

## QUESTIONS and ANSWERS

### The Dapivirine Vaginal Ring: MTN Studies and Next Steps in the Regulatory Review Process

#### I. Progress and Next Steps for the Dapivirine Ring

##### What is the dapivirine vaginal ring?

The [dapivirine vaginal ring](#) is a new HIV prevention product that was developed specifically for cisgender women. The ring is made of a flexible silicone material containing 25mg of an antiretroviral (ARV) drug called dapivirine and is used for a month at a time. Women can insert and replace the dapivirine ring themselves each month. When placed inside the vagina, the ring delivers the drug directly to the site of potential infection over the course of a month, with low absorption elsewhere in the body, which could help minimize side effects. Dapivirine belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors (NNRTI) that block HIV's ability to replicate itself inside a healthy cell.



##### Who developed the ring?

The ring was developed by the nonprofit [International Partnership for Microbicides](#) (IPM), which holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, designed to ensure that women in low-resource settings have affordable access to any dapivirine-based microbicide. IPM is seeking regulatory approval of the ring for women ages 18 and older. If approved, the dapivirine ring would be the first biomedical prevention method designed specifically for cisgender women and the first long-acting method.

##### How is the Microbicide Trials Network (MTN) involved?

The [Microbicide Trials Network](#) (MTN) is funded by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the U.S. National Institutes of Health (NIH), for the express purpose of designing and conducting the kind of studies needed to support potential licensure and regulatory approval of promising HIV prevention products. As such, and as IPM's clinical partner, the MTN conducted several studies of the monthly dapivirine ring that were included in IPM's application to the European Medicines Agency (EMA) and that will be included in other regulatory submissions as well. The MTN is also conducting important studies that will provide data on the ring's safety in key populations, namely, adolescent girls and young women and pregnant and breastfeeding women, so that expanded approval may be considered for these groups should the ring be approved in the first place. In addition, the MTN has conducted early phase trials of next-generation dapivirine rings – one intended to be used for three months at a time and a three-month dual-purpose ring for both HIV prevention and contraception.

##### What do we know about the dapivirine vaginal ring? Is it effective?

Multiple studies of the ring conducted in Africa, Europe and the US have shown it to be well-tolerated in HIV-negative women, with no safety concerns. The largest of these were two Phase III clinical trials – [ASPIRE](#) (MTN-020), conducted by the MTN, and [The Ring Study](#) (IPM 027), led by IPM – involving more than 4,500 women ages 18-45 in Malawi, South Africa, Uganda and Zimbabwe. Results, reported in 2016, found the dapivirine ring reduced the risk of HIV by approximately 30 percent overall. Higher levels of protection were

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seen in women who used the ring most regularly. Results of the [HOPE](#) (MTN-025) open-label extension (OLE) study for former ASPIRE participants, and the [DREAM](#) (IPM 032) OLE for former Ring Study participants, which were first reported in 2019, showed increased ring use and suggested a greater reduction in HIV risk (about 50 percent) than in the Phase III trials. Without a placebo group, however, these findings don't have the same strength of evidence.

### **Why did IPM submit an application to the European Medicines Agency?**

Through a procedure called Article 58, the European Medicines Agency (EMA), in cooperation with the World Health Organization (WHO), reviews applications for products that are intended for use outside of the European Union and specifically address a disease of major public health interest in low- and middle-income countries. Applications reviewed under Article 58 are conducted according to the same standards as medicines intended for use in the European Union. Following its review, the EMA provides an opinion on the use of the drug. A positive opinion from a regulatory authority such as the EMA is recognized by many national regulatory agencies in Africa, where the dapivirine ring is intended for use, and can help facilitate regulatory reviews in those countries. In addition, a positive opinion under Article 58 streamlines a decision by the WHO on a product's "prequalification," a global quality assurance designation that can also facilitate reviews by many national regulatory authorities in Africa.

### **What was included in IPM's application to the EMA?**

IPM's application to the EMA included chemistry, manufacturing and controls (CMC) data, results from 183 non-clinical studies, 11 Phase I and Phase II safety and pharmacokinetics trials, the two Phase III trials, ASPIRE conducted by the MTN and The Ring Study, led by IPM; and the two Phase IIIb OLE studies, HOPE and DREAM. Additional data from 33 other studies were also included as supplemental data.

### **Which of these studies were conducted by MTN?**

In addition to the ASPIRE Phase III trial and HOPE Phase IIIb OLE study, IPM's application to the EMA included data from six other MTN studies – three supporting studies and three studies that contributed supplemental information. Most all were conducted in the United States. Supporting studies were Phase IIa safety studies in adolescent girls ([MTN-023/IPM 030](#)) and post-menopausal women ([MTN-024/IPM 031](#)) and a Phase I safety and pharmacokinetic study in lactating women ([MTN-029/IPM 039](#)). Supplemental studies included in the EMA application were [MTN-012/IPM 010](#), a Phase I penile safety study; [MTN-013/IPM 026](#), a Phase I study that augments data on the safety and pharmacokinetics of the dapivirine ring; and [MTN-015](#), an observational study of women who acquired HIV while participating in ASPIRE and HOPE.

### **Was ASPIRE efficacy data considered by the EMA?**

During its review process, the EMA informed IPM that its assessment of the ring's efficacy would be based solely on data from The Ring Study, but its assessment of safety would be based on data from both ASPIRE and The Ring Study. The EMA excluded ASPIRE efficacy data due to its finding of non-compliance with Good Clinical Practice (GCP). Its determination was because of gaps in documentation for certain processes and decisions related to how the ASPIRE efficacy data analysis was performed, and was not related to any site-level concerns. The EMA indicated that participant safety was not an issue and confirmed that ASPIRE trial sites were fully compliant with GCP and the data collected by these sites were sound. Importantly, IPM, MTN and NIAID immediately took steps to address the matter together, and each partner has worked to strengthen processes across their organizations to improve documentation and oversight and ensure GCP compliance in all ongoing and future studies.

### **What did ASPIRE contribute?**

The safety data collected in ASPIRE was crucial for the EMA review and contributed to its positive opinion. Other key ASPIRE data of interest to the EMA in its review included safety and pregnancy outcome data from women who became pregnant while on study product as well as virology data used to assess HIV drug resistance among women who acquired HIV in ASPIRE and their clinical response to antiretroviral treatment. MTN, IPM and NIAID stand by the validity of both the efficacy and safety data from ASPIRE, and IPM intends to include these data in future regulatory submissions.

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### **What does a positive opinion from the EMA mean for the dapivirine ring? What happens now?**

A positive EMA opinion opens the door to the next steps needed to approve the monthly dapivirine ring in countries where women are particularly vulnerable to HIV. As such, IPM will be working with the WHO to submit the ring for review in specific African countries through the WHO's collaborative registration procedure; in which a country's national regulatory authority, in collaboration with the WHO, conducts an accelerated review of a product that has already received a positive decision from a stringent regulatory body such as the EMA. In parallel, the WHO is expected to review published data on the ring and revise HIV/AIDS treatment and prevention guidelines with evidence-based recommendations for policymakers and healthcare providers on its use, and make a determination for prequalification, a global quality assurance designation.

### **Where is IPM seeking the ring's approval?**

IPM's first submissions will be to drug regulatory authorities in Kenya, Malawi, Rwanda, South Africa, Tanzania, Uganda and Zimbabwe, where the public health need is great and previous studies of the dapivirine ring took place. IPM will also be seeking approval from the U.S. Food and Drug Administration (FDA) later this year (2020). In addition to enabling the ring's potential use in the US, an FDA approval would also create a regulatory pathway for next-generation dapivirine rings – a ring to be used for three months at a time, and a ring containing both dapivirine and a contraceptive hormone.

### **Will ASPIRE data be included in IPM's other regulatory submissions?**

The national drug regulatory authorities in Africa will receive the same application that IPM submitted to the EMA, and will therefore receive all efficacy and safety data from ASPIRE. IPM intends to include all ASPIRE data in its application to the FDA as well.

### **How long does this process take – when would the ring be available?**

IPM hopes to have the first approvals in some African countries in 2021. When the ring will actually be available depends on a variety of factors, including the timing of country approvals and national policy decisions. IPM is doing all it can to speed access planning along so that ring is available as soon as countries are ready to launch the product.

### **If approved, who would the ring be for?**

IPM's regulatory submissions are for the ring's use by cisgender women who are 18 years or older and not pregnant or breastfeeding. This is the same demographic represented in the ASPIRE and Ring Study Phase III trials as well as a safety study in post-menopausal women (MTN-024/IPM 031) conducted by the MTN.

### **Why wouldn't the ring also be for girls under 18 and pregnant and breastfeeding women?**

Initial approvals would not apply to girls under the age of 18 or to pregnant and breastfeeding women because there isn't sufficient information about the safety of the dapivirine ring in these populations. Included in the application to the EMA (and to be included in future regulatory submissions) were data from a study of the ring's safety among adolescent girls in the US ages 15-17 (MTN-023/IPM 031), as well as from a study that analyzed how much drug from the vaginal ring gets into breastmilk (MTN-029/IPM 039). While results of these studies are encouraging, regulators and national programs will require additional data in order to consider expanding approval for these populations.

### **What is being done to ensure the ring can be considered for and be made available to adolescent girls and women who are pregnant or breastfeeding?**

The MTN is conducting trials designed specifically to collect the kind of information regulators and national programs would need to consider expanded approval in these populations should the ring be approved in the first place. Moreover, these studies – [REACH](#) (MTN-034) for adolescent girls and young women ages 16-21, and [DELIVER](#) (MTN-042) and [B-PROTECTED](#) (MTN-043) for pregnant and breastfeeding women, respectively – are being conducted in parallel with the regulatory review process to shorten the time period between potential approval and the availability of this data. *(Please see next sections for more about these studies)*

### **Why did the EMA ask for additional safety and efficacy data in women ages 18-25?**

In the Phase III trials of the ring, younger women used the ring least regularly, and as a group, had the lowest rates of protection. In ASPIRE, for example, the ring was not effective among women younger than age 21. The EMA recommended that additional research be conducted to help better understand the ring's safety and efficacy among women ages 18-25, as well as help to identify approaches that could help encourage better use of the monthly ring, which would augment what will be learned in the REACH study among adolescent girls and young women ages 16-21.

### **Why do we need the ring when PrEP is already approved and becoming increasing more available?**

No single HIV prevention method will work for everyone – people's needs and preferences are different and can change over time. As with contraception, the more HIV prevention options available to women, the more likely one will and can be used. Daily use of an ARV tablet, an approach called oral pre-exposure prophylaxis (PrEP), is approved in many countries, including countries in Africa, and recommended by WHO for persons at substantial HIV risk. Oral PrEP is highly effective with consistent use, but daily pill-taking can be challenging for some people or not desired. If approved, the monthly dapivirine ring could fill an important gap as a long-acting prevention method for women who are unable or unwilling to use daily oral PrEP. At the same time, a vaginal ring may not be suited for everyone either. Controlling the epidemic will only be possible with a comprehensive HIV prevention portfolio that includes multiple options.

### **Are there plans to develop multi-purpose rings and 90-day rings?**

While a ring used for a month at a time may appeal to some women, others may prefer a product they replace every three months, or a ring that provides contraception in addition to protecting against HIV. With its monthly dapivirine ring on track toward potential licensure and approval, IPM hopes to accelerate development of these next-generation dapivirine rings which are already in Phase I clinical trials being led by the MTN. Results of [MTN-036/IPM 047](#), a Phase I open-label study of two formulations of a dapivirine vaginal ring intended to be used for 90 days – one with 100 mg of dapivirine and the other with 200 mg – are expected by early next year, as are results of a Phase I study, [MTN-044/IPM 053/CCN019](#), evaluating a 90-day vaginal ring containing both dapivirine (200 mg) and the contraceptive hormone levonorgestrel. In an earlier Phase I study ([MTN-030/IPM 041](#)) of the combination ring, which was a first-in-human study, participants used the ring for 14 days, with results finding the ring was well-tolerated and no safety concerns. In MTN-044/IPM 053/CCN019, participants are using the dapivirine-levonorgestrel ring as intended for 90 days.

## **II. What about the dapivirine ring for adolescent girls and young women?**

### **What is the REACH study?**

REACH (Reversing the Epidemic in Africa with Choices in HIV prevention), or MTN-034, is a study that seeks to understand the HIV prevention needs and preferences of adolescent girls and young women in sub-Saharan Africa, who are among those most vulnerable to HIV. Specifically, the study is evaluating how adolescent girls and young women use the monthly dapivirine vaginal ring and Truvada® as daily PrEP and their preferences for each, as well as evaluating the safety of both approaches in this population. Both methods must be used consistently and regularly to be effective – daily for oral PrEP, and monthly for the ring – which has been a challenge for younger women in clinical trials with a placebo. As such, REACH also seeks to understand what support young women need to use these products better. The study has enrolled 247 participants ages 16 to 21, including 85 under the age of 18, at four sites in South Africa, Uganda and Zimbabwe.

### **When did REACH start and how long will it take to be conducted?**

REACH began in February 2019 and is expected to be completed in 2021, with results anticipated in 2022.

### **Why is REACH important?**

Globally, more than half of all people living with HIV are women, and in sub-Saharan Africa, women account for nearly 60 percent of adults with HIV. Rates of infection are especially high among adolescent girls and young women. Ensuring that young women and girls have access to and benefit from safe and effective HIV prevention methods is vitally important.

If approved, the dapivirine vaginal ring would be the first biomedical prevention method specifically for cisgender women 18 and older. REACH will provide information about the ring's safety among girls as young as 16 so that regulatory bodies can consider expanded approval to include a younger population. And while Truvada as oral PrEP is already approved in many countries, relatively little data is available about its safety in young women – REACH will contribute additional data about this as well. Importantly, REACH will also help to understand how best to support young women and girls to use these methods as best they can, which is important for broader implementation of both PrEP and the ring, as well as the development of other HIV prevention methods.

### **How is REACH designed?**

REACH is the first HIV prevention study incorporating the concept of informed choice into its design. After having experienced both oral PrEP and the ring, each for six months, participants are able to choose which of the two they want to use for the remaining six months of the study, or they may choose neither. Moreover, participants may change their minds during these last six months as often as they like. Researchers designed the study this way to collect the data needed about the safety and acceptability of the monthly dapivirine ring and Truvada as daily PrEP, as well as understand the HIV prevention preferences of adolescent girls and young women.

### **How will data about the dapivirine ring from REACH be used by IPM?**

Results from REACH, expected in 2022, along with a study that looked at the ring's safety among adolescent girls in the US, are expected to provide the data needed to guide IPM's decision-making on seeking regulatory approvals for this group in the coming years. IPM is engaging with the regulators regarding the data and next steps for a potential adolescent indication for the ring.

### **What exactly was the US study in adolescent girls and why does it matter?**

MTN-023/IPM 030 was a Phase IIa study that evaluated the safety and acceptability of the dapivirine vaginal ring among 96 girls between the ages of 15-17 at six sites in the United States. The study, which the MTN conducted in collaboration with the NIH-funded Adolescent Trials Medicine Network for HIV/AIDS Interventions, provided the first ring safety data in a younger population, and was the first to demonstrate that high levels of adherence to ring use could be achieved among young women, and, as such, paved the way for REACH. Participants in MTN-023/IPM 030 were randomly assigned to use either the dapivirine ring or a placebo ring, each month for a total of six months. Results, which were reported in 2017, found no differences in safety outcomes between the dapivirine ring and the placebo ring. Adherence to the ring was also high, with 95 percent of the rings participants returned to the clinic having drug levels suggesting regular use during the previous month.

## **III. What about the dapivirine ring for pregnant and breastfeeding women**

### **What are the DELIVER and B-PROTECTED studies?**

The DELIVER (MTN-042) and B-PROTECTED (MTN-043) studies are designed to evaluate the safety and acceptability of both the monthly dapivirine vaginal ring and Truvada as daily oral PrEP in women who are pregnant and breastfeeding, respectively. As Phase IIIb open-label studies, all women will use an active product. Both studies are being conducted at four MTN-affiliated clinical research sites in Malawi, South Africa, Uganda and Zimbabwe

### **When did these studies start and how long will they take to be conducted?**

DELIVER began in February 2020 and is expected to take up to four years to conduct, with results anticipated in 2024. Pending in-country and ethics approvals, B-PROTECTED is anticipated to begin in the coming weeks (mid-2020) and be completed by early 2021, with results anticipated later that year.

### **Why are the DELIVER and B-PROTECTED studies important?**

While the development of safe and effective prevention methods for women has long been a priority, much less attention has been paid to women's HIV prevention needs during periods of pregnancy or breastfeeding, when they are up to three to four times more likely to acquire HIV. For many women, the amount of time spent pregnant, breastfeeding, or both, represents a significant portion of their reproductive years when they are at heightened risk.

Both Truvada as PrEP and the dapivirine ring have been shown to reduce the risk of HIV in previous clinical trials involving nonpregnant and non-breastfeeding women, with safety parameters indicating these methods were also well tolerated. Typical of most clinical trials, however, women who were pregnant or breastfeeding were excluded from participation, and those who enrolled had to use contraception, and, if they became pregnant, stop using study product. Such measures primarily intend to protect the fetus and baby from potential harm but also mean that little or no information about the safety of a drug during pregnancy or breastfeeding will be available. In particular, during pregnancy, the body undergoes many changes that could affect how a drug gets absorbed and distributed such that the drug may not be as effective, or its use may be harmful to the mother, her pregnancy, fetus or baby. During breastfeeding, there's concern that the drug may be taken up by the infant through breast milk and cause harm.

If approved, the ring would be contraindicated for women who are pregnant or breastfeeding. While Truvada as oral PrEP is approved in several African countries, not all are willing to offer it to pregnant and breastfeeding women until more is known about its safety during pregnancy and breastfeeding. DELIVER and B-PROTECTED aim to collect the kind of information needed for regulatory authorities and national programs to consider making these methods available to pregnant and breastfeeding women. Knowing they are safe for both mother and baby is vitally important. After all, protecting moms against HIV would be protecting their babies, too.

### **How is DELIVER designed?**

DELIVER (MTN-042) will enroll 750 HIV-negative women at different times during pregnancy, who will use either the monthly dapivirine vaginal ring or Truvada as daily PrEP until the time they deliver. Of the 750 women who will be enrolled, 500 will be randomly assigned to use the vaginal ring. The study consists of four phases and will be conducted in a stepwise, backward fashion, enrolling one group of women at a time, beginning with women who are late in pregnancy, with each successive group of women at an earlier stage of pregnancy and using their assigned product longer. Women will be followed for an additional six weeks after giving birth and their babies will be in the study for one year.

Interim reviews of study data by an independent panel of experts will take place after completion of each phase and before determining whether it is safe to proceed to the next phase.

### **How is B-PROTECTED Designed?**

B-PROTECTED will enroll up to 200 breastfeeding mothers and their 6- to 12-week-old babies. Participants will be randomly assigned to use either the month dapivirine ring or Truvada as daily oral PrEP, with more participants assigned to use the dapivirine ring than oral Truvada. Women will use their assigned product for three months and be followed for an additional two weeks. Researchers will assess how much drug from Truvada and the dapivirine ring passes into breast milk and how much passes to the baby after breastfeeding, and will measure the effects, if any, this may have on their health. Safety of both moms and their babies will also be assessed.

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### **What is known about the dapivirine ring in pregnant women?**

Information about the safety of the dapivirine ring during pregnancy and breastfeeding is reassuring but still very limited. Though animal studies of dapivirine indicate no concerns related to pregnancy or fetal development, the only human data is from about 250 women who became pregnant while participating in ASPIRE and The Ring Study and stopped use of the ring as soon as it became known they were pregnant and then followed throughout their pregnancies to monitor any negative effects. Notably, there were no significant differences in pregnancy and infant outcomes between women assigned to use the dapivirine ring and those assigned to use a placebo, but more information is needed about the ring when it used for longer periods and at different stages during pregnancy.

### **What do we know about the dapivirine ring in breastfeeding women?**

Only one study has been conducted to date, in which 16 women who were no longer nursing their babies but still producing milk used the dapivirine ring for 14 consecutive days. Results of the study, called [MTN-029/IPM 039](#), found no safety concerns and that dapivirine was absorbed at very low levels in breast milk. While babies weren't actually exposed to drug, based on levels measured in maternal breast milk, researchers estimated that an infant's daily exposure to drug would be very low.

### **If clinical trials don't typically include pregnant and breastfeeding women why is it safe to conduct these studies?**

Both the DELIVER and B-PROTECTED studies are designed to learn about the safety of the dapivirine vaginal ring, as well as Truvada as daily oral PrEP, in the safest, most efficient way possible. For instance, DELIVER is being conducted in a stepwise, backward fashion, enrolling one group of women at a time, beginning with women who are late in pregnancy, when use of the ring or PrEP is likely to pose the least risk. Interim reviews of study data will be conducted after completion of each phase to determine whether it is safe to proceed to the next phase. One reason for this design is to be attentive to the potential risks and complications that can occur at different times during pregnancy and fetal development and to ensure that use of the dapivirine ring or oral PrEP does not pose additional risk or harm to either the mother or her fetus. Both studies also include multiple layers of safety monitoring. Ensuring the safety of mothers and babies is what's most important, and site staff will stop a woman's use of PrEP or the ring if there are any concerns.

While DELIVER is the first study of its kind of the dapivirine ring in pregnant women, and B-PROTECTED is the first study of the ring in women who are actively breastfeeding, the MTN is uniquely qualified to conduct such studies. Since its inception 14 years ago, MTN's scientific portfolio has included a comprehensive research program purposefully designed to take incremental steps for determining whether HIV prevention products are safe to use by women during pregnancy and breastfeeding.

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More information about the MTN and its studies is available at [www.mtnstopshiv.org/](http://www.mtnstopshiv.org/). For more information about the dapivirine ring go to [www.ipmglobal.org](http://www.ipmglobal.org).

#### *About the Microbicide Trials Network*

*The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners whose work is focused on the rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use.*