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BACKGROUNDER

MTN-037
Phase 1 Safety and Pharmacokinetic Study of PC-1005 for Rectal Use

Summary

- MTN-037 is a Phase I study evaluating whether a microbicide gel called PC-1005 is safe for use in the rectum. The study, which will include approximately 12 HIV-uninfected cisgender and transgender men and women at two sites in the United States, will help determine whether further testing on the safety and acceptability of PC-1005 as a potential rectal microbicide for preventing HIV and other sexually transmitted infections (STIs) can be conducted in a larger population. Results are anticipated by mid-2019.

- PC-1005 is a multipurpose gel made up of three compounds that include MIV-150 (a potent antiretroviral), zinc acetate dihydrate (an antiviral agent) and carrageenan (a gelling agent derived from seaweed). In laboratory and animal studies, PC-1005 has been shown to be active against several STIs, including HIV, human papillomavirus (HPV) and herpes simplex virus type 2 (HSV-2), and has undergone early clinical testing as a vaginal microbicide. If proven effective, PC-1005 would be the first multipurpose gel designed for both vaginal and rectal use to simultaneously prevent all three STIs.

- MTN-037 is a study of the Microbicide Trials Network (MTN), 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. PC-1005 gel was developed by the Population Council, a nonprofit, non-governmental organization that conducts research in biomedicine, social science and public health based in New York, NY. Protocol chair for the study is Craig Hendrix, M.D., of Johns Hopkins University in Baltimore.

- MTN-037 is part of a research agenda at the MTN focused on the development of HIV prevention products for cisgender and transgender men and women who engage in condomless anal sex, a major risk factor for HIV infection.

Why this Study is Important

Microbicides are products applied inside the vagina or rectum that are intended to protect against HIV infection acquired through sex. Products currently being tested in clinical trials contain

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antiretroviral (ARV) drugs, many of which are commonly used to treat people with HIV. Although the majority of microbicide research has focused on products to prevent HIV infection associated with vaginal sex, important strides are being made in research aimed at addressing the need for rectal microbicides.

Anal sex is a common sexual behavior practiced by both men and women around the world. According to some estimates, the risk of becoming infected with HIV during anal sex is 20 times greater than vaginal sex because the rectal lining is thinner and more fragile than the vaginal lining. While condoms are an effective method to prevent HIV infection through anal sex, many people can't or don't want to use them every time they have sex. Similarly, oral pre-exposure prophylaxis (PrEP) – an HIV prevention strategy in which people take a pill called Truvada® daily to prevent infection – has been shown to be highly effective, however, not all at risk individuals may be willing or able to access it. Just as there are multiple contraception options for women who choose to prevent pregnancy, a rectal microbicide could give people who practice anal sex an additional choice for HIV prevention.

MTN researchers reported results from the first Phase II study of a rectal microbicide, a gel containing the ARV tenofovir, in early 2016. The study, MTN-017, evaluated whether a reduced-glycerin formulation of tenofovir gel was safe and acceptable as a rectal microbicide. Results indicated that the gel used in MTN-017 was safe, with most study participants highly adherent to its use. The gel was found most acceptable when used around the time of sex, compared to daily use.

In addition to reduced-glycerin tenofovir gel, researchers are exploring other ARV-based products as potential candidates for rectal microbicides. A gel containing dapivirine is one such product. An ongoing study called MTN-026 is the first study to assess the safety of dapivirine gel used rectally.

MTN-037 is an important addition to these studies because the drug being studied, PC-1005, is active not only against HIV, but HPV and HSV-2 as well. HPV infection is common men who have sex with men and is a primary risk factor for developing anal cancer, while HSV-2 increases susceptibility to HIV. PC-1005 is the only product designed for vaginal and rectal use targeting all three STIs that has undergone a Phase 1 study to date.

How the Study is Designed

MTN-037 is a Phase I trial designed to evaluate the safety of PC-1005 gel used rectally, as well as determine the degree that drug concentrates in the blood, rectal fluid and tissue. The study is enrolling approximately 12 HIV-uninfected cisgender and transgender men and women who will receive three increasing doses of the gel in the clinic administered rectally with an applicator. Participants will initially receive a 4-milliliter (about a quarter of a tablespoon) dose of the gel. Two to six weeks later, and after testing determines it is safe to move forward, participants will receive a 16-milliliter dose of gel, followed by another two to six weeks and additional safety testing. Provided there are no safety issues, participants will receive a final 32-milliliter dose of the gel followed by a concluding safety assessment.

MTN-037 is being conducted at the University of Pittsburgh, site investigator Ken Ho, M.D., and the University of Alabama at Birmingham, site investigator Craig Hoesley, M.D. Tests and procedures performed as part of the study will determine the clinical safety of the products, and how much drug is absorbed in blood, rectal fluid and tissue. To explore the acceptability of the gel, study

participants will be asked about any side effects they may have experienced and their likes and dislikes about the product overall, and the different volume of gel doses, as well as the applicator and administration method. All participants will receive HIV risk reduction counseling and condoms, and be tested for HIV and sexually transmitted infections.

The Product Being Studied

PC-1005 is microbicide gel comprised of a nonnucleoside reverse transcriptase inhibitor (NNRTI) called MIV-150. NNRTIs bind to and disable HIV's reverse transcriptase enzyme, a protein that HIV needs to make copies of itself. MIV-150 was originally developed as an oral ARV, but it was deemed more suitable as a topical microbicide. In addition to MIV-150, PC-1005 is composed of zinc acetate dihydrate, an antiviral agent that inhibits HIV and HSV-2, and carrageenan, a thickening agent derived from red seaweed that blocks HPV and is used in commercially available lubes and condoms.

In animal and laboratory studies, PC-1005 displayed robust anti-HIV, HPV and HSV-2 activity, and was found safe for vaginal use in a Phase 1 study in which cisgender women used it for 14 consecutive days. Acceptability of the gel was high, with 94 percent of participants reporting that they would be willing to use it in the future. Most found it easy to apply, and appreciated that the gel had no color or scent. MTN-037 is the first clinical study to explore rectal use of the gel.

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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 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 www.mtnstopshiv.org.

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