968), respectively.

As sexual risk taking behaviour may differ in younger versus older age groups, STIs at baseline were tabulated by age in this section. In the Dapivirine group, 33.1% (193/583) of subjects ≤ 21 years of age versus 22.1% (450/2036) of subjects > 21 years of age were positive for any STI at baseline, with most subjects being positive for Chlamydia trachomatis: 26.1% (152/583) for ≤ 21 years of age versus 11.9% (242/2036) for > 21 years of age.

Overall, no relevant differences in demographic and baseline diseases characteristics were noted between the Dapivirine and placebo groups.

**Table 19 Demographic and Other Characteristics (Phase III Pooled Analysis)**

	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Age (years), N</b>	<b>1306</b>	<b>652</b>	<b>1313</b>	<b>1316</b>	<b>2619</b>	<b>1968</b>
Mean (SD)	25.9 (5.85)	26.1 (5.92)	27.2 (6.09)	27.3 (6.28)	26.5 (6.00)	26.9 (6.19)
Range	18; 45	18; 45	18; 44	18; 45	18; 45	18; 45
<b>Age Category, N</b>	<b>1306</b>	<b>652</b>	<b>1313</b>	<b>1316</b>	<b>2619</b>	<b>1968</b>
≤ 21 years	314 (24.0%)	158 (24.2%)	269 (20.5%)	247 (18.8%)	583 (22.3%)	405 (20.6%)
> 21 years	992 (76.0%)	494 (75.8%)	1044 (79.5%)	1069 (81.2%)	2036 (77.7%)	1563 (79.4%)
<b>Race, N</b>	<b>1306</b>	<b>652</b>	<b>1313</b>	<b>1316</b>	<b>2619</b>	<b>1968</b>
Black	1299 (99.5%)	642 (98.5%)	1228 (93.5%)	1226 (93.2%)	2527 (96.5%)	1868 (94.9%)
Asian	0	0	13 (1.0%)	3 (0.2%)	13 (0.5%)	3 (0.2%)
White	0	0	2 (0.2%)	0	2 (0.1%)	0
Other	7 (0.5%)	10 (1.5%)	70 (5.3%)	87 (6.6%)	77 (2.9%)	97 (4.9%)

	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<b>BMI (kg/m<sup>2</sup>), N</b>	<b>1306</b>	<b>652</b>	<b>1311</b>	<b>1316</b>	<b>2617</b>	<b>1968</b>
Mean (SD)	28.08 (7.116)	28.23 (6.796)	26.80 (6.414)	27.25 (6.933)	27.44 (6.802)	27.57 (6.902)
Range	15.0; 80.0	15.8; 53.8	11.3; 108.4	11.8; 147.0	11.3; 108.4	11.8; 147.0
<b>Marital Status, N</b>	<b>1306</b>	<b>652</b>	<b>1313</b>	<b>1316</b>	<b>2619</b>	<b>1968</b>
Not married	1188 (91.0%)	589 (90.3%)	786 (59.9%)	767 (58.3%)	1974 (75.4%)	1356 (68.9%)
Married	118 (9.0%)	63 (9.7%)	527 (40.1%)	547 (41.6%)	645 (24.6%)	610 (31.0%)
<b>Baseline Method of Contraception<sup>a</sup>, N</b>	<b>1306</b>	<b>652</b>	<b>1313</b>	<b>1316</b>	<b>2619</b>	<b>1968</b>
Long-acting injectable progestins	1033 (79.1%)	520 (79.8%)	706 (53.8%)	734 (55.8%)	1739 (66.4%)	1254 (63.7%)
Transdermal contraceptive patch	0	1 (0.2%)	256 (19.5%)	242 (18.4%)	256 (9.8%)	243 (12.3%)
Oral contraceptive regimen	112 (8.6%)	59 (9.0%)	137 (10.4%)	141 (10.7%)	249 (9.5%)	200 (10.2%)
IUD	19 (1.5%)	6 (0.9%)	159 (12.1%)	162 (12.3%)	178 (6.8%)	168 (8.5%)
Surgical sterilization	49 (3.8%)	24 (3.7%)	45 (3.4%)	33 (2.5%)	94 (3.6%)	57 (2.9%)
Subcutaneous implant	93 (7.1%)	41 (6.3%)	0	0	93 (3.6%)	41 (2.1%)
Long-acting injectable progestins; oral contraceptive regimen	0	0	5 (0.4%)	2 (0.2%)	5 (0.2%)	2 (0.1%)
IUD; long-acting injectable progestins	0	0	3 (0.2%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Long-acting injectable progestins; transdermal contraceptive patch	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Oral contraceptive regimen; transdermal contraceptive patch	0	0	1 (0.1%)	1 (0.1%)	1 (< 0.1%)	1 (0.1%)
Other	0	1 (0.2%)	0	0	0	1 (0.1%)
<b>Baseline STIs</b>						
Any STI at baseline, N	1306	652	1313	1316	2619	1968
Positive test result	358 (27.4%)	178 (27.3%)	285 (21.7%)	264 (20.1%)	643 (24.6%)	442 (22.5%)
<i>Chlamydia trachomatis</i> , N	1306	652	1313	1316	2619	1968
Positive test result	219 (16.8%)	118 (18.1%)	175 (13.3%)	141 (10.7%)	394 (15.0%)	259 (13.2%)
<i>Trichomonas vaginalis</i> , N	1303	652	1312	1313	2615	1965
Positive test result	123 (9.4%)	60 (9.2%)	91 (6.9%)	91 (6.9%)	214 (8.2%)	151 (7.7%)
<i>Neisseria gonorrhoeae</i> , N	1306	652	1313	1316	2619	1968
Positive test result	64 (4.9%)	29 (4.4%)	58 (4.4%)	51 (3.9%)	122 (4.7%)	80 (4.1%)
Syphilis <sup>b, N</sup>	1306	652	1313	1316	2619	1968

	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Positive test result	17 (1.3%)	5 (0.8%)	16 (1.2%)	23 (1.7%)	33 (1.3%)	28 (1.4%)
<b>Baseline Nugent Score, N</b>	<b>1303</b>	<b>650</b>	<b>1024</b>	<b>1019</b>	<b>2327</b>	<b>1669</b>
Normal (< 4)	808 (62.0%)	412 (63.4%)	413 (40.3%)	428 (42.0%)	1221 (52.5%)	840 (50.3%)

n = number of participants with this observation, N = number of participants with data, SD = standard deviation, BMI = body mass index (weight in kg divided by the square of height in meters), IUD = intrauterine device, STI = sexually transmitted infection

<sup>a</sup> Participants could use more than one contraception method.

<sup>b</sup> The syphilis result was derived from the available syphilis test. A positive rapid plasma reagin screening test and/or titer test was only positive with a confirmatory test.

**Table 20 Sexually Transmitted Infections at Baseline by Age (Phase III Pooled Analysis)**

Positive Test Result	Dapivirine (28 Days)		Placebo (28 Days)	
	≤ 21 years	> 21 years	≤ 21 years	> 21 years
	n (%)	n (%)	n (%)	n (%)
Any STI at baseline, N	583	2036	405	1563
	193 (33.1%)	450 (22.1%)	119 (29.4%)	323 (20.7%)
<i>Chlamydia trachomatis</i> , N	583	2036	405	1563
	152 (26.1%)	242 (11.9%)	93 (23.0%)	166 (10.6%)
<i>Trichomonas vaginalis</i> , N	582	2033	405	1560
	40 (6.9%)	174 (8.6%)	22 (5.4%)	129 (8.3%)
<i>Neisseria gonorrhoeae</i> , N	583	2036	405	1563
	42 (7.2%)	80 (3.9%)	21 (5.2%)	59 (3.8%)
Syphilis <sup>a</sup> , N	583	2036	405	1563
	4 (0.7%)	29 (1.4%)	6 (1.5%)	22 (1.4%)

n = number of participants with this observation, N = number of participants with data, STI = sexually transmitted infection

<sup>a</sup> The syphilis result was derived from the available syphilis test. A positive rapid plasma reagin screening test and/or titer test was only positive with a confirmatory test.

#### Adverse events pattern

In the Phase III analysis, the incidence of at least one TEAE were comparable between the Dapivirine group (90.8% (2378/2619)) and the placebo group ( 90.6% (1783/1968)) (Table 21).

The most commonly reported TEAEs in the Phase III pooled analysis were metrorrhagia (39.9% and 45.8% for the Dapivirine and the placebo group, respectively), genitourinary chlamydia infection/gynaecological chlamydia infection (25.5% and 24.1%), urinary tract infection (15.2% and 16.6%), menorrhagia (14.6% and 15.3%), genitourinary tract gonococcal infection (14.3% and 13.2%), upper respiratory tract infection (13.9% and 12.5%), vulvovaginal candidiasis (11.9% and 10.2%), genital infection female (11.0% and 5.8%), and bacterial vaginosis (10.0% and 9.9%) (Table 22). The Applicant stated that the higher incidence in genital infection female in the Dapivirine group was considered not clinically relevant as there is no indication of an excess of pelvic infections or curable STIs

considered related to the Dapivirine ring. This is further supported by the fact that the incidence in genital infection female decreased within the first year and was constant afterwards.

The majority of TEAEs were mild or moderate in severity. Grade 3 (severe) or Grade 4 (potentially life-threatening) TEAEs were slightly lower in the Dapivirine group (8.4% (219/2619)) compared with the placebo group (9.3% (184/1968)). The incidence in different types of TEAEs Grade 3 and Grade 4 (preferred term) were low and approximately similar in both groups between both trials (Table 23).

IP-related TEAEs were slightly lower in the Dapivirine group (4.6% (121/2619)) compared with the placebo group (6.8% (133/1968)) (Table 24). The incidences in the different types IP-related TEAEs (preferred term) were low and approximately similar between both groups. The most commonly reported IP-related TEAEs (*i.e* in  $\geq 0.5\%$  of the subjects in the Dapivirine group) were metrorrhagia (0.7% and 0.5% for the Dapivirine and placebo group, respectively), vaginal discharge (0.6% and 1.0%), and pelvic pain (0.6% and 1.0%).

In general, TEAEs were reported less frequently in trial IPM 027 than in trial MTN-020. These between-trial differences are likely due to a difference in AE reporting, differences in frequency of testing or the result of the subjective assessment of causality and severity which may be influenced by Investigator experience with Dapivirine, with the exception of metrorrhagia and menorrhagia. The between-trial differences regarding metrorrhagia and menorrhagia is due to differences in inclusion criteria with respect to the use of contraception. IPM-027 subjects were required to be on stable contraception at enrollment, whereas MTN-020 subjects could have started contraceptive method just prior to enrollment or were allowed to switch contraception during the trial. The incidence over time of metrorrhagia in trial MTN-020 showed that most cases occurred in the first three months when breakthrough vaginal bleeding is expected due to recent initiation of contraception or a change in contraception at enrolment. Furthermore, in trial IPM-027, a new event was reported for every case of metrorrhagia, while in trial MTN-020 one event of metrorrhagia was reported starting on the date of the first episode and keeping the AE open until the last episode was reported.

With respect to vaginal discharge, in trial IPM 027, the majority of vaginal discharges were included in the term "*genital infection female*". However, in trial MTN-020, these were reported under the term that reflects the underlying etiology or, for asymptomatic abnormal vaginal discharge observed by a clinician which was found to be yeast or bacterial vaginosis and vaginal discharge reported by the participant that did not require treatment and did not yield a specific etiology, these were reported as "*vaginal discharge*".

**Table 21 Treatment-emergent Adverse Events Summary Table (Phase III Pooled Analysis)**

Total Number of Participants With:	IPM 027			MTN-020			Phase III		
	Dapivirine (28 Days)	Placebo (28 Days)	P-value <sup>a</sup>	Dapivirine (28 Days)	Placebo (28 Days)	P-value <sup>a</sup>	Dapivirine (28 Days)	Placebo (28 Days)	P-value <sup>a</sup>
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
<i>Safety Population</i>	1306	652		1313	1316		2619	1968	
At least one TEAE	1142 (87.4%)	559 (85.7%)	0.295	1236 (94.1%)	1224 (93.0%)	0.239	2378 (90.8%)	1783 (90.6%)	0.122
At least one DAIDS Grade 3 or 4 TEAE	64 (4.9%)	22 (3.4%)	0.112	155 (11.8%)	162 (12.3%)	0.691	219 (8.4%)	184 (9.3%)	0.311
At least one IP-related <sup>b</sup> TEAE	5 (0.4%)	3 (0.5%)	0.802	116 (8.8%)	130 (9.9%)	0.358	121 (4.6%)	133 (6.8%)	0.626
At least one serious IP-related TEAE	0	0	-	0	0	-	0	0	-
At least one non-serious IP-related TEAE	5 (0.4%)	3 (0.5%)	0.802	116 (8.8%)	130 (9.9%)	0.358	121 (4.6%)	133 (6.8%)	0.626
TEAEs leading to death	2 (0.2%)	1 (0.2%)	0.999	4 (0.3%)	3 (0.2%)	0.702	6 (0.2%)	4 (0.2%)	0.797
At least one serious TEAE	38 (2.9%)	6 (0.9%)	0.003	41 (3.1%)	42 (3.2%)	0.920	79 (3.0%)	48 (2.4%)	0.042
TEAEs leading to permanent IP discontinuation	0	1 (0.2%)	-	1 (0.1%)	0	0.239	1 (< 0.1%)	1 (0.1%)	0.941
TEAEs leading to temporary IP discontinuation	11 (0.8%)	3 (0.5%)	0.326	65 (5.0%)	62 (4.7%)	0.775	76 (2.9%)	65 (3.3%)	0.312
At least one specific TEAE <sup>c</sup>	86 (6.6%)	28 (4.3%)	0.037	199 (15.2%)	200 (15.2%)	0.976	285 (10.9%)	228 (11.6%)	0.106
n = number of participants with this observation, TEAE = treatment-emergent adverse event, DAIDS = Division of Acquired Immunodeficiency Syndrome, IP = investigational product									
<sup>a</sup> P-value of the likelihood-ratio chi-square test (stratified by trial) comparing the two groups is presented.									
<sup>b</sup> A TEAE was considered as IP-related if the relationship was classified as "related" by the Investigator. If the assessment of the causal relationship was missing, the TEAE was also considered related to the IP.									
<sup>c</sup> This refers to Grade 2 IP-related TEAEs, Grade 3 or 4 TEAEs, serious TEAEs, and TEAEs leading to IP discontinuation.									

**Table 22 Treatment-emergent Adverse Events in  $\geq 5.0\%$  of Participants in the Pooled Phase III Dapivirine Vaginal Ring 004 Group, Regardless of Severity or Causality (Phase III Pooled Analysis)**

System Organ Class, Preferred term	IPM 027				MTN-020				Phase III			
	Dapivirine (28 Days)		Placebo (28 Days)		Dapivirine (28 Days)		Placebo (28 Days)		Dapivirine (28 Days)		Placebo (28 Days)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
<i>Safety Population</i>	1306		652		1313		1316		2619		1968	
<i>Any TEAE</i>	1142 (87.4%)		559 (85.7%)		1236 (94.1%)		1224 (93.0%)		2378 (90.8%)		1783 (90.6%)	
<i>Mean (SD) IP Use Duration (Weeks)</i>	83.70 (33.649)		80.58 (34.415)		85.64 (33.595)		86.09 (33.315)		84.64 (33.630)		84.18 (33.794)	
<b>Infections and Infestations</b>	<b>987 (75.6%)</b>	<b>3916</b>	<b>487 (74.7%)</b>	<b>1850</b>	<b>905 (68.9%)</b>	<b>2522</b>	<b>890 (67.6%)</b>	<b>2519</b>	<b>1892 (72.2%)</b>	<b>6438</b>	<b>1377 (70.0%)</b>	<b>4369</b>
<i>Gynaecological chlamydia infection/ Genitourinary chlamydia infection<sup>a</sup></i>	400 (30.6%)	617	205 (31.4%)	309	267 (20.3%)	353	269 (20.4%)	373	667 (25.5%)	970	474 (24.1%)	682
Urinary tract infection	180 (13.8%)	250	97 (14.9%)	145	217 (16.5%)	274	230 (17.5%)	298	397 (15.2%)	524	327 (16.6%)	443
Genitourinary tract gonococcal infection	234 (17.9%)	302	106 (16.3%)	140	141 (10.7%)	180	154 (11.7%)	191	375 (14.3%)	482	260 (13.2%)	331
Upper respiratory tract infection	225 (17.2%)	493	109 (16.7%)	219	138 (10.5%)	173	137 (10.4%)	182	363 (13.9%)	666	246 (12.5%)	401
Vulvovaginal candidiasis	165 (12.6%)	241	76 (11.7%)	99	147 (11.2%)	183	124 (9.4%)	158	312 (11.9%)	424	200 (10.2%)	257
Genital infection female <sup>b</sup>	287 (22.0%)	371	115 (17.6%)	150	NA	NA	NA	NA	287 (11.0%)	371	115 (5.8%)	150
Bacterial vaginosis	96 (7.4%)	124	39 (6.0%)	49	165 (12.6%)	208	155 (11.8%)	200	261 (10.0%)	332	194 (9.9%)	249
<i>Trichomoniasis<sup>a</sup></i>	217 (16.6%)	322	95 (14.6%)	137	2 (0.2%)	2	0	0	219 (8.4%)	324	95 (4.8%)	137
<i>Vulvovaginitis trichomonal<sup>a</sup></i>	32 (2.5%)	41	16 (2.5%)	22	143 (10.9%)	188	153 (11.6%)	194	175 (6.7%)	229	169 (8.6%)	216
Vulvovaginitis	114 (8.7%)	233	68 (10.4%)	122	53 (4.0%)	56	49 (3.7%)	59	167 (6.4%)	289	117 (5.9%)	181
Malaria	60 (4.6%)	89	30 (4.6%)	41	72 (5.5%)	106	74 (5.6%)	119	132 (5.0%)	195	104 (5.3%)	160
<b>Reproductive System and Breast Disorders</b>	<b>606 (46.4%)</b>	<b>1432</b>	<b>304 (46.6%)</b>	<b>796</b>	<b>1027 (78.2%)</b>	<b>2418</b>	<b>1032 (78.4%)</b>	<b>2458</b>	<b>1633 (62.4%)</b>	<b>3850</b>	<b>1336 (67.9%)</b>	<b>3254</b>
Metrorrhagia	335 (25.7%)	585	182 (27.9%)	316	710 (54.1%)	959	719 (54.6%)	1006	1045 (39.9%)	1544	901 (45.8%)	1322
Menorrhagia	124 (9.5%)	201	64 (9.8%)	95	259 (19.7%)	307	237 (18.0%)	276	383 (14.6%)	508	301 (15.3%)	371
Menometrorrhagia	82 (6.3%)	116	40 (6.1%)	54	159 (12.1%)	170	145 (11.0%)	160	241 (9.2%)	286	185 (9.4%)	214
Cervical dysplasia	73 (5.6%)	81	44 (6.7%)	49	122 (9.3%)	125	114 (8.7%)	117	195 (7.4%)	206	158 (8.0%)	166

System Organ Class, Preferred term	IPM 027				MTN-020				Phase III			
	Dapivirine (28 Days)		Placebo (28 Days)		Dapivirine (28 Days)		Placebo (28 Days)		Dapivirine (28 Days)		Placebo (28 Days)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Vaginal discharge	15 (1.1%)	15	10 (1.5%)	10	171 (13.0%)	205	171 (13.0%)	214	186 (7.1%)	220	181 (9.2%)	224
Vulvovaginal pruritus	41 (3.1%)	45	19 (2.9%)	20	128 (9.7%)	148	134 (10.2%)	155	169 (6.5%)	193	153 (7.8%)	175
Pelvic pain	55 (4.2%)	62	24 (3.7%)	25	108 (8.2%)	128	122 (9.3%)	139	163 (6.2%)	190	146 (7.4%)	164
<b>Investigations</b>	<b>72 (5.5%)</b>	<b>91</b>	<b>46 (7.1%)</b>	<b>66</b>	<b>419 (31.9%)</b>	<b>870</b>	<b>459 (34.9%)</b>	<b>985</b>	<b>491 (18.7%)</b>	<b>961</b>	<b>505 (25.7%)</b>	<b>1051</b>
Alanine aminotransferase increased	6 (0.5%)	6	9 (1.4%)	9	142 (10.8%)	204	160 (12.2%)	244	148 (5.7%)	210	169 (8.6%)	253
Aspartate aminotransferase increased	4 (0.3%)	5	6 (0.9%)	6	140 (10.7%)	195	144 (10.9%)	203	144 (5.5%)	200	150 (8.6%)	209
Haemoglobin decreased	17 (1.3%)	18	8 (1.2%)	14	115 (8.8%)	167	125 (9.5%)	199	132 (5.0%)	185	133 (6.8%)	213
<b>Gastrointestinal Disorders</b>	<b>255 (19.5%)</b>	<b>402</b>	<b>148 (22.7%)</b>	<b>239</b>	<b>113 (8.6%)</b>	<b>143</b>	<b>115 (8.7%)</b>	<b>154</b>	<b>368 (14.1%)</b>	<b>545</b>	<b>263 (13.4%)</b>	<b>393</b>
<b>Injury, Poisoning and Procedural Complications</b>	<b>100 (7.7%)</b>	<b>128</b>	<b>62 (9.5%)</b>	<b>72</b>	<b>148 (11.3%)</b>	<b>180</b>	<b>164 (12.5%)</b>	<b>194</b>	<b>248 (9.5%)</b>	<b>308</b>	<b>226 (11.5%)</b>	<b>266</b>
<b>Metabolism and Nutrition Disorders</b>	<b>6 (0.5%)</b>	<b>6</b>	<b>3 (0.5%)</b>	<b>3</b>	<b>186 (14.2%)</b>	<b>273</b>	<b>201 (15.3%)</b>	<b>295</b>	<b>192 (7.3%)</b>	<b>279</b>	<b>204 (10.4%)</b>	<b>298</b>
Abnormal loss of weight	0	0	0	0	169 (12.9%)	242	170 (12.9%)	250	169 (6.5%)	242	170 (8.6%)	250
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>192 (14.7%)</b>	<b>297</b>	<b>82 (12.6%)</b>	<b>164</b>	<b>41 (3.1%)</b>	<b>43</b>	<b>43 (3.3%)</b>	<b>46</b>	<b>233 (8.9%)</b>	<b>340</b>	<b>125 (6.4%)</b>	<b>210</b>
<b>Nervous System Disorders</b>	<b>135 (10.3%)</b>	<b>175</b>	<b>88 (13.5%)</b>	<b>114</b>	<b>62 (4.7%)</b>	<b>69</b>	<b>67 (5.1%)</b>	<b>83</b>	<b>197 (7.5%)</b>	<b>244</b>	<b>155 (7.9%)</b>	<b>197</b>
Headache	100 (7.7%)	127	70 (10.7%)	86	40 (3.0%)	42	45 (3.4%)	50	140 (5.3%)	169	115 (5.8%)	136
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>103 (7.9%)</b>	<b>119</b>	<b>59 (9.0%)</b>	<b>76</b>	<b>54 (4.1%)</b>	<b>66</b>	<b>72 (5.5%)</b>	<b>79</b>	<b>157 (6.0%)</b>	<b>185</b>	<b>131 (6.7%)</b>	<b>155</b>



System Organ Class, Preferred term	IPM 027				MTN-020				Phase III			
	Dapivirine (28 Days)		Placebo (28 Days)		Dapivirine (28 Days)		Placebo (28 Days)		Dapivirine (28 Days)		Placebo (28 Days)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
<p>n = number of participants with this observation, m = number of events, TEAE = treatment-emergent adverse event, SD = standard deviation, IP = investigational product, NA = not applicable (see footnote b)</p> <p><sup>a</sup> The following pairs of preferred terms present the same medical concept. "Genitourinary chlamydia infection" was reported only in trial IPM 027; "gynecological chlamydia infection" was reported only in trial MTN-020. The pooled incidence was manually calculated by adding together the respective individual trial incidences for the two event terms. "Trichomoniasis" was mostly reported in trial IPM 027; "vulvovaginitis trichomonal" was mostly reported in trial MTN-020.</p> <p><sup>b</sup> The verbatim for the preferred term "genital infection female" are chronic gynaecological infection, gynaecologic infection, and gynaecological infection confirmed. The term "gynecological infection" (preferred term: genital infection female) is a term that was used to report an adverse event for participants who presented with a vaginal discharge mainly and for whom syndromic antibiotic treatment was given. This term was used when a vaginal discharge did not meet the criteria for more specific DAIDS conditions such as vulvovaginitis. This term enabled coding to the Infections and Infestations system organ class which was deemed necessary due to the antimicrobial treatment given even though there was no proven organism (either because testing was not done or the tests results were negative). This term was only used for trial IPM 027.</p>												

**Table 23 Grade 3 or 4 Treatment-emergent Adverse Events in > 2 (0.1%) Participants in the Pooled Phase III Dapivirine Vaginal Ring 004 Group, Regardless of Causality (Phase III Pooled Analysis)**

System Organ Class, Preferred term	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<i>Safety Population</i>	1306	652	1313	1316	2619	1968
<i>Any Grade 3 (Severe) or Grade 4 (Potentially Life-threatening) TEAE</i>	64 (4.9%)	22 (3.4%)	155 (11.8%)	162 (12.3%)	219 (8.4%)	184 (9.3%)
<b>Infections and Infestations</b>	<b>11 (0.8%)</b>	<b>5 (0.8%)</b>	<b>44 (3.4%)</b>	<b>29 (2.2%)</b>	<b>55 (2.1%)</b>	<b>34 (1.7%)</b>
Gastroenteritis	2 (0.2%)	0	7 (0.5%)	5 (0.4%)	9 (0.3%)	5 (0.3%)
Malaria	2 (0.2%)	0	5 (0.4%)	5 (0.4%)	7 (0.3%)	5 (0.3%)
Genitourinary tract gonococcal infection	0	0	4 (0.3%)	6 (0.5%)	4 (0.2%)	6 (0.3%)
Pulmonary tuberculosis	1 (0.1%)	0	2 (0.2%)	2 (0.2%)	3 (0.1%)	2 (0.1%)
Cellulitis	1 (0.1%)	0	2 (0.2%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Urinary tract infection	0	0	3 (0.2%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Acute hepatitis B	0	0	3 (0.2%)	0	3 (0.1%)	0
<b>Investigations</b>	<b>16 (1.2%)</b>	<b>8 (1.2%)</b>	<b>32 (2.4%)</b>	<b>20 (1.5%)</b>	<b>48 (1.8%)</b>	<b>28 (1.4%)</b>
Alanine aminotransferase increased	2 (0.2%)	2 (0.3%)	7 (0.5%)	8 (0.6%)	9 (0.3%)	10 (0.5%)
Aspartate aminotransferase increased	1 (0.1%)	1 (0.2%)	8 (0.6%)	4 (0.3%)	9 (0.3%)	5 (0.3%)
Blood phosphorus decreased	8 (0.6%)	3 (0.5%)	0	0	8 (0.3%)	3 (0.2%)
Haemoglobin decreased	2 (0.2%)	2 (0.3%)	5 (0.4%)	4 (0.3%)	7 (0.3%)	6 (0.3%)
Neutrophil count decreased	0	0	7 (0.5%)	5 (0.4%)	7 (0.3%)	5 (0.3%)
Blood pressure increased	1 (0.1%)	0	4 (0.3%)	3 (0.2%)	5 (0.2%)	3 (0.2%)

System Organ Class, Preferred term	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Platelet count decreased	0	0	3 (0.2%)	0	3 (0.1%)	0
<b>Metabolism and Nutrition Disorders</b>	<b>3 (0.2%)</b>	<b>0</b>	<b>44 (3.4%)</b>	<b>62 (4.7%)</b>	<b>47 (1.8%)</b>	<b>62 (3.2%)</b>
Abnormal loss of weight	0	0	36 (2.7%)	47 (3.6%)	36 (1.4%)	47 (2.4%)
Decreased appetite	0	0	8 (0.6%)	9 (0.7%)	8 (0.3%)	9 (0.5%)
Diabetes mellitus	3 (0.2%)	0	1 (0.1%)	5 (0.4%)	4 (0.2%)	5 (0.3%)
<b>Reproductive System and Breast Disorders</b>	<b>9 (0.7%)</b>	<b>5 (0.8%)</b>	<b>10 (0.8%)</b>	<b>7 (0.5%)</b>	<b>19 (0.7%)</b>	<b>12 (0.6%)</b>
Cervical dysplasia	4 (0.3%)	1 (0.2%)	3 (0.2%)	1 (0.1%)	7 (0.3%)	2 (0.1%)
Coital bleeding	4 (0.3%)	2 (0.3%)	2 (0.2%)	0	6 (0.2%)	2 (0.1%)
<b>Injury, Poisoning and Procedural Complications</b>	<b>7 (0.5%)</b>	<b>0</b>	<b>10 (0.8%)</b>	<b>16 (1.2%)</b>	<b>17 (0.6%)</b>	<b>16 (0.8%)</b>
Head injury	1 (0.1%)	0	2 (0.2%)	3 (0.2%)	3 (0.1%)	3 (0.2%)
<b>Blood and Lymphatic System Disorders</b>	<b>2 (0.2%)</b>	<b>1 (0.2%)</b>	<b>9 (0.7%)</b>	<b>7 (0.5%)</b>	<b>11 (0.4%)</b>	<b>8 (0.4%)</b>
Anaemia	2 (0.2%)	0	6 (0.5%)	1 (0.1%)	8 (0.3%)	1 (0.1%)
<b>Gastrointestinal Disorders</b>	<b>2 (0.2%)</b>	<b>1 (0.2%)</b>	<b>6 (0.5%)</b>	<b>8 (0.6%)</b>	<b>8 (0.3%)</b>	<b>9 (0.5%)</b>
<b>Psychiatric Disorders</b>	<b>1 (0.1%)</b>	<b>1 (0.2%)</b>	<b>6 (0.5%)</b>	<b>7 (0.5%)</b>	<b>7 (0.3%)</b>	<b>8 (0.4%)</b>
<b>Nervous System Disorders</b>	<b>4 (0.3%)</b>	<b>0</b>	<b>4 (0.3%)</b>	<b>8 (0.6%)</b>	<b>8 (0.3%)</b>	<b>8 (0.4%)</b>
Headache	3 (0.2%)	0	2 (0.2%)	3 (0.2%)	5 (0.2%)	3 (0.2%)
<b>Pregnancy, Puerperium and Perinatal Conditions</b>	<b>5 (0.4%)</b>	<b>1 (0.2%)</b>	<b>2 (0.2%)</b>	<b>2 (0.2%)</b>	<b>7 (0.3%)</b>	<b>3 (0.2%)</b>
Abortion spontaneous	5 (0.4%)	1 (0.2%)	0	0	5 (0.2%)	1 (0.1%)
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>4 (0.2%)</b>	<b>0</b>
<b>Vascular Disorders</b>	<b>3 (0.2%)</b>	<b>0</b>	<b>0</b>	<b>6 (0.5%)</b>	<b>3 (0.1%)</b>	<b>6 (0.3%)</b>
<b>Hepatobiliary Disorders</b>	<b>1 (0.1%)</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>3 (0.2%)</b>	<b>3 (0.1%)</b>	<b>3 (0.2%)</b>
<b>General Disorders and Administration Site Conditions</b>	<b>0</b>	<b>0</b>	<b>3 (0.2%)</b>	<b>2 (0.2%)</b>	<b>3 (0.1%)</b>	<b>2 (0.1%)</b>
n = number of participants with this observation, TEAE = treatment-emergent adverse event						

**Table 24 Treatment-emergent Adverse Events Assessed as Related to the Investigational Product by the Investigator in > 2 (0.1%) Participants in the Pooled Phase III Dapivirine Vaginal Ring 004 Group, Regardless of Severity (Phase III Pooled Analysis)**

System Organ Class, Preferred term	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<i>Safety Population</i>	1306	652	1313	1316	2619	1968
<i>Any Investigational Product-related<sup>a</sup> TEAE</i>	5 (0.4%)	3 (0.5%)	116 (8.8%)	130 (9.9%)	121 (4.6%)	133 (6.8%)
<b>Reproductive System and Breast Disorders</b>	<b>4 (0.3%)</b>	<b>2 (0.3%)</b>	<b>85 (6.5%)</b>	<b>96 (7.3%)</b>	<b>89 (3.4%)</b>	<b>98 (5.0%)</b>
Metrorrhagia	2 (0.2%)	0	16 (1.2%)	9 (0.7%)	18 (0.7%)	9 (0.5%)
Vaginal discharge	0	0	17 (1.3%)	20 (1.5%)	17 (0.6%)	20 (1.0%)
Pelvic pain	1 (0.1%)	0	15 (1.1%)	20 (1.5%)	16 (0.6%)	20 (1.0%)
Vulvovaginal pruritus	0	0	10 (0.8%)	12 (0.9%)	10 (0.4%)	12 (0.6%)
Vulvovaginal discomfort	0	0	9 (0.7%)	5 (0.4%)	9 (0.3%)	5 (0.3%)
Cervix erythema	0	0	6 (0.5%)	5 (0.4%)	6 (0.2%)	5 (0.3%)
Dyspareunia	0	0	4 (0.3%)	2 (0.2%)	4 (0.2%)	2 (0.1%)
Menorrhagia	0	0	3 (0.2%)	3 (0.2%)	3 (0.1%)	3 (0.2%)
Pelvic discomfort	1 (0.1%)	1 (0.2%)	2 (0.2%)	3 (0.2%)	3 (0.1%)	4 (0.2%)
Vaginal odour	0	0	3 (0.2%)	8 (0.6%)	3 (0.1%)	8 (0.4%)
<b>Investigations</b>	<b>0</b>	<b>0</b>	<b>15 (1.1%)</b>	<b>18 (1.4%)</b>	<b>15 (0.6%)</b>	<b>18 (0.9%)</b>
Aspartate aminotransferase increased	0	0	4 (0.3%)	9 (0.7%)	4 (0.2%)	9 (0.5%)
Neutrophil count decreased	0	0	4 (0.3%)	6 (0.5%)	4 (0.2%)	6 (0.3%)
Alanine aminotransferase increased	0	0	3 (0.2%)	7 (0.5%)	3 (0.1%)	7 (0.4%)
Haemoglobin decreased	0	0	3 (0.2%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
<b>Renal and Urinary Disorders</b>	<b>0</b>	<b>0</b>	<b>7 (0.5%)</b>	<b>5 (0.4%)</b>	<b>7 (0.3%)</b>	<b>5 (0.3%)</b>
Pollakiuria	0	0	4 (0.3%)	2 (0.2%)	4 (0.2%)	2 (0.1%)
<b>General Disorders and Administration Site Conditions</b>	<b>1 (0.1%)</b>	<b>1 (0.2%)</b>	<b>5 (0.4%)</b>	<b>7 (0.5%)</b>	<b>6 (0.2%)</b>	<b>8 (0.4%)</b>
Application site discomfort	0	0	4 (0.3%)	2 (0.2%)	4 (0.2%)	2 (0.1%)
<b>Infections and Infestations</b>	<b>0</b>	<b>0</b>	<b>6 (0.5%)</b>	<b>12 (0.9%)</b>	<b>6 (0.2%)</b>	<b>12 (0.6%)</b>

n = number of participants with this observation, TEAE = treatment-emergent adverse event

<sup>a</sup> A TEAE was considered as investigational product-related if the relationship was classified as "related" by the Investigator. If the assessment of the causal relationship was missing, the TEAE was also considered related to the investigational product.

### **Adverse events of special interest**

In all the three safety analyses sets, the incidences of TEAEs of interest were approximately similar between the Dapivirine and placebo group.

In the Phase I analysis, the most commonly reported TEAEs of interest (*i.e.*, in  $\geq 10.0\%$  of the subjects in the Dapivirine [28 days] group) were metrorrhagia (25.0% and 28.6%), vaginal hemorrhage (12.0% and 28.6%), and menometrorrhagia (10.2% and 0%) for the Dapivirine (28 days) and placebo group, respectively (Table 25). The relatively large difference in TEAE menometrorrhagia (10.2% versus 0% for Dapivirine and placebo, respectively) has not been observed in the Phase II and Phase III pooled analysis sets and is probably due to the very limited amount of subjects ( $n=14$ ) included in the placebo group, compared to 108 subjects in the Dapivirine (28 days) group. Overall, bleeding disorders were reported very commonly for both, the dapivirine as well as the placebo ring group, and further clarification is sought, particularly as study participants were on stable contraception, mostly combination oral contraceptives.

**Table 25 Treatment-emergent Adverse Events of Interest in  $\geq 2.0\%$  of Participants in the Dapivirine Vaginal Ring-004 (28 Days) Group, Regardless of Severity or Causality (Phase I Pooled Analysis)**

System Organ Class, Grouped/Preferred term	Dapivirine (28 Days)	Dapivirine (Any Duration)	Placebo (28 Days)
	n (%)	n (%)	n (%)
<i>Safety Population</i>	108	158	14
<i>Any TEAE of Interest</i>	62 (57.4%)	88 (55.7%)	10 (71.4%)
<b>Reproductive System and Breast Disorders</b>	<b>61 (56.5%)</b>	<b>84 (53.2%)</b>	<b>9 (64.3%)</b>
Metrorrhagia	27 (25.0%)	40 (25.3%)	4 (28.6%)
Vaginal haemorrhage	13 (12.0%)	21 (13.3%)	4 (28.6%)
Menometrorrhagia	11 (10.2%)	11 (7.0%)	0
Vulvovaginal discomfort	5 (4.6%)	7 (4.4%)	0
Vulvovaginal pruritus	5 (4.6%)	6 (3.8%)	1 (7.1%)
Vaginal discharge	4 (3.7%)	9 (5.7%)	2 (14.3%)
Vulvovaginal burning sensation	3 (2.8%)	3 (1.9%)	0
<b>Renal and Urinary Disorders</b>	<b>6 (5.6%)</b>	<b>6 (3.8%)</b>	<b>1 (7.1%)</b>
Dysuria	5 (4.6%)	5 (3.2%)	1 (7.1%)
<b>Infections and Infestations</b>	<b>5 (4.6%)</b>	<b>6 (3.8%)</b>	<b>1 (7.1%)</b>
Vulvovaginal candidiasis	3 (2.8%)	3 (1.9%)	0
<b>Injury, Poisoning and Procedural Complications</b>	<b>3 (2.8%)</b>	<b>3 (1.9%)</b>	<b>0</b>

n = number of participants with this observation, TEAE = treatment-emergent adverse event

In the Phase II IPM 015 trial, at least one TEAE of interest was less frequently reported in the Dapivirine group 65.0% (91/140) compared with the placebo group (71.2% (99/139)). The most commonly reported TEAEs were metrorrhagia (18.6% and 19.3% for the Dapivirine and the placebo groups, respectively), genital tract candidiasis (14.3% and 8.6%), chlamydia urogenital events (15.7% and 15.7%), and renal infections (mostly urinary tract infections) (10.7% and 11.4%).

In the Phase III pooled analysis, TEAEs of interest were reported in a lower proportion of subjects in trial IPM 027 than in trial MTN-020 (Table 26). Within trial IPM 027 and MTN-020, no differences were observed between the Dapivirine and placebo ring group.

The most commonly reported TEAEs of interest were metrorrhagia (39.7% and 45.7% for the Dapivirine and the placebo group, respectively), menorrhagia (14.5% and 15.3%), Chlamydia urogenital events (26.0% and 24.0%), renal infections (15.2% and 16.8%), gonococcal urogenital events (14.9% and 13.4%), trichomonal urogenital events (14.3% and 13.2%), genital tract candidiasis (12.0% and 10.4%), gynaecological infection (11.0% and 5.8%), and bacterial vaginosis (10.0% and 9.8%).

In all three safety analyses sets, the most of the common TEAEs of interest were related to vaginal bleeding of which metrorrhagia (irregular bleeding between menses) showed the highest incidence (25.0% and 25.3% for the Phase I pooled analysis set, 18.6% and 19.3% in the Phase II IPM 015 trial, and 39.7% and 45.7% in the Phase III pooled analysis for the Dapivirine and the placebo group respectively).

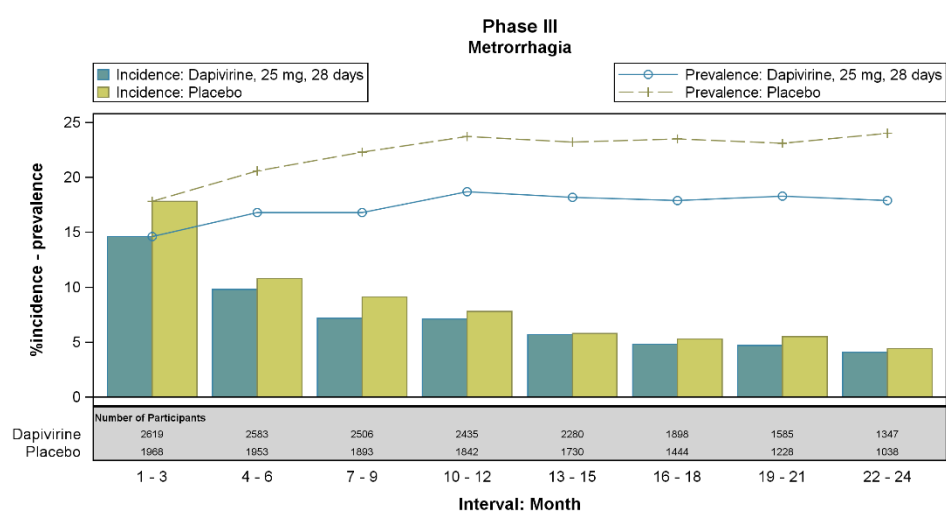
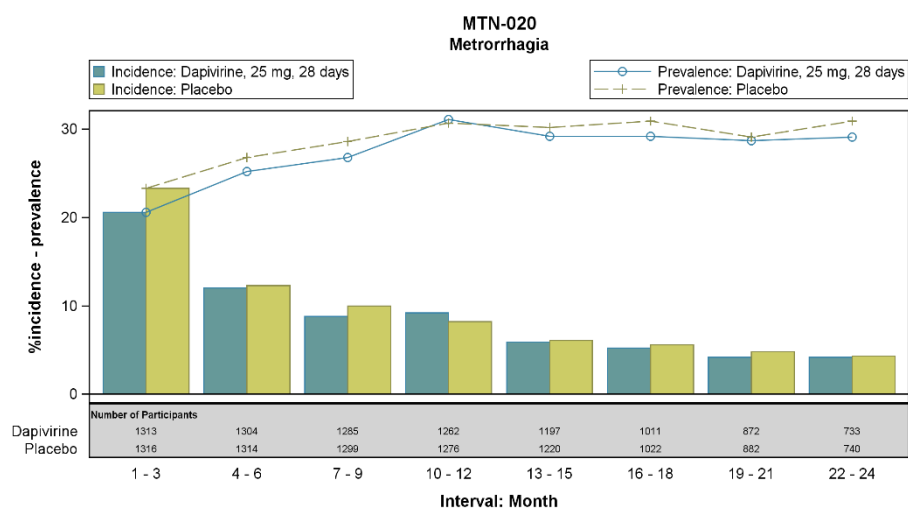
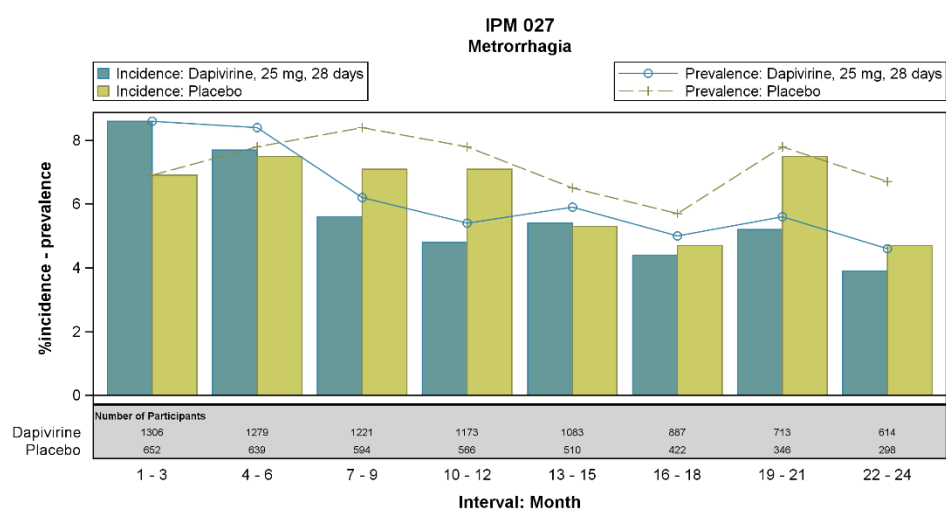
The incidence over time of the adverse of interest metrorrhagia (Figure 8) showed that most cases occurred in the first three months in trial MTN-020 when vaginal bleeding is expected due recent initiation of contraception or a change in contraception at enrolment.

With respect to IP-related metrorrhagia, in the Phase II safety set, the percentage was slightly higher in the Dapivirine group compared with the placebo group (6.4% and 2.9%, respectively). Approximately similar incidences in IP-related metrorrhagia were found in the Phase III pooled analysis set (0.7% and 0.5% for Dapivirine and placebo, respectively) and in the individual trials IPM 027 trial (0.2% and 0%) and the MTN-020 trial (1.2% and 0.7%).

**Table 26 Treatment-emergent Adverse Events of Interest in  $\geq 2.0\%$  of Participants in the Pooled Phase III Dapivirine Vaginal Ring 004 Group, Regardless of Severity or Causality (Phase III Pooled Analysis)**

System Organ Class, Grouped/Preferred term <sup>a</sup>	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<i>Safety Population</i>	1306	652	1313	1316	2619	1968
<i>Any TEAE of Interest</i>	1029 (78.8%)	508 (77.9%)	1174 (89.4%)	1158 (88.0%)	2203 (84.1%)	1666 (84.7%)
<b>Reproductive System and Breast Disorders of Interest</b>	<b>579 (44.3%)</b>	<b>293 (44.9%)</b>	<b>1020 (77.7%)</b>	<b>1024 (77.8%)</b>	<b>1599 (61.1%)</b>	<b>1317 (66.9%)</b>
Metrorrhagia <sup>b</sup>	335 (25.7%)	182 (27.9%)	706 (53.8%)	717 (54.5%)	1041 (39.7%)	899 (45.7%)
Menorrhagia <sup>b</sup>	124 (9.5%)	64 (9.8%)	257 (19.6%)	237 (18.0%)	381 (14.5%)	301 (15.3%)
Menometrorrhagia <sup>b</sup>	82 (6.3%)	40 (6.1%)	159 (12.1%)	145 (11.0%)	241 (9.2%)	185 (9.4%)
Vaginal discharge <sup>b</sup>	15 (1.1%)	10 (1.5%)	171 (13.0%)	171 (13.0%)	186 (7.1%)	181 (9.2%)
Cervical dysplasia <sup>b</sup>	73 (5.6%)	44 (6.7%)	122 (9.3%)	114 (8.7%)	195 (7.4%)	158 (8.0%)
Vulvovaginal pruritus <sup>b</sup>	41 (3.1%)	19 (2.9%)	128 (9.7%)	134 (10.2%)	169 (6.5%)	153 (7.8%)
Pelvic pain <sup>b</sup>	55 (4.2%)	24 (3.7%)	108 (8.2%)	122 (9.3%)	163 (6.2%)	146 (7.4%)

System Organ Class, Grouped/Preferred term <sup>a</sup>	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Vulval ulceration <sup>b</sup>	30 (2.3%)	20 (3.1%)	28 (2.1%)	34 (2.6%)	58 (2.2%)	54 (2.7%)
<b>Infections and Infestations of Interest</b>	<b>883 (67.6%)</b>	<b>440 (67.5%)</b>	<b>710 (54.1%)</b>	<b>697 (53.0%)</b>	<b>1593 (60.8%)</b>	<b>1137 (57.8%)</b>
Chlamydia urogenital events <sup>b</sup>	413 (31.6%)	210 (32.2%)	267 (20.3%)	268 (20.4%)	680 (26.0%)	478 (24.3%)
Renal infections	180 (13.8%)	97 (14.9%)	218 (16.6%)	233 (17.7%)	398 (15.2%)	330 (16.8%)
Gonococcal urogenital events <sup>b</sup>	250 (19.1%)	110 (16.9%)	141 (10.7%)	153 (11.6%)	391 (14.9%)	263 (13.4%)
Trichomonal urogenital events <sup>b</sup>	227 (17.4%)	103 (15.8%)	147 (11.2%)	157 (11.9%)	374 (14.3%)	260 (13.2%)
Genital tract candidiasis <sup>b</sup>	167 (12.8%)	78 (12.0%)	147 (11.2%)	126 (9.6%)	314 (12.0%)	204 (10.4%)
Gynaecological infection <sup>b, c</sup>	287 (22.0%)	115 (17.6%)	NA	NA	287 (11.0%)	115 (5.8%)
Bacterial vaginosis <sup>b</sup>	96 (7.4%)	39 (6.0%)	165 (12.6%)	154 (11.7%)	261 (10.0%)	193 (9.8%)
Vulvovaginitis <sup>b</sup>	128 (9.8%)	74 (11.3%)	96 (7.3%)	98 (7.4%)	224 (8.6%)	172 (8.7%)
<b>Investigations of Interest</b>	<b>8 (0.6%)</b>	<b>10 (1.5%)</b>	<b>294 (22.4%)</b>	<b>329 (25.0%)</b>	<b>302 (11.5%)</b>	<b>339 (17.2%)</b>
Alanine aminotransferase increased	6 (0.5%)	9 (1.4%)	142 (10.8%)	160 (12.2%)	148 (5.7%)	169 (8.6%)
Aspartate aminotransferase increased	4 (0.3%)	6 (0.9%)	139 (10.6%)	141 (10.7%)	143 (5.5%)	147 (7.5%)
Neutrophil count decreased	1 (0.1%)	1 (0.2%)	117 (8.9%)	144 (10.9%)	118 (4.5%)	145 (7.4%)
<b>Skin and Subcutaneous Tissue Disorders of Interest</b>	<b>67 (5.1%)</b>	<b>33 (5.1%)</b>	<b>38 (2.9%)</b>	<b>45 (3.4%)</b>	<b>105 (4.0%)</b>	<b>78 (4.0%)</b>
n = number of participants with this observation, TEAE = treatment-emergent adverse event, NA = not applicable (see footnote c)						
<sup>a</sup> The list of verbatim terms coded to preferred terms and preferred terms grouped to a grouped term considered adverse events of interest, can be found in <a href="#">SAP ISS</a> .						
<sup>b</sup> This preferred term is also a gynecological event of interest. See SAP ISS, Appendix 2 for details.						
<sup>c</sup> The grouped term "gynecological infection" only included the PT "genital infection female", which was only reported in IPM 027						



**Figure 8 Incidence and prevalence of Metrorrhagia over time (Phase III pooled analysis)**

## **Pregnancies**

In the Phase III analysis, the proportion of subjects with confirmed pregnancies was similar between the Dapivirine group (4.4% [114/2619]) and placebo ring group (5.3% [105/1968]). A subject who became pregnant at any time during the clinical trial had the IP temporarily or permanently held. After giving birth or after termination of the pregnancy, a urine pregnancy test was performed. If it was negative, the Investigator could have considered recommencing the IP.

Pregnancy outcomes were available for 120 subjects in the Dapivirine group and 113 in the placebo ring group (Table 27). Live births were slightly lower in the Dapivirine group (51.7% (62/120)) in the Dapivirine compared with the placebo group 57.5% (65/113). The proportion of subjects with adverse pregnancy outcomes was similar between the Dapivirine and placebo ring groups. No major congenital abnormalities were reported.

**Table 27 Pregnancy Outcome (Phase III Pooled Analysis)**

Pregnancy Outcome	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of pregnancies	33	20	87	93	120	113
Live birth	11 (33.3%)	6 (30.0%)	51 (58.6%)	59 (63.4%)	62 (51.7%)	65 (57.5%)
Spontaneous abortion	7 (21.2%)	2 (10.0%)	17 (19.5%)	22 (23.7%)	24 (20.0%)	24 (21.2%)
Therapeutic/Elective abortion	0	0	14 (16.1%)	8 (8.6%)	14 (11.7%)	8 (7.1%)
Non-therapeutic abortion	5 (15.2%)	6 (30.0%)	NA	NA	5 (4.2%)	6 (5.3%)
Stillbirth/Intrauterine fetal demise	0	1 (5.0%)	3 (3.4%)	2 (2.2%)	3 (2.5%)	3 (2.7%)
Ectopic pregnancy	0	0	1 (1.1%)	1 (1.1%)	1 (0.8%)	1 (0.9%)
Outcome unavailable	0	0	0	1 (1.1%)	0	1 (0.9%)
Missing	10 (30.3%)	5 (25.0%)	1 (1.1%)	0	11 (9.2%)	5 (4.4%)
n = number of participants with this observation, NA = not applicable (category not present on Case Report Form) Notes: Only Phase III trials were included in this analysis. Per participant, multiple of pregnancies outcomes were possible.						

## **Sexually Transmitted infections**

The Phase I pooled analysis described the safety profile of five Phase I trials which are all conducted in healthy women in Belgium. In these Phase I trials no post-baseline sexually transmitted infections (STI) were reported. The Phase II trial IPM 015 and the Phase III pooled analysis sets are conducted in healthy women in Sub-Saharan Africa. In the Phase II IPM 015 trial, the post-baseline STI in the Dapivirine group was slightly lower compared with placebo (20.9% and 24.8%).

In the Phase III pooled analysis, post-baseline sexually transmitted infections were higher in the Dapivirine group (42.7%) compared with the placebo group (39.2%) (Table 28). Differentiating to the individual trials, the post-baseline STI were approximately similar (51.2% and 49.4% in the IPM 027 trial and 34.2% and 34.2% in the MTN-202 trial for Dapivirine and placebo, respectively. In the Phase III analysis set, the incidence in post-baseline STI was higher in trial IPM 027 than in trial MTN-020,



which was probably due to the differences in frequency of testing (IPM 027, STI testing was performed 12 weekly; in trial MTN-020 testing was 6 monthly).

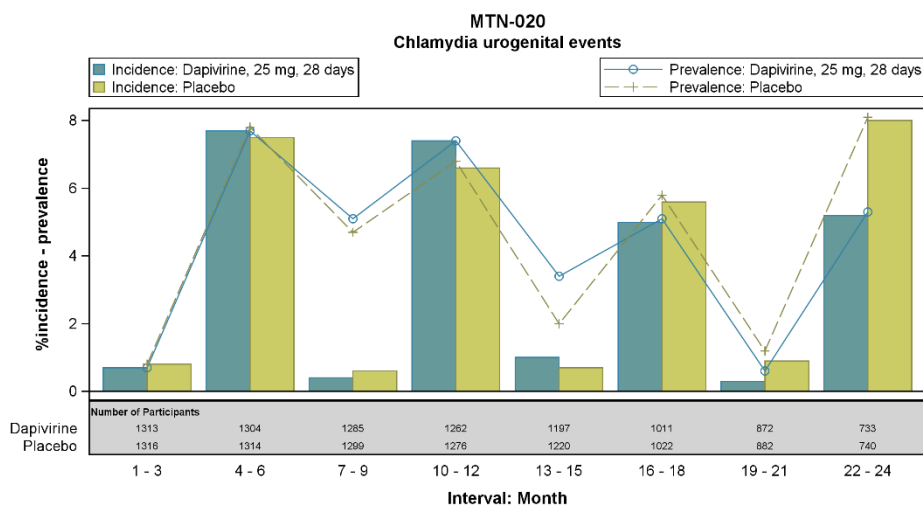
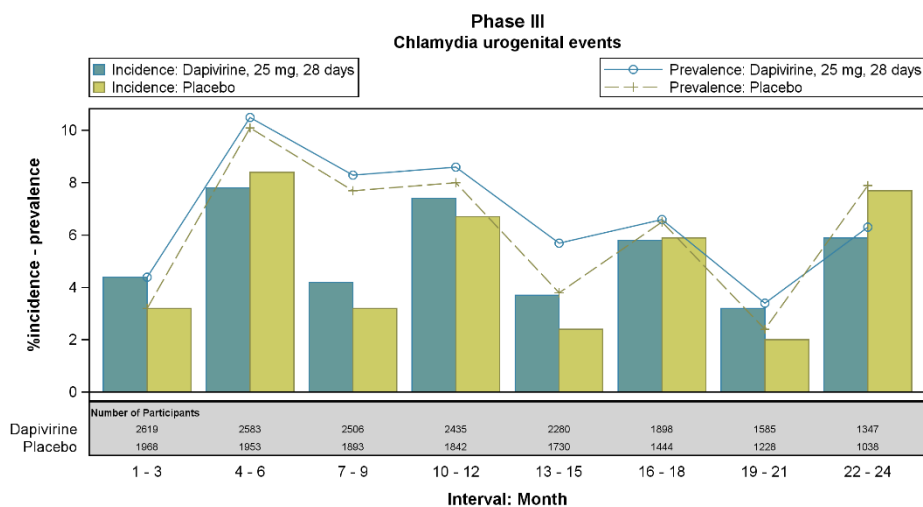
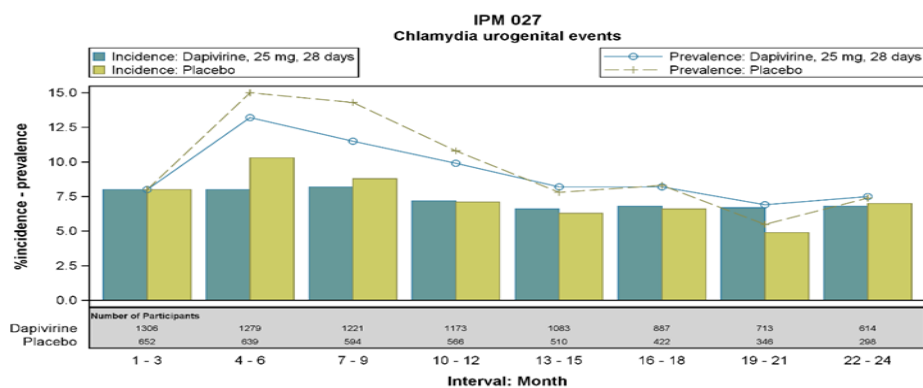
For chlamydia urogenital events, incidence and prevalence were consistent or decreased over time (Figure 9).

Subgroup analysis indicated that at baseline, more subjects  $\leq 21$  years of age had an STI present compared to subjects  $> 21$  years of age. In the Dapivirine group, 33.1% (193/583) of subjects  $\leq 21$  years of age versus 22.1% (450/2036) of subjects  $> 21$  years of age were positive for any STI at baseline, with most subjects being positive for *Chlamydia trachomatis*: 26.1% (152/583) for  $\leq 21$  years of age versus 11.9% (242/2036) for  $> 21$  years of age. This difference between the two age groups remained consistent throughout the trial in both the Dapivirine and placebo ring groups.

No major differences in the proportion of subjects with STIs were observed between subgroups of BMI, country, and region at baseline and any time point after baseline (worst result).

**Table 28 Treatment-emergent Sexually Transmitted Infections (Phase III Pooled Analysis)**

	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Any post-baseline STI (worst result)	651/1271 (51.2%)	308/624 (49.4%)	437/1277 (34.2%)	434/1268 (34.2%)	1088/2548 (42.7%)	742/1892 (39.2%)
<i>Chlamydia trachomatis</i> positive	411/1271 (32.3%)	209/624 (33.5%)	267/1250 (21.4%)	261/1252 (20.8%)	678/2521 (26.9%)	470/1876 (25.1%)
<i>Neisseria gonorrhoeae</i> positive	250/1271 (19.7%)	110/624 (17.6%)	136/1250 (10.9%)	149/1252 (11.9%)	386/2521 (15.3%)	259/1876 (13.8%)
<i>Trichomonas vaginalis</i> positive	222/1270 (17.5%)	101/624 (16.2%)	141/1252 (11.3%)	148/1250 (11.8%)	363/2522 (14.4%)	249/1874 (13.3%)
Syphilis positive <sup>a</sup>	17/824 (2.1%)	5/419 (1.2%)	24/1185 (2.0%)	32/1177 (2.7%)	41/2009 (2.0%)	37/1596 (2.3%)
n = number of participants with this observation, N = number of participants with data, STI = sexually transmitted infection						
<sup>a</sup> The syphilis result was derived from the available syphilis test. A positive rapid plasma reagin screening test and/or titer test was only positive with a confirmatory test.						



**Figure 9 Incidence and Prevalence of Chlamydia Urogenital Events Over Time (Phase III Pooled Analysis)**

## Vaginal Flora and pH

In the Phase III trials, the proportion of participants with a finding of abnormal vaginal flora, as indicated by a Nugent score  $\geq 7$ , was lower in trial IPM 027 than in trial MTN 020 at baseline and each 6-monthly visit up to Month 24 (Table 29). At all time points post-baseline in the Phase III pooled analysis, the proportion of participants with Nugent score  $\geq 7$  was similar between the two groups in both trials.

When considering the worst result at any time point post-baseline, no differences were observed between trials IPM 027 and MTN-020. In the Phase III pooled analysis, a small difference was observed between the Dapivirine (54.2% [1144/2112]) and placebo ring (49.6% [721/1455]) groups in findings of abnormal vaginal flora (Nugent score  $\geq 7$ ) (Table 30), and there is no potential biological explanation for this difference. No pH differences over time were observed.

**Table 29 Treatment-emergent Abnormal Nugent Score Over Time (Phase III Pooled Analysis)**

Abnormal Nugent Score ( $\geq 7$ )	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline	337/1303 (25.9%)	142/650 (21.8%)	438/1024 (42.8%)	412/1019 (40.4%)	775/2327 (33.3%)	554/1669 (33.2%)
Month 6/ Week 24	284/1147 (24.8%)	138/566 (24.4%)	298/735 (40.5%)	269/739 (36.4%)	582/1882 (30.9%)	407/1305 (31.2%)
Month 12/ Week 48	277/1074 (25.8%)	121/505 (24.0%)	188/444 (42.3%)	157/435 (36.1%)	465/1518 (30.6%)	278/940 (29.6%)
Month 18/ Week 72	196/733 (26.7%)	80/357 (22.4%)	101/234 (43.2%)	94/235 (40.0%)	297/967 (30.7%)	174/592 (29.4%)
Month 24/ Week 96	155/579 (26.8%)	77/285 (27.0%)	14/35 (40.0%)	17/39 (43.6%)	169/614 (27.5%)	94/324 (29.0%)
n = number of participants with this observation, N = number of participants with data Note: Only time points are included where data was available from both IPM 027 and MTN-020.						

**Table 30 Worst Post-baseline Treatment-emergent Nugent Score (Phase III Pooled Analysis)**

Nugent Score	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
N	2171	624	841	831	2112	1455
Normal (< 4)	377 (29.7%)	201 (32.2%)	275 (32.7%)	312 (37.5%)	652 (30.9%)	513 (35.3%)
Altered (4 - 6)	193 (15.2%)	103 (16.5%)	123 (14.6%)	118 (14.2%)	316 (15.0%)	221 (15.2%)
Abnormal ( $\geq 7$ )	701 (55.2%)	320 (51.3%)	443 (52.7%)	401 (48.3%)	1144 (54.2%)	721 (49.6%)
n = number of participants with this observation, N = number of participants with data						

## ***Serious adverse events and deaths***

### **Phase I Pooled Analysis**

In the Phase I pooled analysis, serious TEAE was reported in two (1.9% [2/108]) subjects in the Dapivirine (28 days) group. Food poisoning and thoracic vertebral fracture were reported as a serious TEAE in one (0.9% [1/108]) subject each in the Dapivirine Vaginal Ring-004 (28 days) group. None of the serious TEAEs were considered related to the IP. No deaths were reported in the Phase I pooled analysis.

### **Phase II IPM 015 trial**

The incidence in serious TEAE was slightly lower in the Dapivirine group compared with the placebo group, *i.e.* serious TEAE was reported in 0.7% (1/140) of the subjects in the Dapivirine group (tonsillitis) and 2.9% (4/139) of the subjects in the placebo ring group (bronchiectasis, peritonsillar abscess, tonsillitis, suicide attempt, and haemopneumothorax). None of the serious TEAEs were considered related to the IP. No deaths were reported.

### **Phase III Pooled Analysis**

The incidence of serious TEAE was slightly higher in the Dapivirine group (3.0% (79/2619) compared with the placebo group (2.4% (4/139) (Table 31). None of the serious TEAEs were considered related to the IP. No relevant difference between the treatment groups was observed for any individual preferred term TEAE.

The incidence in treatment-emergent adverse events leading to death were similar between both groups (0.2% [6/2619]) in the Dapivirine group and 0.2% [4/1968]) in the placebo ring group (Table 32). None of the deaths were considered to be related to the IP.

**Table 31 Serious Treatment-emergent Adverse Events in > 1 Participant in the Pooled Phase III Dapivirine Vaginal Ring 004 Group, Regardless of Severity or Causality (Phase III Pooled Analysis)**

System Organ Class, Preferred term	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<i>Safety Population</i>	1306	652	1313	1316	2619	1968
<i>Any Serious TEAE</i>	38 (2.9%)	6 (0.9%)	41 (3.1%)	42 (3.2%)	79 (3.0%)	48 (2.4%)
<i>At Least One Serious IP-related TEAE<sup>a</sup></i>	0	0	0	0	0	0
<b>Infections and Infestations</b>	<b>15 (1.1%)</b>	<b>1 (0.2%)</b>	<b>15 (1.1%)</b>	<b>16 (1.2%)</b>	<b>30 (1.1%)</b>	<b>17 (0.9%)</b>
Malaria	3 (0.2%)	0	3 (0.2%)	2 (0.2%)	6 (0.2%)	2 (0.1%)
Febrile infection	3 (0.2%)	0	0	0	3 (0.1%)	0
Pneumonia	1 (0.1%)	0	1 (0.1%)	2 (0.2%)	2 (0.1%)	2 (0.1%)
Cellulitis	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Pulmonary tuberculosis	1 (0.1%)	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Abscess limb	0	0	2 (0.2%)	0	2 (0.1%)	0
Tuberculosis	0	0	2 (0.2%)	0	2 (0.1%)	0
Urinary tract infection	0	0	2 (0.2%)	0	2 (0.1%)	0
<b>Injury, Poisoning and Procedural Complications</b>	<b>8 (0.6%)</b>	<b>0</b>	<b>8 (0.6%)</b>	<b>11 (0.8%)</b>	<b>16 (0.6%)</b>	<b>11 (0.6%)</b>
Stab wound	0	0	2 (0.2%)	2 (0.2%)	2 (0.1%)	2 (0.1%)
Gun shot wound	2 (0.2%)	0	0	0	2 (0.1%)	0
<b>Psychiatric Disorders</b>	<b>0</b>	<b>1 (0.2%)</b>	<b>6 (0.5%)</b>	<b>5 (0.4%)</b>	<b>6 (0.2%)</b>	<b>6 (0.3%)</b>
Intentional self-injury	0	0	2 (0.2%)	2 (0.2%)	2 (0.1%)	2 (0.1%)
Suicide attempt	0	1 (0.2%)	2 (0.2%)	1 (0.1%)	2 (0.1%)	2 (0.1%)
<b>Reproductive System and Breast Disorders</b>	<b>3 (0.2%)</b>	<b>3 (0.5%)</b>	<b>3 (0.2%)</b>	<b>1 (0.1%)</b>	<b>6 (0.2%)</b>	<b>4 (0.2%)</b>
Cervical dysplasia	3 (0.2%)	1 (0.2%)	0	0	3 (0.1%)	1 (0.1%)
<b>Pregnancy, Puerperium and Perinatal Conditions</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>1 (0.1%)</b>	<b>4 (0.2%)</b>	<b>1 (0.1%)</b>
Post abortion haemorrhage	0	0	2 (0.2%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
<b>Gastrointestinal Disorders</b>	<b>1 (0.1%)</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>3 (0.2%)</b>	<b>3 (0.1%)</b>	<b>3 (0.2%)</b>
<b>General Disorders and Administration Site Conditions</b>	<b>1 (0.1%)</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>3 (0.1%)</b>	<b>0</b>
Pyrexia	1 (0.1%)	0	1 (0.1%)	0	2 (0.1%)	0
<b>Hepatobiliary Disorders</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>1 (0.1%)</b>	<b>1 (0.1%)</b>	<b>3 (0.1%)</b>	<b>1 (0.1%)</b>
Cholelithiasis	1 (0.1%)	0	1 (0.1%)	0	2 (0.1%)	0
<b>Nervous System Disorders</b>	<b>3 (0.2%)</b>	<b>0</b>	<b>0</b>	<b>5 (0.4%)</b>	<b>3 (0.1%)</b>	<b>5 (0.3%)</b>
Headache	3 (0.2%)	0	0	1 (0.1%)	3 (0.1%)	1 (0.1%)
<b>Investigations</b>	<b>0</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>2 (0.1%)</b>	<b>0</b>

System Organ Class, Preferred term	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>1 (0.1%)</b>	<b>0</b>	<b>1 (0.1%)</b>	<b>1 (0.1%)</b>	<b>2 (0.1%)</b>	<b>1 (0.1%)</b>
Pulmonary embolism	1 (0.1%)	0	1 (0.1%)	0	2 (0.1%)	0
n = number of participants with this observation, TEAE = treatment-emergent adverse event, IP = investigational product						
<sup>a</sup> A TEAE was considered as investigational product related if the relationship was classified as "related" by the Investigator. If the assessment of the causal relationship was missing, the TEAE was also considered related to the investigational product.						

**Table 32 Fatal Treatment-emergent Adverse Events, Regardless of Causality (Phase III Pooled Analysis)**

System Organ Class, Preferred term	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<i>Safety Population</i>	1306	652	1313	1316	2619	1968
<i>Any Fatal TEAE</i>	2 (0.2%)	1 (0.2%)	4 (0.3%)	3 (0.2%)	6 (0.2%)	4 (0.2%)
<i>At Least One Serious IP-related TEAE<sup>a</sup></i>	0	0	0	0	0	0
<b>Injury, Poisoning and Procedural Complications</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>3 (0.2%)</b>	<b>1 (0.1%)</b>	<b>5 (0.2%)</b>	<b>1 (0.1%)</b>
Stab wound	0	0	2 (0.2%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Abdominal injury	0	0	1 (0.1%)	0	1 (< 0.1%)	0
Gun shot wound	1 (0.1%)	0	0	0	1 (< 0.1%)	0
Multiple injuries	1 (0.1%)	0	0	0	1 (< 0.1%)	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>0</b>	<b>0</b>	<b>1 (0.1%)</b>	<b>0</b>	<b>1 (&lt; 0.1%)</b>	<b>0</b>
Pulmonary embolism	0	0	1 (0.1%)	0	1 (< 0.1%)	0
<b>Infections and Infestations</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>2 (0.1%)</b>
Pulmonary tuberculosis	0	0	0	1 (0.1%)	0	1 (0.1%)
Tuberculosis gastrointestinal	0	0	0	1 (0.1%)	0	1 (0.1%)
<b>Vascular Disorders</b>	<b>0</b>	<b>1 (0.2%)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.1%)</b>
Circulatory collapse	0	1 (0.2%)	0	0	0	1 (0.1%)
n = number of participants with this observation, TEAE = treatment-emergent adverse event, IP = investigational product						
<sup>a</sup> A TEAE was considered as investigational product related if the relationship was classified as "related" by the Investigator. If the assessment of the causal relationship was missing, the TEAE was also considered related to the investigational product.						

## Laboratory findings

In the Phase III pooled analysis, the incidences in laboratory abnormalities between the Dapivirine and placebo group were comparable (Table 33).

The most commonly observed laboratory abnormalities (*i.e.* in  $\geq 10.0\%$  of the subjects in the Dapivirine group) were leukocytes below normal (16.7% and 19.2%) and ALT increased (11.1% and 11.9%), for the Dapivirine and placebo group, respectively.

Grade 3 or 4 laboratory abnormalities included increased ALT, increased AST, decreased absolute neutrophil count, and decreased haemoglobin in at most 1.0% of subjects in either group.

**Table 33 Laboratory Abnormalities in  $\geq 5.0\%$  of Participants in the Pooled Phase III Dapivirine Vaginal Ring 004 Group (Phase III Pooled Analysis)**

Laboratory Abnormality	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<i>Graded Laboratory Abnormalities</i>						
<b>Alanine Aminotransferase Increased, N</b>	<b>1271</b>	<b>625</b>	<b>1293</b>	<b>1285</b>	<b>2564</b>	<b>1910</b>
Grade 1	113 (8.9%)	54 (8.6%)	116 (9.0%)	128 (10.0%)	229 (8.9%)	182 (9.5%)
Grade 2	22 (1.7%)	13 (2.1%)	19 (1.5%)	20 (1.6%)	41 (1.6%)	33 (1.7%)
Grade 3	4 (0.3%)	2 (0.3%)	5 (0.4%)	5 (0.4%)	9 (0.4%)	7 (0.4%)
Grade 4	3 (0.2%)	4 (0.6%)	2 (0.2%)	2 (0.2%)	5 (0.2%)	6 (0.3%)
Total	142 (11.2%)	73 (11.7%)	142 (11.0%)	155 (12.1%)	284 (11.1%)	228 (11.9%)
<b>Aspartate Aminotransferase Increased, N</b>	<b>1271</b>	<b>625</b>	<b>1293</b>	<b>1285</b>	<b>2564</b>	<b>1910</b>
Grade 1	58 (4.6%)	29 (4.6%)	125 (9.7%)	118 (9.2%)	183 (7.1%)	147 (7.7%)
Grade 2	8 (0.6%)	7 (1.1%)	8 (0.6%)	18 (1.4%)	16 (0.6%)	25 (1.3%)
Grade 3	1 (0.1%)	1 (0.2%)	5 (0.4%)	2 (0.2%)	6 (0.2%)	3 (0.2%)
Grade 4	3 (0.2%)	2 (0.3%)	2 (0.2%)	1 (0.1%)	5 (0.2%)	3 (0.2%)
Total	70 (5.5%)	39 (6.2%)	140 (10.8%)	139 (10.8%)	210 (8.2%)	178 (9.3%)
<b>Absolute Neutrophil Count Decreased, N</b>	<b>1271</b>	<b>624</b>	<b>1294</b>	<b>1286</b>	<b>2565</b>	<b>1910</b>
Grade 1	52 (4.1%)	40 (6.4%)	90 (7.0%)	113 (8.8%)	142 (5.5%)	153 (8.0%)
Grade 2	11 (0.9%)	7 (1.1%)	49 (3.8%)	34 (2.6%)	60 (2.3%)	41 (2.1%)
Grade 3	2 (0.2%)	1 (0.2%)	9 (0.7%)	6 (0.5%)	11 (0.4%)	7 (0.4%)
Grade 4	0	1 (0.2%)	0	1 (0.1%)	0	2 (0.1%)

## Safety in special populations

### Age

For TEAEs in general, there were no relevant differences between female subjects who were  $\leq 21$  years of age and subjects  $> 21$  years of age (age at baseline; inclusion criteria was 18-45 years of age).

For the TEAEs of interest, events of metrorrhagia and infections (mainly chlamydia urogenital events and gonococcal urogenital events) were reported more frequently in subjects  $\leq 21$  years of age versus subjects  $> 21$  years of age (Table 34). These differences between both baseline age categories were present in both the Dapivirine group and the placebo group.

Already at baseline, more subjects  $\leq 21$  years of age had an STI present compared to subjects  $> 21$  years of age. In the Phase III pooled analysis, 33.1% (193/583) of subjects  $\leq 21$  years of age versus 22.1% (450/2036) of subjects  $> 21$  years of age were positive for any STI at baseline. Evaluation of STIs over time during trials demonstrated that the differences between the age groups remained consistent throughout the trial and similar in both trial arms.

**Table 34 Adverse Events of Interest by Age, Regardless of Severity or Causality (Phase III Pooled Analysis)**

System Organ Class, Grouped/Preferred term <sup>a</sup>	Dapivirine (28 Days)		Placebo (28 Days)	
	$\leq 21$ years	$> 21$ years	$\leq 21$ years	$> 21$ years
	n (%)	n (%)	n (%)	n (%)
<i>Safety Population</i>	583	2036	405	1563
<i>Any TEAE of Interest</i>	511 (87.7%)	1692 (83.1%)	351 (86.7%)	1315 (84.1%)
<b>Reproductive System and Breast Disorders of Interest</b>	<b>379 (65.0%)</b>	<b>1220 (59.9%)</b>	<b>275 (67.9%)</b>	<b>1042 (66.7%)</b>
Metrorrhagia	274 (47.0%)	767 (37.7%)	213 (52.6%)	686 (43.9%)
Menorrhagia	88 (15.1%)	293 (14.4%)	59 (14.6%)	242 (15.5%)
<b>Infections and Infestations of Interest</b>	<b>402 (69.0%)</b>	<b>1191 (58.5%)</b>	<b>268 (66.2%)</b>	<b>869 (55.6%)</b>
Chlamydia urogenital events <sup>b</sup>	234 (40.1%)	446 (21.9%)	159 (39.3%)	319 (20.4%)
Renal infections <sup>b</sup>	98 (16.8%)	300 (14.7%)	76 (18.8%)	254 (16.3%)
Gonococcal urogenital events <sup>b</sup>	131 (22.5%)	260 (12.8%)	74 (18.3%)	189 (12.1%)
Trichomonal urogenital events <sup>b</sup>	77 (13.2%)	297 (14.6%)	51 (12.6%)	209 (13.4%)
Genital tract candidiasis <sup>b</sup>	75 (12.9%)	239 (11.7%)	49 (12.1%)	155 (9.9%)
Bacterial vaginosis	67 (11.5%)	194 (9.5%)	52 (12.8%)	141 (9.0%)
Gynaecological infection <sup>b</sup>	64 (11.0%)	223 (11.0%)	34 (8.4%)	81 (5.2%)
<b>Investigations of Interest</b>	<b>59 (10.1%)</b>	<b>243 (11.9%)</b>	<b>68 (16.8%)</b>	<b>271 (17.3%)</b>
n = number of participants with this observation, TEAE = treatment-emergent adverse event				
<sup>a</sup> Reported in $\geq 10.0\%$ of participants in the Dapivirine Vaginal Ring-004 pooled Phase III group				
<sup>b</sup> A list of the preferred terms included in this grouped term can be found in <a href="#">SAP ISS</a> .				



### **Postmenopausal women**

In the Phase IIA MTN-024/IPM 031 trial, the tolerability and safety of the Dapivirine ring were evaluated for a 12-week period in HIV-negative postmenopausal females in the USA.

The majority of subjects (89%) found the vaginal ring to be as acceptable as other HIV prevention methods. The self-reported adherence to daily use of the vaginal ring during the 12 weeks of follow-up was high, *i.e.* 83% of the subjects reported to never have had their ring out for any reason.

117 TEAEs were reported for 46 (46/72; 63.9%) subjects in the Dapivirine vaginal ring arm, and 35 AEs were reported for 14 (14/24; 58.3%) subjects in the placebo vaginal ring arm.

The most commonly reported AEs (occurring in more than 2 subjects in either treatment arm) regardless of causality were: lower abdominal pain (5.6% and 0% in the Dapivirine and the placebo group, respectively), diarrhea (4.2% and 3.1%), vomiting (4.2% and 3.1%), upper respiratory tract infection (8.3% and 12.5%), urinary tract infection (8.3% and 12.5%), and vulvovaginitis (2.8% and 8.3%), vaginal discharge (11.1% and 12.5%), vaginal odour (6.9% and 0%), cervix hemorrhage uterine (5.6% and 4.2%), vaginal haemorrhage (5.6% and 0%), vulvovaginal erythema (4.2% and 12.5%), and vulvovaginal pruritus (4.2% and 4.2%). the incidence of TEAEs assessed as related to IP was slightly higher in the Dapivirine group as compared to the placebo group, which is probably due to the limited number of subjects included in combination with the 3:1 randomization to the Dapivirine and the placebo arm, respectively.

For a total of 42 (42/96; 43.8%) subjects the AEs were determined by the Investigator to be related to the vaginal ring use: 34 (34/72; 47.2%) participants were in the Dapivirine vaginal ring arm and 8 (8/24; 33.3%) participants in the placebo vaginal ring arm.

The most commonly reported IP-related AEs (occurring in more than 2 participants in either treatment arm) were: lower abdominal pain (4.3% and 3.1% in the Dapivirine group and placebo group, respectively), urinary tract infections (1.4% and 8.3%), vulvovaginitis (2.8% and 8.3%), vaginal discharge (11.1% and 8.3%), cervix hemorrhage uterine (5.6% and 4.2%), vaginal haemorrhage (5.6% and 0%), vaginal odour (5.6% and 0%), vulvovaginal erythema (4.2% and 12.5%), and vulvovaginal pruritus (4.2% and 4.2%). All AEs were determined by the Investigator to be mild (Grade 1) in severity (Table 35).

**Table 35 Adverse events related to vaginal ring use occurring in > subjects in either treatment arm by System Organ Class and Preferred Term- Intent-to-treat Population**

<b>System Organ Class Preferred term</b>	<b>Severity (DAIDS Grade)*</b>	<b>Dapivirine Vaginal Ring n (%)</b>	<b>Placebo Ring (N=24) n (%)</b>	<b>All Participants (N=96) n (%)</b>
Number of participants with one or more product-related AEs		34 (47.2%)	8 (33.3%)	42 (43.8%)
Total number of related AEs		57	16	73
Gastrointestinal Disorders				
<i>Abdominal discomfort</i>	1	2 (2.8%)	0	2 (2.1%)
<i>Abdominal pain lower</i>	1	3 (4.2%)	0	3 (3.1%)
<i>Nausea</i>	1	2 (2.8%)	0	2 (2.1%)
Infections and Infestations				
<i>Urinary tract infection</i>	2	1 (1.4%)	2 (8.3%)	3 (3.1%)
<i>Vulvovaginitis</i>	1,2	2 (2.8%)	2 (8.3%)	4 (4.2%)
Reproductive System and Breast Disorders				
<i>Dyspareunia</i>	1,2	2 (2.8%)	0	2 (2.1%)
<i>Cervix haemorrhage uterine</i>	1	4 (5.6%)	1 (4.2%)	5 (5.2%)
<i>Vaginal discharge</i>	1	8 (11.1%)	2 (8.3%)	10 (10.4%)
<i>Vaginal erosion</i>	1	2 (2.8%)	0	2 (2.1%)
<i>Vaginal haemorrhage</i>	1	4 (5.6%)	0	4 (4.2%)
<i>Vaginal odour</i>	1	4 (5.6%)	0	4 (4.2%)
<i>Vulvovaginal discomfort</i>	1	2 (2.8%)	0	2 (2.1%)
<i>Vulvovaginal dryness</i>	1	2 (2.8%)	0	2 (2.1%)
<i>Vulvovaginal erythema</i>	1	3 (4.2%)	3 (12.5%)	6 (6.3%)
<i>Vulvovaginal pruritus</i>	1	3 (4.2%)	1 (4.2%)	4 (4.2%)

DAIDS = Division of Acquired Immunodeficiency Syndrome, MedDRA = Medical Dictionary for Regulatory

Activities, AE = adverse event.

MedDRA Version 18.1 was used.

Percentages are calculated as the number of participants (n) reporting an event of a specific relationship divided by the number of participants enrolled.

### **Paediatric population (postmenarchal adolescent girls aged 15-17 years)**

MTN-023/IPM 030 was a pharmacokinetic Phase IIa, double-blind, randomized, placebo-controlled, multicenter trial evaluating the safety of the dapivirine vaginal ring in adolescents aged 15-17 years. In total, 96 participants were enrolled and randomized: 73 participants to the Dapivirine Vaginal Ring group and 23 participants to the placebo ring group. The Dapivirine Vaginal Ring was well tolerated in adolescent females when inserted once every 4 weeks and used continuously during 24 weeks. The type and nature of adverse events reported were similar to those reported in trials conducted in women of reproductive age 18 years and older.

## Other subgroups

Subgroup analysis with respect to country, region, BMI, and sexually transmitted infections at first screening showed no relevant differences in TEAEs.

## Adverse events by average ring residual level

There are no significant differences apparent between the adherence subgroups for either trial or the pooled Phase III data (Table 36). As the subset of participants with a dapivirine ring residual level of > 23.5 mg is very small (approximately 12% of the total number of participants assigned to Dapivirine Vaginal Ring), a more detailed analysis was performed using only two adherence categories, namely ring residual levels of ≤21 mg and >21 mg. In both studies IPM 027 and MTN-020, no differences were observed in the safety profile between participants classified as adherent to Dapivirine treatment (ring residual level ≤ 21 mg) and placebo.

**Table 36 Treatment-Emergent Adverse Events Summary Table by Average Ring Residual Level; Population: Safety**

Total Number of Participants (n [%]) With:	Average Ring Residual Level ≤ 21 mg			Average Ring Residual Level > 21 mg to ≤ 23.5 mg			Average Ring Residual Level > 23.5 mg			Placebo		
	IPM 027	MTN -020	Pooled	IPM 027	MTN -020	Pooled	IPM 027	MTN -020	Pooled	IPM 027	MTN -020	Pooled
Safety Population	555	419	974	550	694	1244	178	126	304	652	1316	1968
At least one TEAE	485 (87.4%)	392 (93.6%)	877 (90.0%)	496 (90.2%)	670 (96.5%)	1166 (93.7%)	154 (86.5%)	119 (94.4%)	273 (89.8%)	559 (85.7%)	1224 (93.0%)	1783 (90.6%)
At least one serious TEAE	17 (3.1%)	12 (2.9%)	29 (3.0%)	16 (2.9%)	26 (3.7%)	42 (3.4%)	5 (2.8%)	2 (1.6%)	7 (2.3%)	6 (0.9%)	42 (3.2%)	48 (2.4%)
At least one DAIDS Grade 3 or 4 TEAE	35 (6.3%)	46 (11.0%)	81 (8.3%)	20 (3.6%)	87 (12.5%)	107 (8.6%)	8 (4.5%)	16 (12.7%)	24 (7.9%)	22 (3.4%)	162 (12.3%)	184 (9.3%)
At least one IP-related TEAE	1 (0.2%)	28 (6.7%)	29 (3.0%)	3 (0.5%)	60 (8.6%)	63 (5.1%)	1 (0.6%)	21 (16.7%)	22 (7.2%)	3 (0.5%)	130 (9.9%)	133 (6.8%)
At least one serious IP-related TEAE	0	0	0	0	0	0	0	0	0	0	0	0
At least one non-serious IP-related TEAE	1 (0.2%)	28 (6.7%)	29 (3.0%)	3 (0.5%)	60 (8.6%)	63 (5.1%)	1 (0.6%)	21 (16.7%)	22 (7.2%)	3 (0.5%)	130 (9.9%)	133 (6.8%)
TEAEs leading to death	1 (0.2%)	0	1 (0.1%)	1 (0.2%)	4 (0.6%)	5 (0.4%)	0	0	0	1 (0.2%)	3 (0.2%)	4 (0.2%)
TEAEs leading to IP interruption	3 (0.5%)	18 (4.3%)	21 (2.2%)	7 (1.3%)	37 (5.3%)	44 (3.5%)	1 (0.6%)	9 (7.1%)	10 (3.3%)	3 (0.5%)	62 (4.7%)	65 (3.3%)
TEAEs leading to premature IP discontinuation	0	0	0	0	0	0	0	0	0	1 (0.2%)	0	1 (0.1%)

### **Baseline method of contraception**

Subgroup analysis with respect to baseline method of contraception showed no relevant differences in metrorrhagia events between the Dapivirine group and the placebo group in both trials (Table 37). One exception is the higher incidence in metrorrhagia in the Dapivirine group (40%) compared with the placebo group (18.2%) for patients who were surgically sterilized in the MTN-020 trial, however conclusion cannot be drawn due to the limited number of patients in this subpopulation (45 vs 33 patients).

**Table 37 Baseline Method of Contraception (Phase III Pooled Analysis)**

Baseline Method of Contraception	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of participants	1306	652	1313	1316	2619	1968
Surgical sterilization	49 (3.8%)	24 (3.7%)	45 (3.4%)	33 (2.5%)	94 (3.6%)	57 (2.9%)
Long-acting injectable progestins	1033 (79.1%)	520 (79.8%)	706 (53.8%)	734 (55.8%)	1739 (66.4%)	1254 (63.7%)
Transdermal contraceptive patch	0	1 (0.2%)	256 (19.5%)	242 (18.4%)	256 (9.8%)	243 (12.3%)
Oral contraceptive regimen	112 (8.6%)	59 (9.0%)	137 (10.4%)	141 (10.7%)	249 (9.5%)	200 (10.2%)
IUD	19 (1.5%)	6 (0.9%)	159 (12.1%)	162 (12.3%)	178 (6.8%)	168 (8.5%)
Subcutaneous implant	93 (7.1%)	41 (6.3%)	0	0	93 (3.6%)	41 (2.1%)
Long-acting injectable progestins; oral contraceptive regimen	0	0	5 (0.4%)	2 (0.2%)	5 (0.2%)	2 (0.1%)
IUD; long-acting injectable progestins	0	0	3 (0.2%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Long-acting injectable progestins; transdermal contraceptive patch	0	0	1 (0.1%)	0	1 (< 0.1%)	0

### **Immunological events**

Not discussed by the Applicant

### **Safety related to drug-drug interactions and other interactions**

Systemic exposure to Dapivirine is low compared to oral formulations and hence the potential for drug-drug interactions and AEs related to interactions is expected to be low.

One clinical drug-drug interaction trial has been conducted with the Dapivirine Vaginal Ring-004 to evaluate the interaction between Dapivirine and miconazole nitrate (trial IPM 028). The data from the

individual trial indicates that no specific safety concerns emerged following concomitant administration of the Dapivirine Vaginal Ring-004 and a vaginal dose of miconazole nitrate.

In addition, one clinical trial was ongoing at the time of the cut-off date of 30 September 2016 to evaluate the interaction between Dapivirine (administered via the Dapivirine Vaginal Ring-004) and vaginally administered clotrimazole (trial IPM 036). Up to the cut-off date of 30 September 2016, no safety concerns were identified.

### ***Discontinuation due to AES***

In the Phase I pooled analysis, TEAE leading to permanent IP discontinuation was reported in one subject in the Dapivirine (28 days) group (generalized pruritus), whereas in the Phase II IPM 015 trial none of the subjects permanently discontinued the trial due to an adverse event. In the Phase III pooled analysis, the incidences in TEAEs leading to permanent discontinuations were similar between both groups. One subject in the Dapivirine group experienced vulvovaginal rash and one subject in the placebo group experienced cervical dysplasia leading to permanent discontinuation, both were considered not related to IP by the Investigator.

The incidence of TEAEs leading to temporary IP discontinuation was slightly lower in the Dapivirine group (2.9%) compared with the placebo group (3.3%) (Table 38). TEAEs leading to temporary IP discontinuation were reported in a lower proportion of subjects in trial IPM 027 (0.8% [11/1306] and 0.5% [3/652] in the Dapivirine and the placebo group, respectively) than in trial MTN-020 (5.0% [65/1313] and 4.7% [62/1316], respectively), which is due to a different approach of temporary discontinuation of IP between the trials IPM 027 and MTN-020. In trial IPM 027, it was based largely on the Investigator's discretion, while trial MTN-020 provided more specific guidelines. In MTN-020 participants who developed a Grade 3 AE which was considered to be related to IP (by the Investigator) or a Grade 4 AE (irrespective of causality), IP use was required to be temporarily discontinued. Additionally, all Grade 3 AEs required temporary discontinuation of IP, unless the investigator in consultation with the Protocol Safety Review Team decided that temporary discontinuation of IP was not warranted.

**Table 38 Treatment-emergent Adverse Events Leading to Temporary Discontinuation in > 1 Participant in the Pooled Phase III Dapivirine Vaginal Ring 004 Group, Regardless of Severity or Causality (Phase III Pooled Analysis)**

System Organ Class, Preferred term	IPM 027		MTN-020		Phase III	
	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)	Dapivirine (28 Days)	Placebo (28 Days)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<i>Safety Population</i>	1306	652	1313	1316	2619	1968
<i>Any TEAE Leading to Temporary Investigational Product Discontinuation</i>	11 (0.8%)	3 (0.5%)	65 (5.0%)	62 (4.7%)	76 (2.9%)	65 (3.3%)
<b>Infections and Infestations</b>	<b>4 (0.3%)</b>	<b>2 (0.3%)</b>	<b>41 (3.1%)</b>	<b>37 (2.8%)</b>	<b>45 (1.7%)</b>	<b>39 (2.0%)</b>
Cervicitis	1 (0.1%)	0	21 (1.6%)	18 (1.4%)	22 (0.8%)	18 (0.9%)
Genitourinary tract gonococcal infection	0	0	8 (0.6%)	5 (0.4%)	8 (0.3%)	5 (0.3%)
Genitourinary chlamydia infection	0	0	7 (0.5%)	6 (0.5%)	7 (0.3%)	6 (0.3%)
Pelvic inflammatory disease	0	0	3 (0.2%)	5 (0.4%)	3 (0.1%)	5 (0.3%)
Acute hepatitis B	1 (0.1%)	0	1 (0.1%)	0	2 (0.1%)	0
<b>Reproductive System and Breast Disorders</b>	<b>5 (0.4%)</b>	<b>1 (0.2%)</b>	<b>11 (0.8%)</b>	<b>7 (0.5%)</b>	<b>16 (0.6%)</b>	<b>8 (0.4%)</b>
Vulvovaginal erythema	0	0	2 (0.2%)	1 (0.1%)	2 (0.1%)	1 (0.1%)
Cervical dysplasia	1 (0.1%)	0	1 (0.1%)	0	2 (0.1%)	0
Genital ulceration	2 (0.2%)	0	0	0	2 (0.1%)	0
Vaginal erosion	0	0	2 (0.2%)	0	2 (0.1%)	0
<b>Investigations</b>	<b>0</b>	<b>0</b>	<b>7 (0.5%)</b>	<b>2 (0.2%)</b>	<b>7 (0.3%)</b>	<b>2 (0.1%)</b>
Aspartate aminotransferase increased	0	0	3 (0.2%)	0	3 (0.1%)	0
Alanine aminotransferase increased	0	0	2 (0.2%)	2 (0.2%)	2 (0.1%)	2 (0.1%)
Platelet count decreased	0	0	2 (0.2%)	0	2 (0.1%)	0
<b>Injury, Poisoning and Procedural Complications</b>	<b>0</b>	<b>0</b>	<b>3 (0.2%)</b>	<b>4 (0.3%)</b>	<b>3 (0.1%)</b>	<b>4 (0.2%)</b>
<b>Psychiatric Disorders</b>	<b>0</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>4 (0.3%)</b>	<b>2 (0.1%)</b>	<b>4 (0.2%)</b>
<b>General Disorders and Administration Site Conditions</b>	<b>0</b>	<b>0</b>	<b>2 (0.2%)</b>	<b>1 (0.1%)</b>	<b>2 (0.1%)</b>	<b>1 (0.1%)</b>
Mass <sup>a</sup>	0	0	2 (0.2%)	0	2 (0.1%)	0
n = number of participants with this observation, TEAE = treatment-emergent adverse event Verbatim terms include vulval mass - in lesser vestibular region and vaginal mass.						

### ***Safety data of trial not included in the pooled safety analyses***

#### **Clinical development of oral administration of Dapivirine**

The Dapivirine molecule was originally developed as an oral ARV drug by Janssen Sciences Ireland UC. The oral clinical development program consisted of 11 Phase I/II trials in more than 200 participants, who were exposed to oral doses of Dapivirine ranging from 50 mg to 1000 mg daily. The maximum tolerated oral dose was established as 300 mg twice daily for multiple doses, and was based on a dose-dependent increase in central nervous system and gastrointestinal TEAEs. The most frequently reported adverse events were dizziness and headache. These TEAEs resolved within one to two days after discontinuation of oral Dapivirine. There were two serious adverse events (SAEs) reported, including one hospitalization due to elevated liver function tests. This participant was also infected with hepatitis C virus. The only other SAE was a hospitalization due to a bicycle accident.

There were no clinically relevant changes observed in the clinical laboratory parameters, ECG parameters, heart rate and blood pressure. There were no changes seen in endocrinology parameters and in immunology parameters.

#### **IPM 011**

IPM 011 was a Phase I, randomized, crossover trial to assess the safety, acceptability of, and adherence to a silicone elastomer placebo ring, inserted for a 12-week period in healthy, HIV-negative, sexually active women 18 to 35 years of age in South Africa and Tanzania. Women either used a placebo ring continuously for 12 weeks, followed by a 12-week (ring-free) safety observation period (Group A); or women were observed first, and used a placebo ring for 12 weeks thereafter (Group B).

The overall incidence in adverse events were comparable between the intervention period (201 events) and the observation period (233 events). No AEs were considered by the Investigator to be definitely related to ring use. 28 events were classified as possibly or probably related to ring use, of which two events were reported in the observation regimen and 26 events in the intervention regimen, which were not associated with any specific safety pattern as most of the TEAEs were only reported once (Table 39).

**Table 39 Incidence of AEs probably or possibly related to ring use - ITT population**

<b>System Organ Class Preferred term</b>	<b>Site 2 n(%)</b>	<b>Site 3 n(%)</b>	<b>Site 4 n(%)</b>	<b>Site 5 n(%)</b>	<b>Total n(%)</b>
Gastrointestinal disorders					
<i>Abdominal pain lower</i>	1 (1%)	0	0	1 (1%)	2 (1%)
<i>Abdominal tenderness</i>	0	0	0	1 (1%)	1 (1%)
Infections and infestations					
<i>Gynaecological chlamydia infection</i>	0	1 (1%)*	0	0	1 (1%)
<i>Vaginitis bacterial</i>	0	0	0	3 (2%)*	3 (2%)
<i>Vaginal candidiasis</i>	0	0	0	2 (1%)	2 (1%)
Reproductive System And Breast Disorders					
<i>Cervical discharge</i>	0	0	0	1 (1%)	1 (1%)
<i>Cervix erythema</i>	0	0	0	2 (1%)	2 (1%)
<i>Cervix haemorrhage uterine</i>	0	1 (1%)	0	0	1 (1%)
<i>Coital bleeding</i>	0	1 (1%)	0	0	1 (1%)
<i>Genital discomfort</i>	0	1 (1%)	0	0	1 (1%)
<i>Genital erythema</i>	0	1 (1%)	0	0	1 (1%)
<i>Uterine pain</i>	0	1 (1%)	0	0	1 (1%)
<i>Vaginal discharge</i>	0	1 (1%)	0	2 (1%)	3 (2%)
<i>Vaginal odour</i>	0	3 (2%)	0	0	3 (2%)
<i>Vulvovaginal discomfort</i>	0	0	0	2 (1%)	2 (1%)

\* The event of gynecological chlamydia infection and one event of bacterial vaginitis were reported in Group A on the day that the ring was removed and the participant crossed over to the observational regimen (Visit 5); these events were subsequently reported as occurring in the observational period.

### **Other studies**

Safety data of the IPM 027 trial after the cut off date, open label extensions trials (IPM 032 and MTN-025) and male tolerability trial (MTN-012/IPM 010, showed no unexpected adverse events of Dapivirine.

### **Adverse Drug reactions**

To determine which events could be added as ADRs in the PIs, data from all reported AEs in the two pivotal Phase III trials (IPM 027 and MTN-020) and the Phase II trial (IPM 015) with the DPV-VR were analysed and reviewed in accordance with a systematic and well-documented structured approach. The methodology for identifying ADRs was described in detail by the applicant. The described approach to identify ADRs is supported. Accordingly, the ADRs identified by the applicant were included in the respective sections of the PI.

## **2.6.1. Discussion on clinical safety**

### **Patient exposure**

An total number of 2917 subjects were exposed to the Dapivirine ring representing 4181 patient years of exposure. In the Phase III studies, 2091 subjects were exposed to the Dapivirine ring for  $\geq 12$  months and 710 subjects were exposed to Dapivirine for  $\geq 24$  months. The number of subjects exposed is sufficient according to guideline recommendations (Reflection paper on the non-clinical and clinical



development for oral and topical HIV pre-exposure prophylaxis (EMA/171264/2012); ICH E1 Population Exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95)).

The Applicant has performed three safety analysis sets:

- The Phase I pooled analysis based on 5 phase I trials (IPM 013, IPM 024, IPM 028, IPM 034, and IPM 035) conducted in healthy HIV-negative women in Belgium.
- The phase II analysis set (IPM 015)
- The Phase III pooled analysis set (IPM 027 and MTN-020) evaluate the safety of Dapivirine in women in sub-Saharan Africa.

Considering that the 4181 patient-years of exposure was mainly attributable to patients from the Phase III pooled analysis, only results of this safety analysis set are discussed in detail. Safety issues of the Phase I pooled analysis and Phase II IPM 0150 set are discussed when relevant.

### **Patient characteristics**

As to baseline characteristics in the pooled phase III analysis, no clear differences were noted between the Dapivirine ring and placebo ring. The majority of subjects in Phase III were Black (96.5% in the Dapivirine group and 94.9% in the placebo group) and older than 21 years (77.7% and 79.4%, respectively), with mean age around 27 years. Mean BMI was 27.4 kg/m<sup>2</sup> in the Dapivirine group and 27.6 kg/m<sup>2</sup> in the placebo group. At baseline, any sexually transmitted infections (STI) (chlamydia trachomatis, Trichomonas vaginalis, Neisseria gonorrhoeae, and Syphilis) was identified in 24.6% of the subjects in the Dapivirine group and 22.5% in the placebo ring group, of which Chlamydia trachomatis was observed most often (~15% in both groups). The subdivision into women younger than 21 years of age or above, showed that STI percentage was highest in younger women in both the dapivirine and placebo group.

When comparing trials IPM 027 and MTN-020, no differences were observed, except for marital status, baseline method of contraception, and abnormal vaginal flora. As to contraception, the majority of women in both groups used a reliable form of contraception. In study IPM 027, almost 80% of women used long-term progestins, while this percentage was about 20% lower in study MTN 020. In study MTN 020, the percentage of women using a transdermal contraception was about 20%, while this method was only used rarely in study IPM 027. Combined oral contraceptives were use in 10% of women in both groups. While only 10% were married in study IPM 027, this percentage was around 40% in study MTN 020.

The percentage of abnormal flora (Nugent score) and percentage of STIs at baseline was also somewhat higher in study IPM 027 than in study MTN 020.

### **Adverse events/adverse drug reactions**

#### **Adverse events**

In the Phase III pooled analysis, the overall incidence of adverse events reported in the Dapivirine ring group was approximately similar to that in the placebo ring (90.8% vs 90.6% women). The most commonly reported adverse events were:

- metrorrhagia (39.9% and 45.8% for the Dapivirine and placebo group, respectively),
- genitourinary chlamydia infection/gynaecological chlamydia infection (25.5% and 24.1%),

- urinary tract infection (15.2% and 16.6%),
- menorrhagia (14.6% and 15.3%),
- genitourinary tract gonococcal infection (14.3% and 13.2%),
- upper respiratory tract infection (13.9% and 12.5%),
- vulvovaginal candidiasis (11.9% and 10.2%),
- genital infection female (11.0% and 5.8%),
- and bacterial vaginosis (10.0% and 9.9%).

In general, the incidence of these common TEAEs decreased over time and the prevalence remained over time.

The majority of TEAEs were mild or moderate in severity. Grade 3 (severe) or Grade 4 (potentially life-threatening) TEAEs were reported in 8.4% (219/2619) of the subjects in the Dapivirine group and 9.3% (184/1968) of the subjects in the placebo group. In the individual trials, the incidence in TEAEs grade 3 (severe) and Grade 4 (life-threatening) was approximately similar in the Dapivirine and placebo group.

### **IP-related TEAEs**

In the Phase III pooled analysis, the overall incidence rate in at least one IP-related TEAE (4.6% and 6.8%) were slightly lower in the Dapivirine group compared with placebo. The most commonly reported IP-related TEAEs (i.e. in  $\geq 0.5\%$  of the subjects in the Dapivirine group) were:

- metrorrhagia (18 (0.7%) and 9 (0.5%) for the Dapivirine and placebo group, respectively)
- vaginal discharge (0.6% and 1.0%),
- pelvic pain (0.6% and 1.0%).

### **Differences in adverse event incidences between phase III trials**

When comparing the individual trials IPM 027 and MTN-020, higher incidences in grade 3 and 4 TEAEs ( $\sim 3$ -fold) and especially IP-related TEAE ( $\sim 18$ -fold) are found in the MTN-020 trial compared with the IPM 027 trial. The Applicant indicated that these between-trial differences are likely due to the following:

- A difference in AE reporting or differences in frequency of testing, with the exception of metrorrhagia and menorrhagia, see also the separate discussion on metrorrhagia.
- The result of the subjective assessment of causality and severity, which may be influenced by Investigator experience with Dapivirine.
- The between-trial differences regarding metrorrhagia and menorrhagia are due to differences in inclusion criteria with respect to contraception:
  - In trial IPM 027, subjects were required to be on stable contraception at enrollment, whereas in trial MTN-020, subjects could have started a contraceptive method just prior to enrollment or were allowed to *switch* contraception during the trial.
  - The incidence over time of metrorrhagia in trial MTN-020 showed that most cases occurred in the first three months when breakthrough vaginal bleeding is expected due to recent initiation of contraception or a change in contraception at enrolment.
  - Furthermore, in trial IPM 027, a new event was reported for every case of metrorrhagia, while in trial MTN-020 one event of metrorrhagia was reported starting on the date of the first episode and keeping the AE open until the last episode was reported.

- With respect to vaginal discharge, in trial IPM 027, the majority of vaginal discharges were included in the term “genital infection female”. However, in trial MTN-020, these were reported under the term that reflects the underlying etiology or, for asymptomatic abnormal vaginal discharge observed by a clinician which was found to be yeast or bacterial vaginosis and vaginal discharge reported by the participant that did not require treatment and did not yield a specific etiology, these were reported as “vaginal discharge”.

## **TEAEs of special interest**

### ***Metrorrhagia (Irregular bleeding)***

Most of the common TEAEs of interest were related to vaginal bleeding of which metrorrhagia (irregular bleeding between menses) showed the highest incidence in all three safety analysis sets (25.0% and 25.3% for the Phase I pooled analysis set, 18.6% and 19.3% in the Phase II IPM 015 trial, and 39.7% and 45.7% in the Phase III pooled analysis for the Dapivirine and placebo group respectively). The subgroup of subjects  $\leq 21$  years of age reported about 10% more events of metrorrhagia compared with subjects  $> 21$  years of age in both the Dapivirine and placebo group, which might suggest that the younger subjects did not use regular contraception or used contraception with a higher risk of irregular bleeding. Subgroup analysis with respect to baseline method of contraception showed no relevant differences in metrorrhagia events between the Dapivirine group and the placebo group in both trials. With respect to IP-related metrorrhagia, approximately similar incidences were found in the Phase III pooled analysis set (0.7% and 0.5% for Dapivirine and placebo, respectively) and also in the individual trials IPM 027 trial (0.2% and 0%) and the MTN-020 trial (1.2% and 0.7%). An analysis over time showed that most cases occurred during the first three months of treatment, which is expected since participants were not required to be on a stable contraceptive method prior enrollment and were allowed to change contraceptive method during the trial.

Despite that the Applicant presents plausible explanations regarding the occurrence of metrorrhagia being related to contraceptives, a small percentage of cases is assessed by the investigator as IP-related to the dapivirine/placebo ring. The Applicant concluded based on pre-clinical data that it is unlikely that the Dapivirine ring could affect oestrogen regulation and, consequently, could affect hormonal uterine bleeding patterns. Although the Applicant could not clarify why these metrorrhagia events were considered IP-related by the investigators, based on the information presented there are no indications suggestive for causality of the ring with the occurrence for metrorrhagia. As such, it is endorsed not to include metrorrhagia as ADR in section 4.8 of the SmPC.

### ***Sexually transmitted infections (STIs)***

The proportion of subjects with sexually transmitted infections (STIs) at any post-baseline investigation was higher in trial IPM 027 than in trial MTN-020, but within these trials, no differences were observed between the Dapivirine and placebo group. This difference is likely due to the differences in testing: in trial IPM 027, STI testing was performed 12 weekly, whereas in trial MTN-020 testing was 6 monthly. For chlamydia urogenital events, incidence and prevalence were consistent or slightly decreased over time. For gonococcal and trichomonal urogenital events, observations were similar. The most likely reason for any decrease is claimed a result of HIV/STI risk reduction counseling and regular STI testing and treatment of any STIs identified during the trials. The decrease noted is marginal but supporting that the use of a ring is not related with increased risk in STI. However, the high percentages of STI indicated that the recommendation to use the ring in combination with condom use was not adhered to.

Subgroup analysis with respect to age showed STI were more frequently reported in younger subjects ( $\leq 21$  years of age) compared with subjects  $> 21$  years of age. This difference was observed in both the

Dapivirine group and the placebo group and was already present at baseline, suggesting that younger subjects ( $\leq 21$  years of age) are less compliant to condom use.

### **Risk of Pelvic inflammatory disease (PID)**

The incidence of pelvic inflammatory disease (PID) was low (21 (1.6%) and 25 (3.8%) women in trial IPM 027 and 27 (2.1%) and 28 (2.1%) women in trial MTN 020 for the dapivirine and placebo group, respectively). There were temporary discontinuations of 3 participants (0.1%) and 5 participants (0.3%) with PID in the Dapivirine and placebo ring groups, respectively. Although the incidence of PID is low, this could well be due to efficient treatment of STI offered in both clinical trials. However, the occurrence of PID, when genital tract infections (including STI) are not immediately treated, is not known. As such, the Applicant proposes a warning in section 4.4 of the SPC that early detection and appropriate treatment of genital infection in women using the Dapivirine ring is considered important. This proposal is endorsed. Further, the proposed health care professional guide and a user guide to be alert on STI- and non-STI vaginal infections is supported.

### ***non-STI-related vulvovaginal infections***

The proportion of subjects was similar between the dapivirine and placebo ring groups for the AESI bacterial vaginosis (BV) (10.0% [261/2619] and 9.8% [193/1968], respectively), vulvovaginitis (8.6% [224/2619] and 8.7% [172/1968], respectively), genital tract candidiasis (12.0% [314/2619] and 10.4% [204/1968], respectively), and vaginal discharge (7.1% [186/2619] and 9.2% [181/1968], respectively).

The use of a vaginal ring may influence risk of non-STI-related vulvovaginal infections. This is already known for vaginal contraception ring Nuvaring®. The risk of non-STI-related vulvovaginal infections could be increased during use of vaginal ring regardless if dapivirine is included into the vaginal ring or not. Therefore, the risk of vulvovaginal infections during use of the dapivirine ring was further analysed. The applicant provided rates of abnormal Nugent Score over time from Phase III studies which is indicative of BV. According to these data the rate of abnormal Nugent Score was comparable at baseline and during study which would indicate that the rate of BV was not increased during use of vaginal ring. Additionally, the Applicant compared the baseline risk of vulvovaginal infections (non-STI-related) in regions where the Phase III studies were performed with the risk evaluated during Phase III studies. Based on this comparison it seems that the rates of non-STI-related vulvovaginal infections are explainable by documented baseline risk in respective countries. Furthermore, data from a trial to assess the impact of a vaginal ring, containing either maraviroc and/or dapivirine, used for 28 days, on vaginal microflora demonstrated that despite biofilms were present on all rings, there was no relationship between the quantity of biofilm and the IP or Nugent Score. Overall, there seems to be no increased risk of non-STI-related vulvovaginal infections when using the Dapivirine ring. Therefore, the initially proposed 'non-STI-related vulvovaginal infections' is deleted as an important potential safety concern.

### ***Vaginal Flora and pH***

The Nugent score is a gram stain scoring system for vaginal swabs to diagnose bacterial vaginoses and was used to categorize the vaginal flora:  $< 4$  reflects normal, between 4 and 6 (extremes included) altered, and  $\geq 7$  abnormal. No clinically relevant differences in abnormal vaginal flora or pH were found between both groups.

### **Urinary tract infections**

The rate of urinary tract infections was comparable between the dapivirine group and placebo ring group. An increased rate of urinary tract infection (UTI) is known for intravaginal contraception Nuvaring®. Rate of urinary tract infection could be influenced by vaginal infection or vaginal irritation after use of vaginal ring (regardless if Dapivirine Vaginal ring or placebo ring is used). Since in the Phase III studies no clean catch midstream samples were collected for urine testing and no urine culture were performed routinely to confirm diagnosis of UTI and that analysis revealed that there was a significant proportion of UTI events associated with an event of vaginal infection (ie, 15 – 20%) and less with vaginal irritation (5% only), it is not unexpected that significant proportion of UTI events was associated with events of vaginal infection taking the anatomical proximity and the partly comparable signs and symptoms of infection into account. Therefore, the true incidence is unknown but very likely much lower if clean catch midstream samples were used for testing. Additionally, it is agreed that acute uncomplicated UTI is very common in young sexually active women with normal genitourinary tracts. Overall, it can therefore be concluded that no safety signal could be identified based on the analysis provided. Nevertheless, cases of urinary tract infection were regarded as ADRs and labelled in section 4.8 of the SmPC, which is agreed upon by CHMP.

### **Vulvovaginal discomfort**

Vulvar ulceration was reported in 58 subjects (2.2%) in the dapivirine ring group and 54 subjects (2.7%) in the placebo ring group. A relationship between use of a vaginal ring and vulvar ulceration is not very likely. With respect to other AEs related to vulvovaginal discomfort, except for vaginal discharge and vulvovaginal pruritis, all other events occurred in relatively low numbers and most AEs are explainable by the reported AEs of vulvovaginal infections (STI related, non-STI related including vulvovaginal candidiasis). However, a causative role for the vaginal ring in events associated with vulvovaginal discomfort cannot be excluded.

### **Serious AEs and deaths**

Six (0.2% [6/2619]) participants died in the dapivirine group (gun shot wound, multiple injuries, stab wound (n=2), abdominal injury, pulmonary embolism) and 4 (0.2% [4/1968]) participants in the placebo ring group (circulatory collapse, stab wound, pulmonary tuberculosis, tuberculosis gastrointestinal). None of the deaths were considered to be related to the IP.

At least one serious TEAE was reported in 3.0% (79/2619) of the participants in the dapivirine ring group and 2.4% (48/1968) of the participants in the placebo ring group. None of the serious TEAEs were considered related to the IP by the Investigator. By PT, SAEs were reported in at most 0.2% (6/2619) of the participants in the dapivirine ring group and 0.1% (2/1968) of the participants in the placebo ring group.

In the Phase III trials, three cases of venous thromboembolism occurred in the dapivirine ring group (3/2619; 0.11%) and no such event in the placebo arm. None of these venous thromboembolism events was considered related to the IP. Details of the two cases reported in the IPM 027 trial support the presence of dapivirine-independent risk factors for the development of venous thromboembolism in these cases. Both participants in IPM 027 had a high BMI at time of the event, and the woman with pulmonary embolism additionally had acute HIV infection and pulmonary tuberculosis as independent risk factors. In both cases, the Investigator did not consider the SAE related to dapivirine ring use. Details regarding the case from the MTN-020 trial reveal inconclusive information, and no confirmed diagnosis of pulmonary embolism. As medical assessment resulted in the identification of dapivirine-independent risk factors in two cases, and an unconfirmed diagnosis in the third case, it is unlikely that this represents a risk related to the use of dapivirine.

## **Pregnancies**

Despite contraceptive and condom recommendations, 4.4% [114/2619] in the Dapivirine group and (5.3% [105/1968] in the placebo group became pregnant. In both groups, about 20% of pregnancies ended in a spontaneous abortion. Slightly lower live births were reported in the Dapivirine group (51.7% (62/120)) compared with the pregnant women in the placebo group (57.5% (65/113)), which is probably due to the higher incidences in therapeutic/elective abortion and missing data in the Dapivirine group. Furthermore, no major abnormalities were reported.

## **Laboratory findings**

No patterns indicative of clinically treatment related laboratory abnormalities were observed.

## **Safety in postmenarchal adolescents aged 15-17 years**

One Phase IIa, double-blind, randomized, placebo-controlled, multicenter trial performed in the US (MTN-023/IPM 030) evaluated the safety of the dapivirine vaginal ring in adolescents aged 15-17 years. In total, 73 participants received the Dapivirine Ring group and 23 the placebo ring. The Dapivirine Vaginal Ring was well tolerated in adolescent females when inserted once every 4 weeks and used continuously during 24 weeks. The type and nature of adverse events reported were similar to those reported in trials conducted in women of reproductive age 18 years and older.

## **Safety in postmenopausal women**

A Phase II trial of 12 weeks duration evaluated the safety of the Dapivirine ring in postmenopausal women (MTN-024/IPM 031) in the USA. The majority of subjects (89%) found the vaginal ring to be as acceptable as other HIV prevention methods and no clinically relevant differences in incidences in adverse events were observed (63.9% and 58.3% in the Dapivirine and placebo group, respectively). However, in comparison with the results of the Phase III pooled analysis conducted in women between 18 to 45 years of age rather higher incidences in IP-related TEAEs were observed in postmenopausal women (47.2% and 33.3% in the MTN-024/IPM 031 trial conducted in postmenopausal women versus 4.6% and 6.8% in the Phase III pooled analysis for the Dapivirine group and placebo group, respectively). Additionally, the pattern of IP-related TEAEs was different, probably due to the influence of vaginal atrophy. The most commonly reported IP-related AEs (occurring in more than 2 participants in either treatment arm) were: lower abdominal pain (4.3% and 3.1% in the Dapivirine group and placebo group, respectively), urinary tract infections (1.4% and 8.3%), vulvovaginitis (2.8% and 8.3%), vaginal discharge (11.1% and 8.3%), cervix hemorrhage uterine (5.6% and 4.2%), vaginal haemorrhage (5.6% and 0%), vaginal odor (5.6% and 0%), vulvovaginal erythema (4.2% and 12.5%), and vulvovaginal pruritus (4.2% and 4.2%). Further information provided revealed that the vaginal bleeding events reported in the post-menopausal women were actually events of ecchymosis, petechiae and spotting and were most likely related to trial procedures, rather than the Dapivirine Vaginal Ring or placebo ring, which is reassuring.

## **Discontinuations**

The Dapivirine ring appears to be well tolerated, as TEAEs leading to permanent IP discontinuations were very low; one in each group of the Phase III pooled analysis discontinued due to a TEAE not related to the IP.

The incidence of TEAEs leading to temporary IP discontinuations were also relatively low and comparable between the Dapivirine (2.9%) and the placebo (3.3%) group. In the MTN-020 trial, a higher incidence in TEAEs leading to temporary IP discontinuations (5.0% and 4.7% in the Dapivirine and the placebo group, respectively) were observed than the IPM 027 trial (0.8% and 0.5%), which was the result of a different approach for temporary discontinuation for the IPM 027 and MTN-020.

In trial IPM 027, AEs leading to temporary discontinuation were reported in at most 2 participants in

either group for any preferred term. In trial MTN-020, the most commonly reported AEs leading to temporary discontinuation were cervicitis (1.6% and 1.4%), genitourinary tract gonococcal infection (0.6% and 0.4%), and genitourinary chlamydia infection (0.5% and 0.5%) (for the Dapivirine and placebo group, respectively.)

**Male exposure**

Male tolerability of 0.05% Dapivirine gel versus placebo following multiple topical penile exposures in circumcised and uncircumcised healthy adult men in the US showed some IP-related local effects in 12.5% (3/24) application site paresthesia, increased ALT, increased AST, and sebaceous gland disorder) in the dapivirine group versus, 8.3% (1/12) in placebo gel group (application site pain), and 16.7% (2/12). However, in the phase III pooled analysis, the reporting of adverse events by male partners was low.

**Oral Dapivirine**

A detailed systematic safety analysis of the eleven Phase I/II trials of the oral clinical development program of Dapivirine have not been provided by the Applicant. However, because of the very low systemic exposure are achieved with the Dapivirine ring, the safety pattern after oral administration of dapivirine is considered not relevant.

**Safety data of trials not included in the pooled safety analysis**

Open-label studies and cross-over study evaluating the safety and acceptability to the silicone ring did not identify clinically relevant safety signals.

**2.6.2. Conclusions on the clinical safety**

The Dapivirine vaginal ring displays an acceptable safety profile comparable to that of the placebo ring with very limited subjects discontinuing treatment or showing serious adverse events. No major safety issues have been identified. Although the clinical file up to now does not indicate increased risk for pelvic inflammatory disease during use of dapivirine ring, a theoretical risk cannot be excluded. Therefore, a warning is included in the SmPC.

Limited safety data in adolescent women aged 15-17 years indicated type and nature of adverse events reported as similar to those reported in trials conducted in women of reproductive age 18 years and older.

**2.7. Risk Management Plan**

**2.7.1. Safety concerns**

The applicant proposed the summary of safety concerns in the RMP as listed below:

**Table 40      Summary of the 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 non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance in women with unrecognized or acute HIV-1 infection



Summary of safety concerns	
	Development of pelvic inflammatory disease
Missing information	Safety during pregnancy
	Safety during breast-feeding
	Long-term use beyond 24 months of treatment
	Use in sexually-active females under 18 years of age
	Local drug-drug interaction with vaginally administered clindamycin and metronidazole

### ***Discussion on safety specification***

The proposed Summary of Safety Concerns can be considered appropriate.

### ***Conclusions on the safety specification***

Having considered the data in the safety specification the CHMP agrees that the safety concerns listed by the Applicant are appropriate.

## **2.7.2. Pharmacovigilance plan *Routine pharmacovigilance activities***

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 behavior), or HIV-1 infection through a route other than vaginal sexual intercourse. The form includes requests for information on user demographics, length of time of use, date of HIV seroconversion and type of test used, sexual practices (including non vaginal intercourse, non-monogamous sex, use of condoms), adherence to continuous use of the ring, contraceptive methods used, concurrent intravaginal medicinal products and use of traditional vaginal practices (eg: herbal products).

The Applicant's proposal to use a follow-up form to obtain patient level data in the event of HIV-1 acquisition is accepted. Minor recommended additions for completeness, including whether accidental expulsion of the DPV vaginal ring occurred and type of vaginal medication used concurrent to use of DPV vaginal ring have been incorporated as requested.

It should be noted however that although the questions have been added for completeness' sake and represent the minimum threshold of pharmacovigilance intended to follow-up events of seroconversion there are significant limitations to the extent to which the form can be relied on to provide sufficient data to reliably inform the situation in the event of lack of efficacy. Being routine pharmacovigilance, this represents a passive form of data collection, being wholly reliant on the initiative for reporting from healthcare professionals, who are likely to be under significant levels of strain in the intended recipient health systems and thus may be unable to complete the form and provide such data. Additionally, the data sought via the form may not be readily available, including data on sexual behaviour. Importantly, data on resistance mutations is likely to be difficult to acquire and likely to be lacking given that in many of the intended recipient health systems, facilities to test for genotypic resistance mutations are frequently not routinely available.



Therefore, although the form has been made as complete as possible, it should be acknowledged that a significant amount of the data intended to be gathered is likely to be missing in real-world use and is unlikely to reliably inform the situation with regards to HIV-1 acquisition or resistance mutations.

The Applicant generally proposes to provide the form via several routes which include distributing the form in person, at specific events such as workshops or with product shipment. The form is also intended to be made available electronically via the dapvirine ring website. It is also noted that the strategy for distributing the form may vary dependent upon each country's local requirements, in conjunction with HIV strategic planning. Similarly, the channels for reporting may vary also. The Applicant plans to flag the need for utilising the form at the same time as highlighting the need for regular HIV testing. As stated previously, the form relies heavily on HCPs reporting in the event of a seroconversion and efforts to encourage this through sufficient distribution and awareness of the form to HCPs may improve this, although the lack of availability of data may still hinder completeness and reliability of information obtained. For example, lack of receipt of forms may not be a true indicator that no seroconversion events have occurred. The ease and reliability of returning the forms is also not known at this point, and this may have an impact on the number of forms returned. The feasibility of the form deserves careful consideration.

It is noted also that the Applicant intends to rely on the Global Evaluation of Microbicide Sensitivity (GEMS) initiative, when developed. The WHO have clarified that the GEMS initiative have funding allocated to conduct genotypic resistance testing in PrEP users who subsequently become HIV infected and this is available in Kenya, South Africa, Zimbabwe and Namibia. This could therefore be a valuable resource for resistance testing, although it is unclear at present how accessible these services will be for all DPV ring users.

The distribution of the forms varies, out of necessity, from usual practices of following-up for information after receipt of a report of an adverse reaction. Therefore, although at present no further clarity can be obtained on the intended distribution locally, the Applicant committed to actively contacting HCPs at set time frequencies, for example on a 6 monthly basis, to ascertain if cases of seroconversion were identified and remind HCPs to complete and return forms via the appropriate 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. This was included in Part V.2 of the RMP.

The Applicant has also discussed possibilities for utilising cloud- based or mobile app systems to enhance routine pharmacovigilance which are proposed to be offered free at point of care to consumers. These include a range of proposed features including reporting adverse drug reactions and lack of efficacy.

It appears at present that these systems are still in the preliminary phase and may be not be available for a length of time. It is therefore uncertain if these systems are likely to be in place at the point of commencement of marketing and general use. However, the Applicant ensures to have a fully operational, regulatory compliant Pharmacovigilance System in place, prior to first product launch in the sub Saharan African market.

The Applicant currently has an established validated global safety database for the Dapivirine Vaginal Ring. The system captures reports of serious adverse events and pregnancy cases received throughout the Dapivirine Vaginal Ring clinical development program.

Pharmacovigilance processes that are already established and currently being routinely performed include the following:

1. Signal detection and management

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2. Safety risk management
3. Expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and aggregate reporting in the annual Development Safety Update Report (DSUR)
4. Literature search activities
5. Product complaint handling and processing in collaboration with the Quality Assurance functional area
6. Maintenance of the PV System Master File (PSMF)

Acknowledging the increased scope of PV activities that will be required in a post-marketing setting and the importance of facilitating the receipt of passive reports from the markets, the Applicant has engaged numerous vendors to provide technological solutions that will provide quality, efficiency and scalability to the PV system.

The Applicant considers that a step wise approach to upscaling the current PV system is warranted given low expected case volumes of Individual Case Safety Reports (ICSRs) during the initial period after product launch. This decision is informed by the emerging favourable safety profile of the Dapivirine Vaginal Ring and the low volumes of serious adverse events reported during the clinical development program.

As a first phase, the Applicant will establish a medical contact call center service to facilitate receipt of safety reports from the intended markets in sub-Saharan Africa. This call center will allow the intake of calls from consumers or healthcare professionals (HCPs) reporting adverse events, product technical and quality complaints, usability issues, as well as triage of medical information requests. The call center contact telephone number(s) and operating hours will be included in the country specific HCP and User Guides. The call center operators will complete a reporting form based on information provided telephonically by the reporter and email the completed form to the dedicated IPM safety mailbox or use an automation platform that will export the form to the global safety database.

Additionally, a vendor hosted industry standard validated safety platform (such as Argus or ArisG), will be established for the Dapivirine Vaginal Ring global safety database in this first phase of development.

A lag time of almost 12 months between receipt of a positive CHMP Scientific Opinion until first product launch is anticipated. This is due to procedures necessary to obtain World Health Organization (WHO) prequalification, and the subsequent submission and granting of a marketing authorization in the first targeted sub-Saharan African country. Preliminary discussions with vendors have indicated an approximate 6-month period to establish the outsourced PV services outlined above. This timeframe includes the time necessary for migration of data from the current safety database to the vendor hosted safety database.

Therefore, a regulatory compliant, operational PV system will be established prior to first product launch. Should there be any unforeseen delays on the vendor side, the Applicant commits to not launching any product until the PV system is operational.

The Applicant has included reference to the call center in the RMP, Section III.1, Routine Pharmacovigilance Activities. The Applicant proposes that a full description of the implemented PV system be included in a future update to the RMP but prior to first product launch.

The Applicant recognizes the value of using data from sentinel cohorts in supporting PV activities and is in discussions with the Southern African Medical Unit of Doctors Without Borders, the Desmond Tutu HIV Centre in Cape Town, the Arum Institute, and the President's Emergency Plan for AIDS Relief (PEPFAR) Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) project in southern Africa. Additional potential partners include the International Planned Parenthood Federation and Marie Stopes

International. Discussions with funders for future demonstration and implementation studies are also ongoing. The WHO and the AIDS Vaccine Advocacy Coalition (AVAC) will also be engaged to support coordination of partners to ensure appropriate data collection.

The Applicant is committed to engaging in collaborations with any partners who have appropriate capabilities to aid in the strengthening of PV for the Dapivirine Vaginal Ring, however greater granularity in respect of planned research activities cannot be provided at this time. The Applicant commits to providing such information in future updates to the RMP in a post CHMP opinion setting.

### 2.7.2.2. Summary of planned additional PhV activities

**Table 41 Ongoing and Planned Additional Pharmacovigilance Activities**

Trial Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
<b>Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization</b>				
<i>Post-authorisation efficacy study (PAES)</i>				
Phase IV, open label, multicentre efficacy trial in healthy HIV-negative young women age 18-25 years.	<ul style="list-style-type: none"> <li>Incidence of HIV-1 infection.</li> <li>Incidence of NNRTI resistance mutations in participants with HIV-1 infection</li> </ul>	<ul style="list-style-type: none"> <li>HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use.</li> <li>Development of NNRTI resistance in women with unrecognized or acute HIV-1 infection</li> </ul>	<p>Draft protocol within 6 months of the CHMP opinion.</p> <p>Final protocol expected Q2 2021</p> <p>Study initiation expected Q2 2022</p> <p>Expected completion of trial conduct Q4 2025</p>	<p>Final CSR expected Q3 2026</p> <p>Data will be reviewed on an ongoing basis and updates provided in the PBRER as applicable.</p>
<b>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</b>				
Not applicable				
<b>Category 3 – Required additional pharmacovigilance activities</b>				
<i>Phase IIIb Open-label Extension Trials with the Dapivirine Vaginal Ring-004</i>				
<p>IPM 052 (DREAM)</p> <p>A Phase IIIb, follow-on, open-label, multicentre trial in healthy, HIV-negative, adult women who had participated in the IPM 027 trial.</p>	<ul style="list-style-type: none"> <li>To assess the safety and acceptability of, and adherence to the Dapivirine Vaginal Ring (25 mg dapivirine), when inserted at monthly intervals.</li> <li>Assess the incidence of HIV-1 seroconversion.</li> </ul>	<ul style="list-style-type: none"> <li>HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use.</li> <li>Development of NNRTI resistance in women with unrecognized or acute HIV-1 infection</li> <li>Development of PID</li> <li>Long-term use beyond 24 months of treatment in a subset of women</li> </ul>	<p>Conduct of trial was completed on 11 January 2019</p> <p>Clinical database locked on 12 April 2019</p>	<p>Final CSR Q2 2020</p> <p>Addendum to CSR expected Q4 2020</p>
<p>MTN-025 (HOPE)</p> <p>A Phase IIIb, follow-on, open-label, multicentre trial in healthy HIV-negative, adult women who had</p>	<ul style="list-style-type: none"> <li>To assess the safety and acceptability of, and adherence to the Dapivirine Vaginal Ring (25 mg</li> </ul>	<ul style="list-style-type: none"> <li>HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from</li> </ul>	<p>Conduct of trial completed on 10 October 2018</p>	<p>Final CSR Q2 2020</p>

<b>Trial Status</b>	<b>Summary of objectives</b>	<b>Safety concerns addressed</b>	<b>Milestones</b>	<b>Due dates</b>
participated in the MTN-020 trial.	dapivirine), when inserted at monthly intervals. <ul style="list-style-type: none"> <li>Assess the incidence of HIV-1 seroconversion.</li> </ul>	non-adherence to ring use <ul style="list-style-type: none"> <li>Development of NNRTI resistance in women with unrecognized or acute HIV-1 infection</li> <li>Development of PID</li> </ul>	Clinical database lock planned for mid-June 2019	Addendum to CSR expected Q4 2020
<i>Long-term Observational Cohort Studies</i>				
<b>IPM 007</b> A long-term observational cohort study of women following HIV-1 seroconversion in IPM trials with the Dapivirine Vaginal Ring.	<ul style="list-style-type: none"> <li>To assess progression of HIV infection and treatment outcomes in participants who had used the Dapivirine Vaginal Ring in the trials IPM 027 and IPM 032.</li> </ul>	<ul style="list-style-type: none"> <li>Assess the impact of the development of NNRTI resistance in women with unrecognized or acute HIV-1 infection in the parent trials</li> </ul>	Completion of clinical conduct expected Q2 2019	Final CSR Q2 2020  Addendum to CSR expected Q4 2020
<b>MTN-015</b> A long-term observational cohort study of women following HIV-1 seroconversion in MTN trials with the Dapivirine Vaginal Ring.	<ul style="list-style-type: none"> <li>To assess progression of HIV infection and treatment outcomes in participants who had used the Dapivirine Vaginal Ring in the trials MTN-020 and MTN-025.</li> </ul>	<ul style="list-style-type: none"> <li>Assess the impact of the development of NNRTI resistance in women with unrecognized or acute HIV-1 infection in the parent trials</li> </ul>	Completion of clinical conduct of former MTN-020 and MTN-025 participants expected Q2 2019	Summary Report of former MTN-020 and MTN-025 participants Q2 2020  Addendum to Summary Report expected Q4 2020
<i>Safety During Pregnancy and Breastfeeding</i>				
<b>MTN-029/IPM 039 CSR</b> A Phase I, open-label, multicentre trial in healthy, HIV-negative adult women 18 years of age or older at least 6 weeks postpartum, and able to produce milk.	<ul style="list-style-type: none"> <li>To assess the pharmacokinetics of the Dapivirine Vaginal Ring (25 mg dapivirine) used for 14 days in lactating but not breastfeeding women.</li> </ul>	<ul style="list-style-type: none"> <li>Safety during breastfeeding</li> </ul>	CSR finalized on 25 May 2018	Not applicable
<b>MTN-016 (EMBRACE)</b>	<ul style="list-style-type: none"> <li>To compare adverse pregnancy and delivery outcomes, and the prevalence of major malformations identified in the first year of life between participant mothers assigned to an active agent with those assigned to placebo/control.</li> </ul>	<ul style="list-style-type: none"> <li>Safety during pregnancy</li> </ul>	Last follow up of infant born to a participant from MTN-025 in Q2 2020	Summary report of MTN-020 and MTN-025 participants expected Q4 2020

Trial Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	<ul style="list-style-type: none"> <li>To compare growth parameters in the first year of life between infants of mothers assigned to an active agent with those of infants from mothers assigned to placebo/control</li> <li>To evaluate the prevalence and persistence of HIV drug resistance mutations in plasma among HIV infected infants.</li> </ul>			
MTN-042 (DELIVER) Phase IIIa, randomized, open-label safety and pharmacokinetic trial of Dapivirine Vaginal Ring and oral TDF/FTC tablet use in pregnancy.	<ul style="list-style-type: none"> <li>Safety and pharmacokinetics of the Dapivirine Vaginal Ring and oral TDF/FTC tablet when used during pregnancy at different stages of gestation.</li> </ul>	<ul style="list-style-type: none"> <li>Safety during pregnancy</li> </ul>	Final Protocol available Trial initiation 09 January 2020 Trial conduct expected to be completed Q3 2023	Final CSR expected Q2 2024
MTN-043 (B-PROTECTED) Open-label, pharmacokinetic, mother-infant pair trial of Dapivirine Vaginal Ring use during breastfeeding.	<ul style="list-style-type: none"> <li>To assess the pharmacokinetics and safety of the Dapivirine Vaginal Ring in breastfeeding women.</li> </ul>	<ul style="list-style-type: none"> <li>Safety during breastfeeding</li> </ul>	Final Protocol available Trial initiation expected Q2 2020 Trial conduct expected to be completed Q4 2021	Final CSR expected Q2 2022
<i>Safety in a Younger Female Population</i>				
MTN-023/IPM 030 CSR A Phase IIa, double-blind, randomized, placebo-controlled, multicentre trial in healthy, HIV-negative, sexually experienced adolescent females between 15 and 17 years of age	<ul style="list-style-type: none"> <li>To assess the safety and acceptability of, and adherence to the Dapivirine Vaginal Ring (25 mg dapivirine) when inserted once every 4 weeks for a 24 week use period.</li> </ul>	<ul style="list-style-type: none"> <li>Use in sexually-active females under 18 years of age.</li> </ul>	CSR finalized on 08 June 2018	Not applicable
MTN-034 (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,	<ul style="list-style-type: none"> <li>To evaluate the safety and acceptability of, and adherence to the Dapivirine Vaginal Ring (25 mg</li> </ul>	<ul style="list-style-type: none"> <li>HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to</li> </ul>	Trial initiated 14 January 2019 Trial conduct expected to be	Final CSR expected Q3 2022

<b>Trial Status</b>	<b>Summary of objectives</b>	<b>Safety concerns addressed</b>	<b>Milestones</b>	<b>Due dates</b>
sexually-active adolescent and young adult female population 16 to 21 years of age	dapivirine) and oral PrEP (TDF/FTC), as well as the preference for either trial product over a 12-month period.	ring use in younger women. <ul style="list-style-type: none"> <li>Use in sexually-active females under 18 years of age.</li> </ul>	completed end Q4 2021	
CSR = clinical study report; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; MTN = Microbicide Trials Network; NNRTI = non-nucleoside reverse transcriptase inhibitor; PID = pelvic inflammatory disease; PrEP = pre-exposure prophylaxis; TDF = tenofovir disoproxil fumarate				

#### Currently proposed additional PhV measures

There is one imposed Category 1 Post-Authorisation Efficacy Study (PAES). It is planned to be conducted in women 18-25 years of age (stratified for 18 to 21 years and > 21 to 25 years) to address the current uncertainty in the efficacy in younger women, and to confirm the overall effect size by establishing an appropriate counterfactual, as well as to systematically collect information on NNRTI resistance in seroconverters. Several study designs are under consideration, a draft protocol will be submitted for review within 6 months of the CHMP opinion, with a final protocol expected in Q2 2021. The study is anticipated to start in Q2 2022 and a CSR for this study is expected to be available in Q3 2026.

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

#### Long-term safety data

Data collected from the two open-label extension trials, IPM 032 and MTN-025, will be analysed to provide further insight in terms of the HIV-1 risk reduction offered by the Dapivirine Vaginal Ring-004 in order to further characterize the important identified risk of HIV-1 acquisition during vaginal sexual intercourse, including HIV-1 infection resulting from non-adherence to ring use.

The two multicentre trials are designed to collect additional safety data, further assess acceptability of and adherence to the Dapivirine Vaginal Ring-004 use, as well as the incidence of HIV-1 seroconversion and the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection. These trials will also provide additional information on the observed frequency and, where applicable, changes in severity of the important potential risks identified, namely the development of NNRTI resistance in women with unrecognized or acute HIV-1 infection, and development of PID. In addition, HIV-negative women who had received the Dapivirine Vaginal Ring-004 in trial IPM 027 and rolled over into the open-label extension trial (IPM 032) without interruption of treatment will allow for the collection of long-term (beyond 24 months) Dapivirine Vaginal Ring-004 use data. A total of 2397 former IPM 027 and MTN-020 adult women have been enrolled in IPM 032 and MTN-025, respectively. The first participant first visit for the IPM 032 trial was on 13 July 2016, and for MTN-025 trial on 18 July 2016. Trial conduct was concluded during Q4 2018 for the MTN-025 trial and Q1 2019 for the IPM 032 trial. The results of next generation sequencing and phenotype susceptibility testing for IPM 032 and MTN-025 will be provided in an addendum to the CSRs as a post-authorisation measure and is anticipated to be available in Q4 2020.

Participants who seroconverted during the IPM 027 trial and who seroconvert during the follow-up trial, IPM 032, can enrol in the long-term observational cohort study, IPM 007. Similarly, the long-term observational cohort study, MTN-015, includes women who seroconverted during the MTN-020 trial and follow-up trial, MTN-025, among other clinical trials conducted by MTN. Information from these two long-

term follow-up observational cohort studies, will provide data on the potential impact of exposure to dapivirine at the time of HIV-1 infection on disease progression (as observed by changes in CD4 count after enrolment; reported HIV-related and AIDS-defining clinical events), as well as monitor participant response to ART.

The number of participants in these two long-term follow-up observational cohort studies is dependent upon the number of HIV seroconverters in the IPM and MTN parent trials, although MTN-015 described power calculations for the primary endpoint based on an anticipated 120 seroconverters.

Data collection for IPM 007 was initiated at the time of first participant first visit on 04 October 2012, and study conduct is expected to be concluded by end of Q2 2019. A final CSR is expected to be available Q2 2020.

Preliminary data from the MTN-015 study was recently published. Analyses of longitudinal outcomes of women who became infected during participation in the MTN-020 trial, and who had at least 6 months of post ARV treatment follow-up, indicated that virologic outcomes, (time to virologic suppression and the rate of virologic failure), were not different among former Dapivirine Vaginal Ring-004 users compared to placebo ring users in MTN-020.

Since clinical conduct of MTN-025 was concluded in Q4 2018, and the last participant last visit in MTN-015 is anticipated to be 30 June 2019, a summary report of longitudinal outcomes of all former MTN-020 and MTN-025 participants who seroconverted and who enrolled in MTN-015, is expected in Q2 2020.

The results of population based genotype resistance testing and the results of next generation sequencing and phenotype susceptibility testing will be provided in an addendum to the report for IPM 007, anticipated to be available in Q4 2020.

#### Exposure during pregnancy and breastfeeding, infant-follow-up

Missing information on the safety of Dapivirine Vaginal Ring use during pregnancy will be assessed by data collected in the planned MTN-042 trial. The protocol for this planned Phase IIIa, randomized, open-label safety and pharmacokinetic trial of Dapivirine Vaginal Ring and oral TDF/FTC tablet use in pregnancy is under development. The draft protocol describes a four-cohort, open-label trial with a 2:1 randomization ratio (Dapivirine Vaginal Ring: oral TDF/FTC tablet) that will use a step-wise reverse gestational age study schema with dosing occurring within pre-defined gestational age ranges. The rationale for the use of this schema is that the lowest risk associated with dapivirine use would be anticipated later in pregnancy, well after organogenesis is complete. The entire trial will enroll approximately 750 healthy, HIV-negative women 18 to 45 years of age across the gestational age ranges. Approximately 150 women at 36 to 37 weeks of gestation will be enrolled first and followed through delivery with an interim safety review performed prior to enrollment of the next gestational age range. This trial was initiated on 09 January 2020 with conduct of the clinical trial expected to be completed in Q3 2023.

In addition to the planned safety in pregnancy study (MTN-042 trial), women who have been exposed to the Dapivirine Vaginal Ring-004 or the placebo ring in the MTN-020 and MTN-025 trials and who became pregnant, and the infants resulting from these pregnancies are offered enrollment in the MTN-016 (EMBRACE) study, a prospective observational cohort investigation. However, it should be noted that similar to MTN-015 (the seroconverter registry study) this protocol is not specific to participants who have been exposed to dapivirine, rather any participants exposed to any of the HIV prevention agents studied in trials conducted by MTN can be enrolled. Study objectives include a comparison of adverse pregnancy and delivery outcomes, and the prevalence of major malformations identified in the offspring (to the first year of life) of participant mothers assigned to an active agent, with those assigned to placebo/control. Secondary study objectives include a comparison of growth parameters in the first year of life between infants of mothers assigned to an active agent with those of infants from mothers



assigned to placebo/control. Additionally, if applicable, the prevalence and persistence of HIV drug resistance mutations in plasma among HIV-infected infants will be evaluated.

Anticipated completion of follow up of the last infant born to a participant from the MTN-025 trial who enrolled in MTN-016 was in Q2 2020. A summary report of all MTN-020 and MTN-025 pregnancy outcomes is expected in Q4 2020.

To address missing information in respect of use of the Dapivirine Vaginal Ring-004 in breastfeeding women, a trial was conducted in healthy, HIV-negative adult women, 18 years of age or older at least 6 weeks postpartum and able to produce breast milk, but who were not breastfeeding (MTN-029/IPM 039 CSR). This trial was completed after the data lock point of this RMP, and enrolled 16 lactating women. A final CSR was available on 25 May 2018.

Additionally, a planned open-label, pharmacokinetic, mother-infant pair trial (MTN-043/IPM 051) of Dapivirine Vaginal Ring use during breastfeeding, is in development. This trial aims to enroll approximately 100 healthy, HIV-negative, breastfeeding women and their healthy infants (6 to 12 weeks of age). The women will receive the Dapivirine Vaginal Ring to be replaced each month for 12 weeks. Pharmacokinetics will be assessed by analysis of maternal serum and milk drug concentrations, as well as infant serum drug levels. In addition, acceptability of and adherence to the Dapivirine Vaginal Ring will be assessed. The trial is planned to be initiated in Q2 2020 with trial conduct expected to be completed by Q4 2021.

#### *Safety in adolescents*

To further characterize the safety, tolerability, and adherence in a population of younger women, a Phase IIa crossover trial to directly compare the safety of and adherence to the Dapivirine Vaginal Ring (25 mg dapivirine) with oral PrEP (TDF/FTC) in a healthy, HIV-negative, sexually-active adolescent and young African adult female population 16 to 21 years of age was initiated on 29 January 2019. This trial, MTN-034 (REACH), will be conducted by MTN under the regulatory sponsorship of NIH/NIAID/DAIDS. Approximately 250 participants are now expected to be enrolled, instead of 300 originally planned, due to challenges of continuing study enrolment during the COVID-19 pandemic. This trial will collect information on the safety and acceptability of, and adherence to the Dapivirine Vaginal Ring (25 mg dapivirine) and oral PrEP (TDF/FTC), as well as the preference for either trial product over a 12-month period. The trial will also explore whether biological or physiological factors affect product efficacy or HIV susceptibility in this age group. IPM will have full access to the data (and CSR), and this information will be used to address the missing information about Dapivirine Vaginal Ring use in sexually-active females under 18 years of age. Trial conduct is expected to be concluded during Q4 2021.

#### ***2.7.2.3. Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures***

In addition to the additional risk minimisation measures (aRMMs) proposed, the effectiveness of the aRMMs should also be evaluated. Therefore, the Applicant also outlined methods to gather data on process outcomes i.e. evaluate the extent to which the distribution of the material has been executed as planned by using appropriate implementation metrics.

It is noted that the Applicant intends to use healthcare professional surveys to help understand any knowledge gaps in user knowledge as part of the measures to gather data on effectiveness of aRMMs. While this is endorsed, the Applicant provided the timelines for when the healthcare professionals will be contacted: HCP surveys will be undertaken 12 months following initial after product launch and periodically thereafter at a frequency no less than every 6 -12 months afterwards. For the User Guide 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.

In order to track distribution of the User Guide, a log is proposed to be maintained at the main pharmacy where the product will be dispensed. This log will provide correlation between the number of unique prescriptions and number of User Guides provided to women who intend to use the Dapivirine Vaginal Ring. It is expected that there should be 100% correlation between the number of new unique prescriptions issued and User Guides issued, unless a reason is documented for cases when receipt of the User Guide was declined.

These measures/ studies to evaluate the effectiveness of aRMMs, along with the appropriate milestones, are reflected in the PV plan.

#### ***2.7.2.4. Studies and other activities completed since last update of PhV Plan***

Not applicable.

#### ***2.7.2.5. Overall conclusions on the PhV Plan***

The CHMP having considered the data submitted, is of the opinion that there are currently no outstanding issues regarding the RMP and that a post-authorisation PhV development plan is required.

Measures / studies to evaluate the effectiveness of aRMMs, along with the appropriate milestones, are reflected in the PV plan.

## 2.7.3 Risk minimisation measures

**Table 42 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	<p>Routine risk communication:</p> <p><i>Prescribing Information (Summary of Product Characteristics), Sections 4.2 and 4.4.</i></p> <p><i>Patient Information Leaflet, Sections 1, 2 and 3.</i></p> <p>Additional risk minimisation measures:</p> <p><i>Healthcare Professional Guide (country-specific)</i></p> <p><i>User Guide (country-specific)</i></p>	<p>Routine pharmacovigilance beyond adverse event reporting and signal detection</p> <p><i>Specific questionnaire for follow-up of "lack of efficacy" reports</i></p> <p>Additional pharmacovigilance activities:</p> <p>IPM 032 (DREAM)</p> <p><i>A Phase IIIb, follow-on, open-label trial in healthy, HIV-negative women who had participated in the IPM 027 trial. Summary report available. Final CSR expected Q2 2020.</i></p> <p>MTN-025 (HOPE)</p> <p><i>A Phase IIIb, follow-on, open-label trial in healthy, HIV-negative women who had participated in the MTN-020 trial.. Final CSR expected Q2 2020.</i></p> <p>PAES</p> <p><i>Phase IV, open label, multicentre efficacy trial in healthy HIV-negative young women age 18-25 years. CSR expected Q3 2026.</i></p>
Development of NNRTI resistance in women with unrecognized or acute HIV-1 infection	<p>Routine risk communication:</p> <p><i>Prescribing Information (Summary of Product Characteristics), Section 4.4.</i></p> <p><i>Patient Information Leaflet, Section 2.</i></p> <p>Additional risk minimisation measures:</p> <p><i>Healthcare Professional Guide (country-specific)</i></p> <p><i>User Guide (country-specific)</i></p>	<p>Additional pharmacovigilance activities:</p> <p>IPM 007</p> <p><i>A long-term observational cohort study of women following HIV-1 seroconversion in IPM studies with the Dapivirine Vaginal Ring. Final CSR Q2 2020. Addendum to CSR expected Q4 2020.</i></p> <p>MTN-015</p> <p><i>A long-term observational cohort study of women following HIV-1 seroconversion in MTN trials with the Dapivirine Vaginal Ring. Final report Q2 2020. Addendum to report expected Q4 2020.</i></p> <p>IPM 032 (DREAM)</p> <p><i>A Phase IIIb, follow-on, open-label trial in healthy, HIV-negative women who had participated in the IPM 027 trial. Final CSR Q2 2020. Addendum to CSR expected Q4 2020.</i></p> <p>MTN-025 (HOPE)</p>

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		<p><i>A Phase IIIb, follow-on, open-label trial in healthy, HIV-negative women who had participated in the MTN-020 trial.</i> Final CSR Q2 2020.</p> <p><i>Addendum to CSR expected Q4 2020.</i></p> <p>PAES</p> <p><i>Phase IV, open label, multicentre efficacy trial in healthy HIV-negative young women age 18-25 years.</i> CSR expected Q3 2026.</p>
Development of PID	<p>Routine risk communication: <i>Prescribing Information (Summary of Product Characteristics), Section 4.4.</i> <i>Patient Information Leaflet, Section 2.</i></p> <p>Additional risk minimisation measures: <i>Healthcare Professional Guide (country-specific)</i> <i>User Guide (country-specific)</i></p>	<p>Additional pharmacovigilance activities</p> <p>IPM 032 (DREAM)</p> <p><i>A Phase IIIb, follow-on, open-label trial in healthy, HIV-negative women who had participated in the IPM 027 trial.</i> Final CSR Q2 2020.</p> <p>MTN-025 (HOPE)</p> <p><i>A Phase IIIb, follow-on, open-label trial in healthy, HIV-negative women who had participated in the MTN-020 trial.</i> Final CSR Q2 2020.</p>
Safety during pregnancy	<p>Routine risk communication: <i>Prescribing Information (Summary of Product Characteristics), Section 4.6.</i> <i>Patient Information Leaflet, Section 2.</i></p> <p>Additional risk minimisation measures: <i>Healthcare Professional Guide (country-specific)</i> <i>User Guide (country-specific)</i></p>	<p>Additional pharmacovigilance activities:</p> <p>MTN-016 (EMBRACE)</p> <p><i>HIV Prevention Agent Pregnancy Exposure Registry: Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure.</i> Last follow up of infant born to MTN-025 participant in Q2 2020.</p> <p><i>Summary report of former MTN-020 and MTN-025 participants pregnancy and infant outcomes expected Q4 2020.</i></p> <p>MTN-042 (DELIVER)</p> <p><i>Phase IIIb, randomized, open-label safety and pharmacokinetic trial of Dapivirine Vaginal Ring and oral tenofovir disoproxil fumarate (TDF)/FTC tablet use in pregnancy.</i> Trial initiation 09 January 2020. Trial conduct expected to be completed by Q3 2023. Final CSR expected Q2 2024.</p>
Safety during breastfeeding	<p>Routine risk communication: <i>Prescribing Information (Summary of Product Characteristics), Section 4.6.</i> <i>Patient Information Leaflet, Section 2.</i></p> <p>Additional risk minimisation measures: <i>Healthcare Professional Guide (country-specific)</i></p>	<p>Additional pharmacovigilance activities</p> <p>Planned trial in breastfeeding women MTN-043 (B-PROTECTED)</p> <p><i>A Phase IIIb, open-label, pharmacokinetic, mother-infant pair trial of Dapivirine Vaginal Ring use during breastfeeding.</i></p>

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	<i>User Guide (country-specific)</i>	<i>Trial initiation expected Q2 2020. Trial conduct expected to be completed Q4 2021. Final CSR expected Q2 2022.</i>
Long-term use beyond 24 months of treatment	Routine risk communication: None	Additional pharmacovigilance activities IPM 032 (DREAM) <i>A Phase IIIb, follow-on, open-label trial in healthy, HIV-negative women who had participated in the IPM 027 trial. Final CSR Q2 2020.</i>
Use in sexually-active females under 18 years of age	Routine risk communication: <i>Prescribing Information (Summary of Product Characteristics), Sections 4.1, 4.2, and 5.1. Patient Information Leaflet, Section 2.</i>	Additional pharmacovigilance activities MTN-034 (REACH) <i>A Phase IIa crossover trial of the Dapivirine Vaginal Ring (25 mg dapivirine) and oral pre-exposure prophylaxis (TDF/FTC) in an adolescent and young adult female population. Trial initiation 14 January 2019. Trial conduct expected to be completed end Q4 2021. Final CSR expected Q3 2022.</i>
Local drug-drug interaction with vaginally administered clindamycin and metronidazole	Routine risk communication: <i>Prescribing Information (Summary of Product Characteristics), Section 4.5. Patient Information Leaflet, Section 2.</i> Additional risk minimisation measures: <i>Healthcare Professional Guide (country-specific) User Guide (country-specific)</i>	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		

Two forms of additional risk minimisation measures are proposed, a healthcare professional guide and a user guide. Key messages for inclusion in both the guides are provided in Annex 6 of the RMP.

#### HCP Guide

The HCP guide will include the following key points to support 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 one 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 well 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 and lactation 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.

The HCP guide is proposed to minimize all safety concerns apart from “Long term use beyond 24 months of treatment” and “Use in sexually active females under 18 years of age”. As the safety concerns of “Development of non-sexually transmitted vulvovaginal infections” and “Increased risk of urinary tract infections due to a higher incidence of vaginal infection or vaginal irritation” were removed from the list of Safety Concerns, it was recommended that reference to non-STI vulvovaginal infections and urinary tract infections in the Healthcare Professional Guide should also be removed. The Guide was modified sufficiently to provide advice on minimising the risk of pelvic inflammatory disease in order to ensure early identification and treatment.

#### User guide

The user guide is intended to provide guidance to the user on use the Dapivirine Vaginal Ring. Key messages are included concerning the need for adherence, the importance of combined use with safer sex practices, recommendations to avoid vaginal practices and recommendations to seek advice from a HCP if the user is pregnant or breast-feeding, may be pregnant or plans to have a baby. The Applicant has also included messages recommended for inclusion previously.

The Applicant has incorporated pictorial descriptions for some of the messages in the User Guide, including on correct insertion of the ring, removal and disposal. Illustrations used to describe avoidance of UTI were deleted. The use of pictorial/ illustrated descriptions was considered important due to variations in literacy and reading ability, and this was acknowledged by the Applicant. As such it is considered that the degree to which illustration is used in the explanation of the key messages was increased to be made more readily understood by Users who may have a lower literacy level.

Illustrations were also provided for the symptoms of HIV. Efforts were made to find culturally appropriate illustrations that can be understood locally.

The Applicant also performed User testing on the material in the areas where the Ring will be provided as there can be a risk of misinterpreting images.

The User guide is proposed to minimize all safety concerns apart from “Long term use beyond 24 months of treatment”, “Use in sexually active females under 18 years of age”. The safety concerns of



“Development of non-sexually transmitted vulvovaginal infections” and “Increased risk of urinary tract infections due to a higher incidence of vaginal infection or vaginal irritation” have been removed from the list of Safety Concerns, as there is no increased risk for these conditions when using the Dapivirine ring. However, in order to prevent PID, which is a complication of an STI or a non-STI vaginal infection, it is recommended to focus on symptoms of STI and Non-STI vulvovaginal infections. Reference to urinary tract Infections in the User Guides has been removed. The Guide was modified sufficiently to provide advice on minimising the risk of pelvic inflammatory disease in order to ensure early identification and treatment. 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.

#### Distribution of materials

It is acknowledged that distribution of educational materials will differ depending on the individual country the Ring is being used. The Applicant has provided a range of routes that is anticipated to be used for dissemination of the material. This includes providing material to HCPs and users during workshops and product demonstration sessions which will be run in collaboration with NGOs.

They also anticipate providing the materials with product shipment, which may be beneficial as it will enable HCPs to receive the material and disseminate it to Users as well.

It is noted the feasibility of these materials in the intended healthcare setting requires careful consideration.

#### Discussion on adherence

The Applicant was requested to discuss the feasibility of extending adherence measures such as those used to support research staff and study participants to support healthcare professionals and users of the marketed product.

The Applicant has reconsidered the use of the Adherence Wheel as part of the additional Risk Minimization Materials. The Adherence Wheel was a visual tool to assist research center teams to message dapivirine residual drug levels in used rings. Since no dapivirine residual levels will be available in a post-marketing setting, the Adherence Wheel will have limited utility and will not be implemented.

The Applicant has also proposed to share counselling advice for HCPs during educational workshops or road shows.

For users, the Applicant is proposing age- specific workshop for young women to enable them to share strategies and motivation for adherence to the ring. Specific counselling sessions are also proposed. These are considered appropriate measures and were included in the RMP. A mobile Application is being explored also, however at present this seems exploratory.

Items such as wristbands and T-shirts were used during the pivotal studies to help with adherence. Use of bracelets, wristbands or key-rings as suggested by the Applicant could be an effective method of promoting adherence, however there is a risk the use of these items could be used purely to promote use of the Ring, rather than promoting correct use of the ring or adherence.

The Applicant has reconsidered its current position on the use of items such as bracelets, wristbands and key rings to promote consistent ring use. As these items will be governed by the in-country regulations and guidelines concerning patient facing items and materials which may be considered promotional in nature, the Applicant considers it premature to provide a detailed elaboration at this time. If any items to promote adherence are to be developed in the future, the Applicant will consider designing them to be discreet visual reminders, with targeted messaging to promote consistent ring use. Details on how they will be utilized, will be included in future updates to the RMP.

The Applicant is also proposing to present information about microbiocides at healthcare facilities or NGO organised health education workshops, however it is anticipated this will involve promotion of use of the Ring, rather than promotion of adherence to the Ring for existing users.

Proposals to use a leaflet to describe low systemic absorption of dapivirine and using Phase III study results to promote adherence are considered less helpful, although they may be useful in a counselling or workshop context. These do not require inclusion as additional Risk Minimisation.

### **2.7.3. Assessment of effectiveness**

#### HCP guide

"Lack of efficacy" information will be collected using routine PV activities and followed-up with a specific questionnaire. Data from the questionnaire will be analyzed on a regular basis, considering the number of "lack of efficacy" reports over time and suspected reasons for lack of efficacy.

#### User guide

In a quarterly period or at visits in between the prescriber will confirm the user's understanding of correct product. "Lack of efficacy" information will be collected using routine PV activities and followed-up with a specific questionnaire. Data from the questionnaire will be analyzed on a regular basis, considering the number of "Lack of efficacy" reports over time and suspected reasons for lack of efficacy.

Measures / studies to evaluate the effectiveness of aRMMs, along with the appropriate milestones, are reflected in the PV plan.

### **2.7.4. Conclusions on risk minimisation measures**

The CHMP, having considered the data submitted, is of the opinion that there are currently no outstanding issues regarding the RMP.

### **2.7.5. Plans for post-authorisation efficacy studies**

A Category 1 PAES has been imposed to address the current uncertainties in the efficacy in younger women and to confirm the overall effect size by establishing an appropriate counterfactual as well as to systematically collect information about NNRTI resistance in seroconverters (Table 43). This study will enrol HIV-negative women, 18-25 years old, stratified for 18 to 21 years and > 21 years to 25 years. Several study designs are under consideration. A draft protocol will be submitted for review within 6 months of the CHMP opinion. The study protocol is expected to be finalised in Q2 2021 and the study is expected to be initiated in Q2 2022, given the complexities of setting up a large number of trial sites across several sub-Saharan African countries. A final CSR is expected by Q3 2026.



**Table 43**      **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
PAES Phase IV, open label, multicentre efficacy trial in healthy HIV-negative young women age 18-25 years. (planned)	Incidence of HIV-1 infection.  Incidence of NNRTI resistance mutations in participants with HIV-1 infection.	Efficacy in younger women 18-25 years of age	Draft protocol within 6 months of the CHMP opinion  Final protocol expected Q2 2021  Study initiation expected Q2 2022  Expected completion of trial conduct Q4 2025	Final CSR Q3 2026

## 2.7.6. "Summary of activities in the risk management plan by medicinal product"

### 2.7.6.1. *Dapivirine Vaginal Ring*

The Applicant has modified the language, as such Part VI Summary of the RMP has been re-written and revised to remove scientific terminology, use simple, lay, and validated language to ensure all women understand how to properly use the product. This revision also includes Section II. A "List of Important Risks and Missing Information". These safety concerns are now explained using a language more appropriate for a lay reader, similar to that used in the Patient Information Leaflet. The Public Summary has been modified and includes a lay summary of the additional RMMs planned, such as the User Guide and Healthcare Professional Guide.

### 2.7.6.2. *Summary of safety concerns*

The language used in the Public Summary has been revised as recommended.

### 2.7.6.3. *Overall conclusions on Public Summary*

The language used in the Public Summary has been revised as recommended. The Public Summary has been modified and includes a lay summary of the additional RMMs planned, such as the User Guide and Healthcare Professional Guide.

## 2.7.7. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.6 is acceptable.

## **2.8. Pharmacovigilance**

### ***Pharmacovigilance system***

The CHMP considered that the pharmacovigilance system summary submitted by the applicant are in line with the requirements of Article 8(3) of Directive 2001/83/EC.

### ***Periodic Safety Update Reports submission requirements***

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on 23 July 2020. Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every year until otherwise agreed by the CHMP.

## **2.9. Product information**

### **2.9.1. User consultation**

A User testing of the Package Leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

## 3. Benefit-Risk Balance

### 3.1. Therapeutic Context

#### 3.1.1. Disease or condition

The following indication was claimed for Dapivirine Vaginal Ring-004 at the start of the procedure:

*The Dapivirine Vaginal Ring is indicated for reducing the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-uninfected women 18 years and older in combination with safer sex practices.*

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

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

#### 3.1.2. Available therapies and unmet medical need

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

Oral PrEP: The World Health Organization (WHO) recommends that PrEP should be offered as an additional prevention choice to people at substantial risk of acquiring HIV infection. To date, only oral tenofovir disoproxil (TDF) + emtricitabine (FTC) are approved to be used as PrEP for the prevention of HIV-1 infection. Daily oral PrEP with TDF alone or in combination with FTC has been shown to reduce the risk of acquisition of HIV-1 infection by  $\geq 50\%$  in several high-risk populations. While initial efficacy trial results in women at high risk of HIV-acquisition due to heterosexual intercourse did not show consistent results, pooled data from 6 randomised studies have shown a risk reduction of 57% (95% CI 0.34–0.94;  $P = 0.03$ ) for women. The effectiveness of PrEP among women in four trials that included both women and men was higher. For example, among women younger than 30 years in a trial that included both men and women, the effectiveness was 72% (95% CI: 29–92%,  $P = 0.01$ ) for TDF and 77% (95% CI: 25–90%,  $P = 0.01$ ) for FTC + TDF PrEP (Baeten et al., N Engl J Med. 2012 Aug 02;367(5):399-410).

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

- Condoms – if used consistently rates of protection of HIV-negative partners were as high as 80%. However, for different reasons condoms are often not used (e.g. due to perceived decrease in sexual enjoyment or cultural and gender-based norms) despite HIV prevention counselling and provision of male or female condoms.
- VMMC - Male circumcision was found to reduce the female-to-male sexual transmission of HIV by approximately 60% among men in sub-Saharan Africa.
- TasP - In HIV-discordant couples, the control of viral load through effective ARV therapy of HIV-infected individuals has been shown to reduce the transmission of HIV to their uninfected partners by 96% (study HPTN 052).

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

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

The Dapivirine Vaginal Ring-004 was developed as a female-initiated option to reduce the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-1 negative women. The ring is recommended by the applicant to be continuously worn into the vagina for a period of 28 days, after which it should be replaced with a new ring. The Dapivirine Vaginal Ring-004 is intended for use by women as a complementary prevention approach to safer sex practices.

### 3.1.3. Main clinical studies

The main studies for the evaluation of the efficacy profile of the Dapivirine Vaginal Ring-004 in reducing the risk of HIV-1 infection via vaginal intercourse in sexually active HIV-1 negative women in combination with safer sex practices, are the two Phase III trials IPM 027 and MTN-020.

Study **IPM 027** is a Phase III, multi-center, randomized, double-blind, placebo-controlled study, conducted to assess the safety and efficacy of Dapivirine Vaginal Ring-004 when inserted once every 4 weeks in healthy, HIV-negative women. IPM 027 was conducted at seven research centers, six research centers were located in South Africa and one research center in Uganda. Eligible subjects were randomized in a 2:1 ratio to either the Dapivirine Vaginal Ring-004 or placebo ring group. A total of 1959 subjects were enrolled, 1307 were randomized to the dapivirine group and 652 to the placebo group. The duration of ring use during the study was planned to be 24 months. The primary efficacy (and safety) analysis of IPM 027 was performed based on a data cut-off date of 16 October 2015 and not on the per-protocol-defined completion of the trial.

Study **MTN-020** is a Phase III, multi-center, randomized, double-blind, placebo-controlled study, conducted to assess the safety and effectiveness of Dapivirine Vaginal Ring-004 when inserted once every 4 weeks in healthy, HIV-negative women. MTN-020 was conducted at 15 research centers in four African countries (Malawi, South Africa, Uganda, and Zimbabwe). Eligible participants were randomly assigned in a 1:1 ratio to either the Dapivirine Vaginal Ring-004 or placebo ring group. A total of 2629 subjects were enrolled, 1313 were randomized to the dapivirine group and 1316 to the placebo group. MTN-020 was designed as an endpoint driven trial with planned trial closure when a minimum of

120 HIV-1 infections were observed. The actual number of confirmed trial endpoints was 168 at trial closure.

### **3.2. Favourable effects**

The proportion of participants with **confirmed seroconversions** in IPM 027 at the primary efficacy (and safety) analysis timepoint was, based on the Quality control-reviewed data, 6.1% (80/1302) of participants in the Dapivirine Vaginal Ring-004 group, and 9.1% (59/650) of participants in the placebo ring group.

The corresponding estimated **rate of HIV-1 seroconversion per 100 person-years** was 4.23 (95% CI: 3.32 to 5.16) in the Dapivirine Vaginal Ring-004 group, and 6.43 (95% CI: 4.79 to 8.08) in the placebo ring group

The estimated **percentage reduction in HIV-1 seroconversion**, adjusted for center, by Dapivirine Vaginal Ring-004 relative to the placebo ring was 35.07% (unadjusted 95% CI: 9.05 to 53.64%; P = 0.012 based on the Cox PH model).

The lower bound of the unadjusted 95% CI exceeds the by the applicant pre-defined superiority margin of 0%.

The vaginal ring was considered **acceptable** by >95% of all participants at the end of the ring use period in both IPM 027 and MTN-020. At the end of follow-up, over 92% of participants in both studies found it not difficult at all to insert the vaginal ring, >85% reported that she did not feel the ring during normal daily activities, and >94% in IPM 027 and >70% in MTN-020 reported that her partner did not feel the ring during vaginal sex.

### **3.3. Uncertainties and limitations about favourable effects**

#### **Conduct of the studies.**

MTN-020 was an endpoint-driven trial, designed to continue until at least 120 HIV-1 seroconversion events were accrued. Ultimately, 168 events were reported. Two of the 6 sites had to definitely stop recruiting and other sites had to recruit more subjects to achieve enough events. These decisions may have led to bias of the estimated efficacy result. The triggered GCP inspection of MTN-020 revealed critical and major clinical findings related to the trial conduct, which do have the potential to impact on the reliability of the results of this study (for more information, see Sponsor Inspection Report, GCP/2017/027). Due to the uncertainties surrounding the data quality and reliability that became evident during the GCP inspection, and due to the possible bias on the estimated effect by stopping the recruitment of two centers, Study MTN-020 is no longer considered confirmatory for efficacy. This means that this application would be based on a single pivotal trial, IPM-027.

The primary safety and efficacy analysis for study IPM 027 were performed earlier than originally anticipated, despite contrary CHMP advice. The Applicant provided updated analyses of all data until the cut-off date of 16 October 2015, as well as additional analyses covering the complete double-blind treatment period. Moreover, during the procedure, inconsistencies concerning the data and analyses for Study IPM 027 were identified, e.g. seroconversions were erroneously not counted as trial endpoints, used follow-up times were not correct, and inconsistencies were noted in and between several of the provided tables. New HIV-1 infections were detected several participants who discontinued the trial early without an exit visit and for whom the applicant was able to perform PCR testing on stored (PK) plasma

samples. It could not be excluded that additional trial participants would be found HIV positive, if the PCR analysis could have been performed also in the samples of the other participants. This is however not possible due to the destruction of a large part of the clinical samples in 2018. The exact number of additional seroconverters, as well as the distribution across the dapivirine and placebo arms, remains unknown. Given the inconsistencies in the data, identified during the assessment, a quality control (QC) review for all clinical data was requested in order to provide a reliable estimate of the primary efficacy measure of Study IPM 027. The Applicant contracted an independent third party to conduct this quality control.

Although the data clean-up did show some discrepancies with the latest reported data, there is no relevant change in the last reported point-estimate as the discrepancies did not result in identification of additional seroconversions. The final updated analyses suggest a statistically significant HIV 1 risk reduction of 35% (9% to 54%;  $p=0.01$ ) for the Dapivirine Vaginal Ring relative to placebo. This means that the figures and different sensitivity analyses presented previously remain valid.

**Clinical relevance.** The impact of the estimated effect is considered to be modest. Pooled data from 6 randomised studies have shown an overall risk reduction of 57% (95% CI 0.34–0.94;  $P=0.03$ ) for women when using tenofovir disoproxil and emtricitabine containing oral PrEP.

Moreover, the downside of an overall efficacy of approximately 30% (relative risk reduction) is that the risk of infection remaining is still 70%. Therefore, the therapeutic options for women failing on dapivirine prevention need to be carefully elucidated. The development of resistance under dapivirine treatment remains unclear. Therefore, the development of resistance under dapivirine should be remain under supervision and follow-up in post-authorisation measures.

The results from two open-label extension trials, IPM 032 (DREAM) and MTN-025 (HOPE) can be regarded as supportive in the efficacy estimate of the Dapivirine Vaginal Ring.

#### **External validity.**

The following uncertainties relating to the external validity of the study results remain:

- Only a very limited number of study centres from a total of four countries participated in the studies, with the vast majority of the women recruited in South Africa, specifically in the province KwaZulu Natal. There were large differences in outcome between the different research centers in each of the two studies. No differences in baseline characteristics between the trial participants enrolled in the centers with vs without a reduced risk in the dapivirine group, that may be related to protection against HIV-1 infection, were identified by the applicant. Socio-economic and cultural conditions as well as gender dynamics and community factors showed some degree of variability already across the study sites –as also discussed by the Applicant - these aspects were considered to impact on the participants' motivation to adhere to the DPV-VR. However, a much larger variability in different respects with an unknown impact on the efficacy of the DPV-VR can be anticipated with wider-spread use of the product, e.g. in other countries. This pertains to host and to viral factors, e.g. to efficacy/safety of the product in women, currently excluded from the studies, e.g. those who underwent genital mutilation or in regions with concomitant conditions, only rarely seen in the population studied, such as HIV-2 infection. Clinical efficacy against HIV-1 viruses, other than subtype C (the by far dominant subtype in the region, where the efficacy trials were conducted, has not been shown). For central and West Africa other subtypes are more prevalent, e.g. A, D, G, and O2.
- Systemic anti-infectives were used for therapy of genital infections in the vast majority of cases, as use of topical (vaginal) therapies was discouraged by protocol. In clinical practice, however, in view of their B/R topical preparations are first-line treatment options. Drug-drug interactions have been investigated only for miconazole capsules and clotrimazole 10 mg/g vaginal cream. Significant effects on dapivirine and miconazole vaginal fluid levels were observed in the miconazole DDI trial, whereas

in the clotrimazole DDI trial only modest effects were observed on dapivirine and clotrimazole vaginal fluid levels. The clinical relevance seems to be low in both cases, but uncertainties remain. In both studies there were methodological issues related to the measurements of the vaginal concentrations of both drugs, making the results unreliable. Moreover, the influence of excipients in the topical formulations remains unknown. No other DDI studies are planned.

- It could be envisaged that some women may consider combining the Dapivirine Vaginal Ring-004 with tenofovir disoproxil-containing oral PrEP. Apart from in-vitro data showing additive antiviral effects of DPV and TDF demonstrating that under suboptimal concentrations fewer NNRTI resistance mutations were found for the combination of DPV and TDF as opposed to DPV alone, no information is available for this combination. Concomitant use of the dapivirine vaginal ring with oral PrEP should not be recommended, until further substantiating data have become available.

### **Dose.**

Based on in vitro studies in cervical tissue, the applicant determined an IC<sub>99</sub> against HIV-1<sub>Bal</sub> of 3.3 ng/ml, and subsequently aimed to achieve dapivirine concentrations in the genital tract in humans well in excess of this concentration. While this strategy is, in principle, reasonable, vaginal fluid concentrations do not necessarily correlate with the concentration within CD4 cells in the tissues of the lower female reproductive tract, which is believed to be the primary site of activity of dapivirine.

No dose response studies have been performed with the dapivirine vaginal ring formulation. It is unclear if the 25mg dapivirine containing vaginal ring provides the most optimal, dapivirine exposure level needed to reliably protect a woman against HIV-1 infection.

### **Treatment compliance.**

Adherence as measured during the study (e.g. residual levels in used vaginal rings after a period of 28 days) does not provide relevant information regarding ring use at the moment of HIV-1 exposure.

## **3.4. Unfavourable effects**

In the Phase III pooled analysis, the overall incidence of **adverse events** reported in the Dapivirine ring group was approximately similar to that in the placebo ring (90.8% vs 90.6% women). The most commonly reported adverse events, for the Dapivirine and placebo group, respectively, were:

- metrorrhagia (39.9% and 45.8%),
- genitourinary chlamydia infection (25.5% and 24.1%),
- urinary tract infection (15.2% and 16.6%),
- menorrhagia (14.6% and 15.3%),
- genitourinary tract gonococcal infection (14.3% and 13.2%),
- upper respiratory tract infection (13.9% and 12.5%),
- vulvovaginal candidiasis (11.9% and 10.2%),
- genital infection female (11.0% and 5.8%),
- bacterial vaginosis (10.0% and 9.9%).



In general, the incidence of these common TEAEs decreased over time and the prevalence remained over time. The majority of TEAEs were mild or moderate in severity. The high incidence of menorrhagia in both the dapivirine and placebo groups is strongly related to the contraceptive use and was reported especially during the first months. Menorrhagia is therefore not considered an adverse event.

The incidences of **serious TEAEs** were low and approximately similar between both groups (3.0% and 2.4% for Dapivirine and placebo, respectively). Importantly, none of the serious TEAEs were considered related to the investigational product (IP) by the investigator. The incidences in death were very low and similar between the groups (0.2% both) and not IP-related.

The overall incidence of **IP-related TEAE** (4.6 % and 6.8%) were slightly lower in the Dapivirine group compared with placebo. None of these were assessed as serious in nature. The most commonly reported IP-related TEAEs (i.e in  $\geq 0.5\%$  of the subjects in the Dapivirine group) were

- metrorrhagia (18 (0.7%) and 9 (0.5%) for the Dapivirine and placebo group, respectively),
- vaginal discharge (0.6% and 1.0%),
- pelvic pain (0.6% and 1.0%).

Further information provided regarding the finding of IP-related metrorrhagia in the dapivirine and placebo groups indicated that in an analysis over time most cases occurred during the first three months of treatment. This strongly suggests that the IP-related metrorrhagia is also related to the type of contraception used, since participants were not required to be on a stable contraceptive method prior enrollment and were allowed to change contraceptive method during the trial. All the IP-related cases were considered by the investigators as Grade 1 (mild) in severity and several of the events were described as spotting/blood on swab/blood on vaginal wall/minimal amount of blood from cervical. However, the Applicant could not clarify why these metrorrhagia events were considered IP-related by the investigators. Nevertheless, based on the information presented there are no indications suggestive for causality of the ring with the occurrence for metrorrhagia.

TEAEs leading to **permanent discontinuations** were very low; one in each group of the Phase III pooled analysis discontinued due to a TEAE not related to the IP.

The incidence of TEAEs leading to **temporary discontinuations** were also relatively low and comparable between the Dapivirine (2.9%) and the placebo (3.3%) group. In the MTN-020 trial, a higher incidence in TEAEs leading to temporary IP discontinuations (5.0% and 4.7% in the Dapivirine and the placebo group, respectively) were observed than the IPM 027 trial (0.8% and 0.5%), which was the result of a different approach for temporary discontinuation for the IPM 027 and MTN-020. In trial IPM 027, AEs leading to temporary discontinuation were reported in at most 2 participants in either group for any preferred term. In trial MTN-020, the most commonly reported AEs leading to temporary discontinuation were cervicitis (1.6% and 1.4%), genitourinary tract gonococcal infection (0.6% and 0.4%), and genitourinary chlamydia infection (0.5% and 0.5%), and pelvic inflammatory disease (PID) (0.3% and 0.4%) (for the Dapivirine and placebo group, respectively.)

During the phase III trials, 4.4% [114/2619] in the Dapivirine group and (5.3% [105/1968] in the placebo group became **pregnant**. In both groups, about 20% of pregnancies ended in a spontaneous abortion. Slightly lower percentage of live births were reported in the Dapivirine group (51.7% (62/120)) compared with the pregnant women in the placebo group (57.5% (65/113)), which is probably due to the higher incidences in therapeutic/elective abortion and missing data in the Dapivirine group. No major abnormalities were reported.

In a phase II safety trial in **postmenopausal women** (USA) the most commonly reported IP-related AEs included: lower abdominal pain (4.3% and 3.1% in the Dapivirine group and placebo group, respectively), urinary tract infections (1.4% and 8.3%), vulvovaginitis (2.8% and 8.3%), vaginal



discharge (11.1% and 8.3%), cervix hemorrhage uterine (5.6% and 4.2%), vaginal haemorrhage (5.6% and 0%), vaginal odor (5.6% and 0%), vulvovaginal erythema (4.2% and 12.5%), and vulvovaginal pruritus (4.2% and 4.2%). Further information provided indicated that vaginal bleeding events observed in the post-menopausal women were events of ecchymosis, petechiae and spotting and were most likely related to trial procedures in the genital area, rather than the Dapivirine Vaginal Ring or placebo ring.

**Male** tolerability of 0.05% Dapivirine gel versus placebo following multiple topical penile exposures in circumcised and uncircumcised men in the US showed some IP-related local effects in 12.5% (3/24) application site paresthesia, increased ALT, increased AST, and sebaceous gland disorder) in the dapivirine group versus, 8.3% (1/12) in placebo gel group (application site pain), and 16.7% (2/12). However, in the phase III pooled analysis, the reporting of adverse events by male partners was low.

### ***3.5. Uncertainties and limitations about unfavourable effects***

The incidence of pelvic inflammatory disease (PID) was low (21 (1.6%) and 25 (3.8%) women in trial IPM 027 and 27 (2.1%) and 28 (2.1%) women in trial MTN-020 for the dapivirine and placebo group, respectively), which could well be due to efficient treatment of STI offered in both clinical trials. The occurrence of PID, when genital tract infections (including STI) are not immediately treated, is not known. As such, the Applicant proposes a warning in section 4.4 of the SmPC that early detection and appropriate treatment of genital infection in women using the Dapivirine ring is considered important.

### 3.6. Effects Table

**Table 44 Effects Table for Dapivirine Vaginal Ring-004.**

The numbers provided in this table are based on the Quality control-reviewed data for the trial period with cut-off date 16 October 2015 (Analysis B).

Effect	Short Description	Unit	Dapivirine Vaginal Ring	Placebo Vaginal Ring	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint of study IPM 027	HIV seroconversion (sc)	n/N (%)	80/1302 (5.9%)	59/650 (8.6%)	- Concerns were raised regarding the quality of the data in IPM 027, leading to the request for a quality control review of all clinical data. - the data clean-up did show some discrepancies with the latest reported data, but did not result in identification of additional seroconversions  Strength of evidence: moderate / strong	CSR IPM 027
	Incidence rate HIV-1 sc	Per 100 py follow-up (95% CI)	4.23 (3.31; 5.16)	6.43 (4.79; 8.08)		
	HR for HIV-1 sc (95% CI)		0.65 (0.46; 0.91)			
	Percentage reduction in HIV-1 sc (95% CI)		35.07% (9.05 to 53.64%)			
Secondary endpoint IPM 027+ MTN-020	Ring acceptability, end of study	%	>95%	>95%	Self-reported  Strength of evidence: low	CSR IPM 027 and MTN-020
Secondary endpoint IPM 027	Resistance associated mutations	n/N (%)	NNRTI: 16/79 (20.0%) NRTI: 2/79 (2.5%) PI: 3/79 (3.8%)	NNRTI: 8/58 (13.8%) NRTI: 0/58 (0%) PI: 0/58 (0%)	Strength of evidence: moderate	Clinical Virology Report
Secondary endpoint MTN-020	Resistance associated mutations	n/N (%)	NNRTI: 8/68 (11.8%) NRTI: 1/68 (1.5%) PI: 0/69 (0%)	NNRTI: 9/96 (9.4%) NRTI: 1/96 (1.0%) PI: 0/96 (0%)		

Effect	Short Description	Unit	Dapivirine Vaginal Ring	Placebo Vaginal Ring	Uncertainties/ Strength of evidence	References
<b>Unfavourable Effects (IP-related TEAEs)</b>						
Metrorrhagia	Incidence	%	18/2619 (0.7)	9/1968 (0.5)	As 50% of women were non-adherent to therapy, this could have led to lower exposure and possible underestimation of TEAE incidence.  In comparison with IPM 027, an 18-fold higher incidence in IP-related TEAE is noted in MTN-020. Although there are between-trial differences with regard to TEAE collection and contraception, further clarification is needed.	CSR IPM 027 and MTN-020
Vaginal discharge	Incidence	%	17/2619 (0.6)	20/1926 (1.0)		
Pelvic Pain	Incidence	%	16/2619 (0.6)	20/1926 (1.0)		

- Abbreviations: Sc: seroconversion; CI: confidence interval; CSR: clinical study report; HR: hazard ratio

### 3.7. Benefit-risk assessment and discussion

#### 3.7.1. Importance of favourable and unfavourable effects

Currently, only tenofovir disoproxil (TDF) + emtricitabine (FTC) are approved to be used as PrEP for the prevention of HIV-1 infection. Accessibility of FTC+TDF as PrEP for target populations can still be limited in sub-Saharan Africa. There is a clear need for alternative PrEP options. Women are an important population to consider for PrEP, as young women are twice as likely to be at risk of HIV infection compared with aged-matched men worldwide, a difference estimated to be, at least in part, related to (unwanted) unsafe sexual activity. In this, special focus is needed on those methods which do not need partner involvement.

FTC+TDF is available as an oral preparation and requires daily dosing. It works systemically and will be effective regardless of the route of HIV-1 exposure (vaginal, anal, blood-blood contact). In US trials a risk reduction of nearly 100% is shown when taken consistently. However, some studies investigating oral FTC+TDF for PrEP in women in sub-Saharan Africa failed to show any protective effect at all (e.g. FEM-PrEP study: overall efficacy 6% (95% CI -52 to 41%), Voice study: overall efficacy -4% (95% CI -49 to 27%)), the reason for this failure was poor adherence. A potential disadvantage of oral

FTC+TDF is that it could have substantial side effects. Moreover, since FTC+TDF is also used for HIV-treatment, stigmatisation with use of these products has been observed.

The Dapivirine Vaginal Ring is working locally and protects only against HIV-1 exposure during vaginal intercourse. It is not likely that dapivirine present in the vagina will protect against *trans*-infection via dendritic cells (DCs). The vaginal ring can be worn continuously for 28 days after which it should be replaced by a new ring. The Dapivirine Vaginal Ring has been investigated only in sub-Saharan Africa and the trials suffered from considerable non-adherence, i.e. about 50% of women were non-adherent to ring use. Of note, the measures used to determine adherence, i.e. residual dapivirine levels in used rings and/or plasma dapivirine concentrations, come with considerable uncertainties. While for oral FTC+TDF, intracellular tenofovir (TVF-DP) concentrations can reliably be determined in dried blood spots and are strongly correlated with efficacy, dapivirine adherence can only be determined indirectly and no information on intracellular levels is available. Regardless of adherence, the overall risk reduction induced by the Dapivirine Vaginal Ring in the two pivotal phase III trials was approximately 30%, which increased to approximately 40% in the subgroup of adherent women (residual dapivirine levels in used rings  $\leq 23.5$  mg and/or plasma dapivirine levels  $\geq 95$  pg/ml). Uncertainties with respect to the actual point estimate of efficacy, and surrounding unadjusted confidence intervals, of the remaining single pivotal study IPM 027 have been identified during the assessment, which resulted in the request for a quality control review of all clinical data.

The totality of the evidence, the quality-control review data of the pivotal study IPM-027 including various sensitivity analyses and supportive efficacy studies, suggesting a risk reduction, between 25% and 40% as compared to placebo.

During the SAG meeting the experts concluded that a PrEP option with an estimated overall risk reduction of approximately 30% should not be ruled out as part of a global strategy to reduce HIV transmission in addition to the current available and effective standard approaches for HIV negative women in sub-Saharan Africa, but that it should not be seen as a first-line intervention. It was concluded that its use may be best restricted to e.g. when oral PrEP is not/cannot be used, and/or is not available.

The true maximum protection of the Dapivirine Vaginal Ring cannot be assessed, as besides vaginal intercourse also other forms of sexual engagement were practiced. Taking also the risks of other transmission routes (e.g. IV drug use, unsterile medical instruments, etc) into account, it is clear that the real-life maximum potential effectiveness of the vaginal ring will be lower than what can be achieved with oral PrEP. How much lower can however not be predicted. Real life effectiveness might be higher in a very adherent population or lower in the context of wide-spread resistance.

Subgroup analyses indicated that age above 21, and partner awareness positively influenced risk reduction. The diminished efficacy in the youngest women (<21 years), who are at highest risk of HIV-infection, is of concern. There is no biological rationale for this observation, and reduced adherence likely plays a role here. Also, the unknown impact of knowledge of using a product providing incomplete protection on sexual behaviour needs to be kept in mind. A prerequisite for the positive opinion for the Article 58 procedure of the DVR is confirmation of a positive benefit risk ratio in young women by means of a study adequately designed to address the uncertainty regarding DVR's efficacy in this population. The CHMP imposed a Category 1 Post-Authorisation Efficacy Study (PAES) to address this, and to confirm the overall effect size as well as to systematically collect information about NNRTI resistance in seroconverters.

The Applicant proposes an open label single arm study of women who cannot/will not use oral PrEP and choose to use the DVR. This design is deemed most feasible and acceptable by community stakeholders and ECs.

The CHMP acknowledges the feasibility argument as brought forward by the Applicant. . However, for an assessment of the proposed study design, more in-depth information would be required, which, as stated by the Applicant will be provided in the context of an upcoming scientific advice procedure (as committed by the Applicant in response to the 4th CHMP List of Outstanding Issues). The Applicant is planning to submit a draft protocol through the Scientific Advice procedure by November 2020.

With respect to the safety, the Dapivirine Vaginal Ring displays an acceptable safety profile comparable to that of the placebo ring with very limited subjects discontinuing treatment or showing serious adverse events. No major safety issues have been identified. Although the clinical file up to now does not indicate increased risk for pelvic inflammatory disease during use of dapivirine ring, a theoretical risk cannot be excluded. Therefore, a warning is included in the SmPC.

Finally, the question of resistance development by use of the Dapivirine Vaginal Ring in women seroconverting and as a matter of fact being not immediately aware of their infections and hence exerting selective pressure, needs to be very carefully weighed in. Cross-resistance with other NNRTIs, used in antiretroviral therapies, has been found in vitro, potentially limiting women's treatment options. Therefore, development of viral resistance to antiretroviral agents by use of the Dapivirine Vaginal Ring should be closely followed post marketing, by means of above-mentioned PAES for which the applicant is planning to submit a draft protocol through the Scientific Advice procedure by November 2020 (and final CSR by Q3 2026).

In addition, data on antiviral activity of Dapivirine on HEV should be provided as a post-authorisation measure (PAM).

### **3.7.2. Balance of benefits and risks**

While both Phase III studies (IPM 027 and MTN-020) suggest that the Dapivirine Vaginal Ring is associated with an approximately 30% lower risk of contracting HIV infection, the unadjusted 95% confidence intervals of each study are wide and barely exclude 0. The clinical relevance of this observed effect per se is uncertain, but according to consulted experts (SAG) the Dapivirine vaginal ring has a place in prevention strategy, e.g. when oral PrEP is not/cannot be used, and/or is not available. Additional uncertainties surrounding the data quality and reliability became evident during GCP inspections and after careful review of all clinical data and resulted in the conclusion that the data of Study MTN-020 was not GCP compliant and bias cannot be excluded. The integrity of the IPM 027 data was insufficient to draw conclusions on. It was therefore considered necessary to perform a careful QC review of all clinical data before the data of Study IPM 027 can be used to base the benefit/risk assessment on.

Although in the QC several discrepancies were identified, it revealed no additional HIV-1 infections. The totality of the evidence, including various sensitivity analyses and supportive efficacy studies suggest a risk reduction, between 25% and 40% as compared to placebo. After several rounds of outstanding issues and their assessment the internal and external validity, data quality and internal consistency have been adequately addressed, also when contextualising these with other PrEP-studies. However, some uncertainties remain with respect to efficacy in young women, particularly those between 18 and 21 years of age. With respect to safety, the Dapivirine Vaginal Ring displays an acceptable safety profile comparable to that of the placebo ring with very limited subjects discontinuing treatment or showing serious adverse events. No major safety issues have been identified. Uncertainties remain with respect to efficacy in younger women and the Applicant should conduct a PAES.

Overall, the benefit-risk balance of the Dapivirine vaginal ring in the currently applied therapeutic indication is considered positive by the CHMP with the condition to the Scientific Opinion, as laid down in the Annex II, that a post authorisation efficacy study (PAES) is being conducted in women from 18 to

25 years (stratified for 18 to 21 years and >21 to 25 years) with systematic collection of information about HIV-resistance in seroconverters (minimum requirements being laid down in the Annex II).

In addition, data on antiviral activity of Dapivirine on HEV should be provided as a post-authorisation measure (PAM).

### **3.7.3. Additional considerations on the benefit-risk balance**

A SAG/AHEG meeting has been held 3 December 2018. Topics for which the input of SAG members was requested were whether the effect size can be considered sufficient to provide a real advantage to women in sub-Saharan Africa (taking external factors such as potentially decreased condom use, financial considerations, and availability of other preventive options into consideration). Also, input was provided on additional analyses and/or studies that could be done by the Applicant to gain more insight into the relationship between measured adherence to and observed efficacy of the Dapivirine vaginal ring, on measures to further increase adherence, and on the risk that dapivirine use may lead to mutation(s) in the virus of women failing on dapivirine PrEP, which confer cross-resistance to efavirenz and nevirapine.

### **3.8. Conclusions**

After a very intense, in-depth assessment, based on the results of a thorough QC review and all the conducted sensitivity analyses, the CHMP considers that the study IPM 027 is pivotal to the application and reliably shows a statistically significant difference between DVR and placebo in favour of DVR. Moreover, looking at the totality of the evidence, other efficacy and safety studies (i.e. MTN-020 and IPM 032), despite their limitations, can be regarded as supportive of a beneficial effect of dapivirine. The effect size of MTN-020, the only other randomised controlled study with its limitations is comparable to that of IPM 027 and in the open-label study IPM 032 DVR's efficacy compares favourably with the adjusted simulated placebo incidence (and external control incidence rates). And also for study MTN-025, when using the (as best as possible) matching (sub)groups as most conservative comparison, the point estimate is still in favour of DVR. For none of the study results/sensitivity analyses the point estimate is zero or even negative, which is regarded as reassuring by the CHMP.

However, since some uncertainties remain with respect to the effect size in younger women, the Applicant is requested by the CHMP to conduct a Post-Authorisation Efficacy Study (PAES) in women from 18 to 25 years of age. There are strong expectations from the CHMP for the results of this study to be submitted, its conduct and results being key to the confirmation of the benefit risk balance of Dapivirine vaginal ring.

Data on antiviral activity of Dapivirine on HEV should also be provided as a post-authorisation measure (PAM).

The overall B/R of Dapivirine Vaginal Ring 25 mg is positive provided general statement on conditions.

Divergent positions are appended to this report.

## 4. Recommendations

### **Outcome**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP adopt by majority decision a scientific opinion as the benefit-risk balance of Dapivirine Vaginal Ring 25 mg in the prophylaxis of:

*"reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 18 years and older in combination with safer sex practices when oral PrEP is not/cannot be used or is not available"*

is favourable. The scientific opinion is subject to the following condition.

Divergent positions to the majority recommendation are appended to this report.

### **Conditions or restrictions regarding supply and use**

Medicinal product subject to medical prescription.

### **Other conditions and requirements of the scientific opinion**

#### **Periodic Safety Update Reports**

The scientific opinion holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every year until otherwise agreed by the CHMP.

### **Conditions or restrictions with regard to the safe and effective use of the medicinal product**

#### **Risk Management Plan (RMP)**

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

#### **Additional risk minimisation measures**

Prior to the launch of the Dapivirine Vaginal Ring the scientific opinion holder must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at the healthcare professional and the patient (user). The main objectives are to provide information for counselling which address the safety concerns and to minimise potential adverse outcomes in the user with emphasis on adherence and the importance of regular (3 monthly) confirmation of HIV-1 seronegative status during use of the Dapivirine Vaginal

Ring. Additionally, the Patient (User) Guide will contain explanations on how to use the product correctly.

The scientific opinion holder shall ensure that in each country where the Dapivirine Vaginal Ring is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use the Dapivirine Vaginal Ring have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals (HCP guide)

Guide for healthcare professionals:

Relevant information of the safety concern(s) addressed by the HCP guide include the following key messages:

- 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-1 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 or breastfeeding.

The patient information pack:

- Patient information leaflet
- A patient (user) guide

Patient (user) guide:

Relevant information of the safety concern(s) addressed by the User guide include the following key messages:

- 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 (eg, 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 accidentally remove the vaginal ring as well.
- If the Dapivirine Vaginal Ring accidentally falls out or is removed and this happens in a clean place (eg, 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 (eg, 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.

Provides guidance that the user should contact her clinic or doctor if

the user suspects she may be HIV-infected and what the signs and symptoms of early HIV infection are.

the Dapivirine Vaginal Ring causes persistent discomfort or pain which does not resolve after repositioning the ring.

the user experiences signs or symptoms suggestive of pelvic inflammatory disease or a genital infection

the user suspects she is pregnant and to remove the vaginal ring immediately

### **Obligation to conduct post-authorisation measures**

The SOH shall complete, within the stated timeframe, the below measures:

<b>Description</b>	<b>Due date</b>
<p>Post-authorisation efficacy study (PAES):</p> <p>Phase IV, open label, multicentre efficacy study in healthy HIV-negative young women age 18-25 years (stratified for 18 to 21 years and &gt;21 to 25 years) using the Dapivirine Vaginal Ring over a period of 12 months to address the current uncertainty in the efficacy in younger women and to confirm the overall effect size by establishing an appropriate counterfactual and to systematically collect information about NNRTI resistance in seroconverters.</p> <p>Minimum requirements should be as follows:</p> <p>1. Primary objective:</p> <ul style="list-style-type: none"><li>• HIV-1 infection rate per 100 woman-years of product use at the end of the DVR use period</li><li>• Incidence of NNRTI resistance mutations in participants who become HIV-1</li></ul>	<p>Final CSR Q3 2026</p>

<p>infected</p> <p>2. Secondary objective:</p> <ul style="list-style-type: none"> <li>• Assessment of genitourinary safety of the DVR, when inserted at monthly intervals, over a period of 12 months</li> </ul> <p>3. Enrolment is expected to be as a minimum of around 2,000 HIV-negative young women age 18-25 years</p>	
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## **Divergent opinion for Dapivirine vaginal ring – Art 58 - EMEA/H/W/002168**

Due to the GCP noncompliance of the MTN-020 study, the results of this study are not considered fit to support regulatory decision-making. Therefore, the application is resting on a single pivotal trial, the IPM-027.

In this study, the primary efficacy metric for risk reduction was 30.67% (95% CI: 0.90%–51.50%;  $p=0.0414$ ). This is a result of borderline statistical significance and is not statistically compelling in the setting of a single pivotal trial. Notably, also for this study there are major concerns on data quality and the conduct of the study.

In summary, the efficacy of the Dapivirine vaginal ring has not been established. Therefore, the B/R balance is negative.

### **CHMP Member expressing a divergent position:**

Simona Badoi

Kristina Dunder

Johann Lodewijk Hillege