CONTACT: Lisa Rossi
+1- 412-641-8940
+1- 412- 916-3315 (mobile)
rossiL@upmc.edu

QUESTIONS AND ANSWERS
HOPE – HIV Open-label Prevention Extension Study

HOPE in Context

- The dapivirine vaginal ring is the first biomedical HIV prevention product specifically for women shown to be safe and to reduce the risk of acquiring HIV in two independently conducted Phase III trials. Higher levels of protection were seen in women who used the monthly ring most regularly. Together these two studies involved 4,588 women in four African countries where HIV rates for women continue to be among the highest globally, with heterosexual intercourse being the primary driver of HIV transmission.
- ASPIRE was conducted by the National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN), while its sister study, The Ring Study, was conducted by the International Partnership for Microbicides (IPM), a non-profit organization that also developed the dapivirine ring. The ring, which women can insert and replace themselves, contains an antiretroviral (ARV) drug called dapivirine that is slowly released during the month it is worn.
- Based on the results of ASPIRE and The Ring Study, and several supporting studies, IPM is seeking regulatory approval of the dapivirine ring for women ages 18-45. The first decision could be received in 2019.
- In parallel, former ASPIRE participants are being offered the opportunity to use the dapivirine ring in the context of an open-label extension study called HOPE. HOPE will help understand issues important for broader implementation of the dapivirine ring, should it be approved. A similar study, called DREAM, is being conducted for former participants of The Ring Study.

HOPE – The HIV Open-label Prevention Extension Study

What is the aim of the HOPE study?
HOPE (HIV Open-label Prevention Extension, or MTN-025) was designed to provide former ASPIRE participants the opportunity to use the dapivirine ring in the context of a study that would build on the results of ASPIRE. HOPE will collect additional information about the ring's safety, how women use the ring knowing that it can help reduce their risk of HIV, and the relationship between adherence and HIV prevention. HOPE also seeks to understand the reasons why some women choose not to enroll in HOPE, and why some who choose to enroll do not want to use the ring. By including all women, researchers hope to better understand why the ring may work well as an HIV prevention strategy for some but not for others, how this might change over time or in different circumstances, and what influences women's decisions about the ring. A similar study, called DREAM, is being conducted for former participants of The Ring Study.

What exactly is the dapivirine ring?
The dapivirine ring is similar to vaginal rings commonly used for contraception except that it contains an ARV drug instead. Each ring contains 25 mg of the ARV dapivirine, about 4 mg of which gets released into the vagina over the month that it is worn. The ring, which is made of a flexible material, sits high inside the vagina. Women can insert and remove it themselves. Dapivirine, also known as TMC-120, belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors that bind to and disable a key protein that HIV needs to make copies of itself. IPM holds an exclusive worldwide license for dapivirine from

-more-

Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen), which is designed to ensure that women in low-resource settings have affordable access to any dapivirine-based microbicide.

Where is HOPE being conducted?
The MTN is conducting HOPE at 14 trial sites in Malawi, South Africa, Uganda and Zimbabwe where ASPIRE was conducted. Jared Baeten, M.D., Ph.D., of the University of Washington in Seattle, is leading HOPE, with Thesla Palanee-Phillips, Ph.D., M.Sc., of the Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; and Nyaradzo Mgodi, MBChB, MMed, from the University of Zimbabwe College of Health Sciences in Harare, Zimbabwe.

When did HOPE start, and when is it expected to be completed?
HOPE enrolled its first participants in August 2016 and will complete enrollment mid-September 2017. The study expects to complete all follow-up in September 2018 and to report results about six months later, in early 2019, within the same timeframe that the first decisions about regulatory approval of the ring could also be available.

How is HOPE designed?
In ASPIRE, participants were using a vaginal ring for the first time and had no knowledge of its efficacy or long-term safety, nor whether they had been randomly assigned to use the dapivirine ring or a placebo ring (that looked the same but had no active drug). In HOPE, there is no randomization and no placebo ring. All women, if they choose, receive the dapivirine ring. Women periodically receive their individual test results that reflect the amount of drug released from the ring to facilitate discussions on adherence and how it relates to protection. Visits are monthly for the first three months and quarterly thereafter – a schedule more in keeping with a public health service delivery model.

What were the results of ASPIRE?
ASPIRE enrolled 2,629 sexually active HIV-negative women ages 18-45, and was conducted between August 2012 and June 2015 at 15 clinical research sites in Malawi, Uganda, South Africa and Zimbabwe. Primary results of both ASPIRE and The Ring Study were reported in February 2016. Overall, the two studies found the ring was safe and reduced women's risk of acquiring HIV by about 30 percent overall (by 27 percent in ASPIRE and by 31 percent in The Ring Study). Higher levels of protection were seen in women who used the ring most consistently. In fact, the ring was not effective among younger women ages 18-21 who used the ring least regularly. Results of an exploratory analysis of ASPIRE data reported at AIDS 2016 found the level of HIV protection for those who appeared to use the ring most consistently was at least 56 percent and as high as 75 percent or more with near perfect use.

Is the expectation that women will use the ring more consistently in HOPE?
Participants in ASPIRE were using a vaginal ring for the first time, and they didn't know whether the ring was safe and effective or whether they had been assigned to use the active ring or the placebo ring. These uncertainties may have influenced willingness to the use the ring. Researchers are hopeful that women will feel more at ease about the ring in HOPE and that those who choose to accept the ring will use it as consistently as possible, knowing that its regular use can reduce their risk of HIV. In similar open-label extension studies of daily oral PrEP, adherence to product use increased, and as a result, the level of effectiveness was higher than in the original Phase III trials. At the same time, women in HOPE are free to choose the ring or not, and to change their minds at any time during the study, without judgement.

Why enroll women who don't want to use the ring?
By including all women, researchers hope to better understand why the ring may work well as an HIV prevention strategy for some but not for others, how this might change over time or in different circumstances, and what factors influence women's decisions about the ring. All participants who join HOPE contribute valuable information to the study, including how to help women use the ring successfully in the future.

How is DREAM, the open-label access study for The Ring Study, different from or the same as HOPE?
As an open-label extension study for former participants of The Ring Study, DREAM (Dapivirine Ring Extended Access and Monitoring) is very similar to HOPE. It, too, is designed to collect additional safety information, explore when, why and how women use the ring, and to help understand how adherence may affect the product's efficacy. Both studies are also interested in understanding why some women do not want to use the ring. Unlike HOPE, the DREAM study may also enroll an additional group of participants – about 600 young women ages 18-25 who would be using the ring for the first time. In addition, IPM is currently working to identify funding so that it can continue DREAM beyond its first year (the study started July 2016). Pending this additional funding, DREAM could continue until a regulatory decision is made, and, if the ring is approved, until the product is available.

Why is participation in HOPE limited to one year?
HOPE is similar to other HIV prevention open-label extension studies that have been conducted to date, which lasted between one and two years. In designing HOPE, researchers determined that a one-year follow-up period would provide answers to the study's questions within a timeframe that could help inform ongoing regulatory submissions, and if the ring is approved, its roll-out into communities.

Will the HOPE or DREAM open-label extension studies contribute to potential dapivirine ring approval?
IPM will be submitting its applications to regulatory authorities as HOPE and DREAM are ongoing. Data from these studies will not be required by regulators in their review, however, IPM plans to provide this information upon the studies' completion or, if requested by regulators, during the review process. Both studies will provide important information that will help guide implementation of the ring should it receive regulatory approval.
(*See also* About the Regulatory Approval Process)

At the Trial Site

What approvals were needed to conduct the study?
HOPE underwent extensive and rigorous review by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and the U.S. Food and Drug Administration (FDA). Moreover, before any site could begin the study, approvals were required of government and drug regulatory authorities in the trial site country and by the site's Institutional Review Board (IRB) or Ethics Committee (EC). IRBs and ECs ensure that studies are scientifically valid and ethically sound and provide oversight throughout the duration of the trial.

Who may participate in HOPE?
Former ASPIRE participants could take part in HOPE provided they were not HIV-infected, pregnant or breastfeeding at the time of enrollment, and they agreed to use contraception during the study. Of the 2,629 women who were in ASPIRE, researchers estimated that about 2,400 would be eligible. Ultimately, about 1,500 of those women who could be contacted were screened for the study, and more than 1,400 have enrolled to date.

Why would some former ASPIRE participants not enroll in HOPE?
Some women are not able to join HOPE because they have acquired HIV or are pregnant and/or breastfeeding. Others may have moved away or are unable to be reached by the trial site. Some women may be eligible to enroll in HOPE but choose not to. Researchers hope to understand the reasons for declining to join the study among women who agree to participate in one-time questionnaires and/or in-depth interviews.

Do women participating in HOPE provide informed consent?
Yes. As with any research study, women who volunteer to join HOPE are informed about all study procedures, possible risks and time requirements. Study staff also explain that women do not have to take part in the study and may leave it at any time, without consequence.

Is safety still being monitored in HOPE?
Results of ASPIRE and The Ring Study found no safety concerns with the dapivirine ring. Nonetheless, one of the reasons for conducting HOPE is to collect additional information about the ring's safety. In HOPE, women are monitored in much the same way as they were in ASPIRE, with routine laboratory tests, including HIV testing, and assessment of any ongoing or recent medical conditions at each study visit. Unlike ASPIRE, which involved monthly visits throughout the study, women in HOPE are seen monthly for the first three months, and then visit the clinic quarterly (every three months) thereafter. Participants with special concerns or needing more immediate attention may contact the trial site at any time.

What happens if a participant becomes HIV-positive while in HOPE?
Some women could become infected during the study due to sexual activity with an HIV-infected partner without protection. Women in the trial who test positive for HIV are asked to stop using the ring immediately and counseled and referred by study staff to local HIV care and support services. Women are encouraged to remain in the study and continue with routine study visits but are also invited to participate in another MTN study called MTN-015. MTN-015 does not provide HIV treatment, but offers laboratory tests indicating how the disease is progressing and how women are responding to treatment. Results from these tests may help local treatment providers better manage their clinical care.

Does HOPE provide antiretroviral therapy, or ART, to women who acquire HIV?
MTN receives funding to conduct clinical trials only, and cannot provide HIV treatment. However, all MTN trial sites are required to have agreements with local service providers so that if a study participant acquires HIV she can be referred to the appropriate services and care in her community.

Can women who are pregnant or breastfeeding use the ring in HOPE?
Researchers don't yet know how dapivirine might affect a woman's pregnancy or the development of her fetus, so HOPE participants must not plan to become pregnant during the study and are required to use effective contraception. If a participant becomes pregnant during the study, she will stop use of the ring, but may remain in the study and continue with all trial site visits.

The MTN recognizes the need for information about the safety of the ring in women during pregnancy and breastfeeding. As a first step, it conducted a safety study in the United States, which found only a very small amount of dapivirine is absorbed into breastmilk. Additional studies involving both pregnant and breastfeeding women are being planned to take place in Africa. If the ring is approved, its intended use will be for sexually active women ages 18-45 – women of reproductive age. Understanding its safety during pregnancy and breastfeeding will be especially important.

What are the medical benefits for women participating in HOPE?
Study participants receive free laboratory tests and physical and pelvic exams, HIV prevention counseling and free condoms. STI risk-reduction counseling, testing and treatment are also provided at no charge to women, and HIV testing and STI treatment is offered to their partners. In addition, HOPE provides effective barrier and hormonal contraception and monthly pregnancy and HIV testing. Women are referred to local service providers for ongoing treatment, management and care for any medical issues that cannot be managed at the clinical research site.

How will women be protected from HIV after they leave HOPE?
The reality is that participants live at high risk of acquiring HIV and their options for protection are limited. That is exactly why researchers are doing this work—to expand the prevention options available to women. Before exiting the study, participants will receive counseling on different HIV prevention options, including how to access certain services after they leave the study. Options may include: using condoms, using oral PrEP (if accessible), reducing their number of sexual partners, engaging in lower-risk sexual behaviors, having frequent HIV and STI testing (and receiving treatment for STIs, if infected), and encouraging their partners to get testing and treatment for HIV and STIs.

Regulatory approvals, new studies and next steps

What are IPM's plans for seeking regulatory approval of the dapivirine ring?
IPM is seeking regulatory approval of the dapivirine ring for women ages 18-45, the same age group represented in the ASPIRE and The Ring Study Phase III trials and among whom there is the most data. IPM's first application was submitted to the European Medicines Agency (EMA) in June 2017, under a procedure called Article 58 in which the EMA, in cooperation with the World Health Organization (WHO), is asked to provide a scientific opinion on the safety, efficacy and quality of the dapivirine ring. Should the EMA grant a favorable opinion, IPM will then seek WHO pre-qualification. This is important because drug regulatory authorities in many developing countries often rely on WHO pre-qualification to determine which new products or drugs to consider for approval.

Separately, IPM plans to submit applications to the South African Health Products Regulatory Authority (formerly the Medicines Control Council) early 2018 and to the U.S. Food and Drug Administration (FDA) later that year. And, if WHO pre-qualification is granted, IPM will also proceed with applications to drug authorities in several African countries, including Malawi, Uganda and Zimbabwe – where, in addition to South Africa, ASPIRE was conducted. (The Ring Study was conducted in South Africa and Uganda.)

What is MTN's role?
The MTN is a clinical trials network that receives its funding from the NIH for the expressed purpose of designing and conducting the kind of studies needed to support potential licensure and regulatory approval of promising HIV prevention products. The MTN plays no role in the regulatory process. But for its part, the MTN conducted several key studies of the dapivirine ring that are included in the dossier of data that IPM is submitting to regulatory authorities. In addition to the ASPIRE Phase III trial, these studies include those conducted in the United States: MTN-023/IPM 030, a Phase IIa safety study of the ring in adolescent girls; MTN-024/IPM 031, a Phase IIa safety study of the ring in post-menopausal women; and MTN-012/IPM 010, a Phase I penile safety study of dapivirine involving sexually abstinent men.

The MTN has also completed a study that assessed whether dapivirine is absorbed in breastmilk and is now planning studies of the ring in breastfeeding and pregnant women in Africa. Its REACH study involving adolescent girls and young women age 16-21 will launch early 2018. Data from these studies will not be part of IPM's initial regulatory submissions but will be provided to regulators when they become available so that the ring can be considered for these important populations who are at increased risk of HIV.

When is a decision expected?
IPM is hopeful that the first regulatory approvals in Africa could be received in 2019. If the ring is approved by the EMA, and WHO has provided pre-qualification, IPM will move quickly to seek approval in other African countries. Timelines for potential approval will likely vary from country to country.

Why does it take so long?
The application, or dossier, that IPM submitted to the EMA included data from more than 250 laboratory and clinical studies, detailing nearly 15 years of research into 260,000 pages. Applications being prepared for other regulatory submissions are likely to be of similar length and complexity. Moreover, because dapivirine is a new drug, the review process may be more complex and take longer than for a drug like Truvada, which was already approved for the treatment of HIV when it was under review for use as prevention, an approach called pre-exposure prophylaxis, or PrEP.

If the ring is approved, when and where will it be available?
The first phase of the dapivirine ring's rollout would be in sub-Saharan Africa. But, while IPM hopes the first regulatory approvals are received 2019, at the soonest, approval would not mean the ring's immediate availability. Governments would still need to decide how they want to implement its delivery, and timelines and processes may differ across countries. Because the dapivirine ring contains an ARV drug, regular HIV testing will be required; some countries may require a health worker to prescribe or dispense the product to women.

How much is the ring expected to cost?
If approved, the ring would likely be publicly funded and provided to women at low or no cost, similar to other HIV prevention services. Initially, IPM expects the cost per monthly ring will be approximately 7 USD, or 84 USD per year for 12 rings. Because such costs would be borne by governments and donors, the ring would be made available to women for free or at very low cost.

Is there need for the dapivirine ring when PrEP is already approved in many countries?
Daily use of an ARV tablet called Truvada (oral PrEP) is an approach now approved in many countries, including South Africa and Kenya, and recommended by WHO for persons at substantial HIV risk. PrEP is highly effective with consistent use. Taking a daily tablet can be difficult for some people. Others may have concerns about the stigma associated with taking an ARV pill. No single method will suit everyone, nor suit everyone at all times. As with contraception, the more HIV prevention options available to women, the more likely one will and can be used.

If approved, the monthly dapivirine ring would be the first biomedical HIV prevention product developed specifically for women – and the first long-acting product. Importantly, it would represent another option from which they may choose. Globally, more than half of all people currently living with HIV are women, and in sub-Saharan Africa, women account for nearly 60 percent of adults with HIV, with unprotected heterosexual sex the primary driver of the epidemic. Women need and deserve a range of safe and effective approaches to protect themselves against HIV.

Are other studies of the dapivirine ring being planned?
Other studies of the ring are planned, including REACH, which will enroll 300 young women ages 16-21 at five trial sites in Kenya, South Africa, Uganda and Zimbabwe. REACH (Reversing the Epidemic in Africa with Choices in HIV prevention, or MTN-034/IPM 045) will evaluate how young women use the monthly dapivirine vaginal ring and Truvada as daily PrEP, and their preferences for either or both approaches. The study, expected to start early 2018, will also collect information on the safety of these methods in young women. This is especially important for the dapivirine ring. While IPM is seeking its regulatory approval for use by women ages 18-45, data specifically on the ring's safety and use among women under 18 would be required if the ring will be made available to this population.

MTN researchers are also planning studies in Africa to determine whether the ring is safe to use during pregnancy (MTN-042) and breastfeeding (MTN-043), when the risk of acquiring HIV from an infected partner may be particularly high. Another study, MTN-041, will explore attitudes about ring and PrEP use during pregnancy and breastfeeding among women, male partners and community stakeholders.

What about next generation 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. Toward this end, the MTN is evaluating IPM's next generation of dapivirine rings. MTN-030/IPM 041 is the first study of a dual-purpose ring containing both a hormonal contraceptive (levonorgestrel) along with dapivirine, in quantities large enough to feasibly provide protection from HIV and unintended pregnancy for up to three months. As a Phase I study, researchers will assess safety of 14-day use and how each active ingredient is taken up in the body in the presence of the other. A second Phase I study, MTN-036/IPM 047, will evaluate a three-month dapivirine-only ring.

# # #

More information about HOPE and other MTN studies are available at http://www.mtnstopshiv.org/news/studies

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 development and 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. More information about the MTN is available at http://www.mtnstopshiv.org.