

EMA's Positive Opinion for the Dapivirine Ring

- [EMA's Opinion and Key Next Steps](#)
- [Additional Questions About the EMA's Review](#)
- [Planning for Ring Introduction](#)
- [Dapivirine Ring: The Basics](#)

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

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

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 III 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

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—p29)4 VITJ-0.004 Td(29)4a (1)3.51 -1.21B-0.0,p29)4 1.3 0-0.0,p. 18 Td(n)6T

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).