EMA's Positive Opinion for the Dapivirine Ring

Frequently asked questions

EMA's Opinion and Key Next Steps

What does today's EMA's positive opinion mean for the monthly dapivirine ring and for women?
Today is a milestone for women at high risk for HIV. The EMA's opinion through Article 58 is validation from a stringent regulatory authority that the monthly dapivirine ring could help fill a critical gap in the HIV prevention portfolio for women with a long-acting option. The positive EMA opinion opens the door to the next steps needed to seek approvals for the ring and make it available in countries where women are at high risk. IPM, which developed the ring, will continue developing follow-on rings—including an even longer-acting three-month dapivirine ring as well as a three-month ring designed to offer simultaneous HIV prevention and contraception.

Who is the ring for?
The EMA provided a positive scientific opinion for the ring's use by cisgender women ages 18 and older in developing countries to reduce their HIV risk. In sub-Saharan Africa, women continue to bear the burden of the HIV epidemic and continue to have an urgent unmet need for new HIV prevention options. The ring could give women a new choice for HIV prevention.

What is the EMA Article 58 procedure?
Through Article 58, the EMA, in cooperation with the World Health Organization (WHO), provides a scientific opinion on a product intended for use outside of the European Union—specifically to address a disease of major public health interest in developing countries. This procedure uses the same rigorous standards as for medicines intended for use in the EU. It involves experts from WHO and observers from national regulatory authorities in representative countries where a product may be used. A positive opinion from the EMA through Article 58 is recognized by many countries in Africa, which can facilitate regulatory reviews there, and it can shorten the timeline to WHO prequalification, a process that ensures a product meets global standards for quality, safety and efficacy.

What are the next steps for the ring's review in African countries?
IPM will be submitting the ring for country reviews in Africa through the WHO's collaborative registration procedure, which facilitates accelerated reviews by national regulatory authorities in Africa for a product that has already received a positive decision from a stringent regulatory body such as the EMA. We currently hope to begin those submissions by the end of 2020. In parallel, the WHO plans to revise HIV/AIDS treatment and prevention guidelines with recommendations on the ring's use, and review the ring for prequalification, a quality assurance designation that ensures a product meets global standards for quality, safety and efficacy.

Where would the ring be available first? Why did you select those countries?
We are prioritizing potential rollout of the ring in sub-Saharan Africa, where women have an urgent unmet need for new tools. We currently plan for the first submissions to regulatory agencies in Kenya, Malawi, Rwanda, South Africa, Tanzania, Uganda and Zimbabwe, where the previous ring studies took place and the need is great. Given women's high risk, making the ring available across Africa is vital, and regulatory submissions to additional countries will follow as soon as possible.

When could the ring be available to women?
IPM hopes to begin making the ring available in some communities in eastern and southern Africa in 2021. Ring availability depends on a variety of factors, including the timing of country reviews, approvals and national policy decisions, which could be affected by various factors, including the COVID-19 pandemic, but may be accelerated with sufficient political will and funding. We're working with our manufacturing and other partners to ensure IPM is ready to begin making the ring available as soon as countries are ready to launch the product.

Will the ring only be available in Africa or will it have a global reach?
In line with IPM's nonprofit mission, the first phase of the dapivirine ring's potential rollout is prioritized for sub-Saharan Africa where it could have the greatest impact given the urgency of the epidemic in that region. However, we are open to providing the ring to women in any country in the future on the basis of need and demand. IPM holds exclusive worldwide rights to dapivirine through Janssen Sciences Ireland UC. This agreement ensures that dapivirine-based products are first distributed in developing countries; however, the agreement also enables access to products in developed countries.

When are you submitting to the US Food & Drug Administration? How long will that review take?
IPM plans to submit to the US FDA at the end of 2020, which has a one-year review period.

Will IPM also seek approval for the ring's use among adolescent girls?
Yes. Addressing adolescent girls' urgent unmet HIV prevention needs is a high priority. Results from one completed study among adolescent girls and young women in the US (led by the US National Institutes of Health-funded Microbicide Trials Network [MTN]) and a two-year study now underway in Africa (REACH, also led by MTN) may support regulatory approvals in the future for the ring's use among this key group.

Can pregnant and/or breastfeeding women use the dapivirine ring if it is approved?
Depending on each country's approval and guidelines for use, women would be advised to consult with their healthcare providers to discuss the potential benefits and risks of using the ring with their clients who are either pregnant or breastfeeding. In addition, IPM's partner MTN is collecting data on the ring's safety to help us understand how the ring would fit into the lives of women in these key groups, who face an estimated two to four times higher risk of HIV (DELIVER and B-PROTECTED).

Additional Questions About the EMA's Review

Why is the EMA looking for additional data among women ages 18-25?
In its positive opinion for the ring, the EMA noted the lower HIV risk reduction seen among women 18-21 due to low product use. The agency recommended additional research both to complement existing efficacy data and to better understand the ring's efficacy among younger women, who remain at alarming risk for HIV. This study will also offer an opportunity to learn how to support young women to

use the ring now that they know that it received a positive regulatory opinion, and to maximize its effectiveness in the real world. The ongoing REACH study by MTN will also help us understand the ring's use among young women in addition to adolescent girls.

When will the research begin?
Details about this research, including timelines, study design and location will require consultation as part of the EMA scientific advice procedure as well as with donors, governments, research partners, communities, women and civil society for their inputs. We will provide updates on our website as we have them.

What data were submitted for review to the EMA?
The application includes chemistry, manufacturing and controls (CMC) data as well as data from 183 non-clinical studies, 11 Phase I and Phase II safety and pharmacokinetics trials, two Phase Ill trials: The Ring Study (IPM 027), led by IPM in South Africa and Uganda, and ASPIRE (MTN-020), which was conducted by the US NIH-funded MTN in Malawi, South Africa, Uganda and Zimbabwe, and two Phase IIIb open-label extension trials, DREAM (IPM 032) and HOPE (MTN-025). Additional data from 33 other studies were also included as supplemental data.

Why did the EMA assess the ring's efficacy based only on one Phase III study if two were conducted?
During its review, the EMA communicated that its assessment of the ring's efficacy would be based solely on data from The Ring Study, led by IPM, the ring's regulatory sponsor, and that its safety assessment would be based on data from both The Ring Study and a second Phase III study called ASPIRE, conducted by the US NIH-funded MTN. The EMA excluded the ASPIRE efficacy data from its assessment due to noncompliance with Good Clinical Practice, known as GCP, an international standard for designing, conducting, recording and reporting clinical trials that involve people. The EMA concluded that there were gaps in documentation for certain processes and decisions related to how the efficacy data analysis was performed. The EMA indicated that participant safety was not at issue and confirmed that the research centers that conducted ASPIRE were GCP compliant and that the data collected by these sites were sound. Importantly, the EMA retained ASPIRE's safety data, which was critical to demonstrating the ring's strong safety profile and enabling today's positive opinion.

What steps have been taken to address those issues?
The ASPIRE trial was a partnership among the NIH, IPM and MTN, and all took this finding very seriously. Upon learning of the EMA's determination, each partner immediately took steps to improve clinical trial documentation and oversight, and have worked together to ensure GCP compliance in all ongoing and future studies. A summary of findings will be included in the EMA's public assessment report, which we expect to be published in late September.

Planning for Ring Introduction

How does the ring fit into the existing HIV prevention portfolio?
As the only long-acting HIV prevention method, the dapivirine ring would help fill a critical gap in the prevention portfolio and offer women an option when they are unable to, or choose not to, use higher efficacy products such as daily oral PrEP. No one method will work for everyone. Women need different options to meet their individual needs and life circumstances, which change over time. Multiple modeling studies show that a combination prevention approach is needed to achieve epidemic control—that includes oral PrEP, treatment-as-prevention, condoms, male circumcision, plus woman-

controlled tools like rings as well as methods in development like injectables, rectal microbicides and vaccines.

What is IPM doing to ensure women can access the ring when approvals are received?
IPM is working with a global network of partners across sectors to shorten the timeline between approval and the ring's introduction as much as possible. This includes engaging with partners in manufacturing and supply chain management; conducting research to inform education and demand creation among women, communities and healthcare providers; and working with policymakers and implementers to learn from the rollout efforts of other biomedical products.

Would women have to pay for the ring?
As a nonprofit, our goal is for the ring to be publicly funded and provided to women at low or no cost. The ring's ultimate cost will vary by country, and IPM is working with donors, governments, civil society and other partners to keep costs to women low.

Where would women get the ring—pharmacies, hospitals, clinics?
The ring's distribution would vary by country. Because the dapivirine ring contains an ARV drug and will require regular HIV testing, a clinician would prescribe the ring, and some countries may also allow pharmacists to dispense the product to women. IPM is working with regulatory agencies, policymakers, health worker associations, implementing organizations, advocates and others to identify distribution channels.

Because IPM's license for dapivirine is through the Janssen Pharmaceutical Companies of Johnson & Johnson, do they get royalties? Does IPM?
No, neither Janssen nor IPM will receive royalties on the ring. In fact, our licensing agreement with Janssen ensures that dapivirine-based products are made available at affordable cost in any low-resource setting where they are approved for use.

Dapivirine Ring: The Basics

What is dapivirine?
Dapivirine is a potent ARV that belongs to a class of ARVs known as non-nucleoside reverse transcriptase inhibitors, or NNRTIs, which work against HIV-1 by blocking its ability to make copies of itself once inside a healthy cell. IPM began developing dapivirine as a microbicide in 2004, when it received a royalty-free license from the Janssen Pharmaceutical Companies of Johnson & Johnson, which was later expanded to a worldwide rights agreement.

What is the dapivirine ring?
The ring is made of a flexible silicone with 25mg of the ARV drug dapivirine dispersed uniformly throughout its matrix. The ring provides sustained release of the drug directly in the vagina at the site of potential infection over the course of a month, with low absorption elsewhere in the body.

Is the ring easy to insert and use?
Yes. A woman can insert the ring easily herself and would replace it each month.

Can women feel the ring once it's inserted?
Women in studies to date overwhelmingly say the ring is comfortable and they cannot feel it once it's inserted and left in place. Some women reported being concerned initially about the size of the ring and how it would feel, but with education and experience, the vast majority of women could no longer even sense it was there after a brief period of time.

How effective is the dapivirine ring?
The Ring Study found that IPM's dapivirine ring reduced women's HIV risk by 35% overall with no safety concerns with long-term use. HIV risk reduction was likely greater among participants who used the ring more regularly. We are also encouraged that two subsequent open-label studies of the ring (DREAM and HOPE) found increased product use and suggest greater risk reduction—by about half across both studies—compared to the Phase IIIs. Although the DREAM and HOPE results are limited because they are estimates based on statistical modeling, it's a trend we hope to see continue.

I thought the ring showed about 30% efficacy. Why are you saying 35% now?
During the EMA's review, the agency requested additional data that resulted in an adjustment of The Ring Study's efficacy result to 35% (95% CI: 9 to 54%; p=0.012), a statistically significant finding.

How safe is the ring?
There were no safety concerns with long-term use of the ring in both The Ring Study and ASPIRE, with no statistical difference in adverse events between the active dapivirine ring and the placebo groups. Data from two open-label studies show a similar strong safety profile as do 12 smaller safety studies.

Does the ring have side effects? What are they?
Side effects in the Phase IIIs were generally mild to moderate genital and urinary tract issues that were minor and transient in most cases, and that resolved without interrupting ring use (for example, vaginal discharge or itching).

How long does the ring need to be in place before it offers HIV protection?
A woman must have the ring in place for at least 24 hours before the ARV can begin to help protect her against HIV. However, it is the level of sustained-release over the course of a month that helps reduce risk, which is why it is so important that women keep the ring in and replace it monthly.

Would widespread use of the ring create resistance to treatment products in the same class?
This is an important issue that IPM will continue to study, including in ongoing and upcoming research. Data from the Phase III studies of the ring show no evidence that the ring increases resistance to NNRTIs, the class of ARV drug to which dapivirine belongs and which is also used in some treatment regimens.

Who funded the development of the ring?
IPM's work is made possible through the generous support of numerous donors. In addition, the ASPIRE and HOPE studies as well as several safety studies were conducted by MTN and funded by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all part of the U.S. National Institutes of Health (NIH).