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## **QUESTIONS AND ANSWERS**

### **MTN-004**

#### **A SAFETY AND ACCEPTABILITY STUDY OF THE CANDIDATE MICROBICIDE VIVAGEL IN SEXUALLY ACTIVE YOUNG WOMEN**

##### **1. What was the aim of MTN-004?**

MTN-004 was a Phase I study that evaluated the safety, acceptability and ease of use of the microbicide candidate VivaGel® (SPL7013 Gel) in sexually active, HIV-negative women ages 18 to 24. The study was conducted to help researchers determine if the product should be advanced to further testing.

##### **2. What is a microbicide?**

Microbicides are substances designed to reduce or prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside of the vagina or rectum. A microbicide can be formulated in many ways, such as a gel or cream, or as a ring that would release the active ingredient over time. Some microbicides are also being developed for rectal use. Several microbicide products are being tested in clinical trials, although none is yet approved or available for use by women.

##### **3. Who conducted and funded the trial?**

MTN-004 was funded by and conducted through a collaboration between the Microbicides Trials Network (MTN), an HIV/AIDS clinical trials network established by the National Institute of Allergy and Infectious Diseases (NIAID), and the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Both NIAID and NICHD are components of the U.S. National Institutes of Health (NIH). The study product was provided free of charge by the study's co-sponsor and owner of VivaGel, Starpharma Holdings Limited of Melbourne, Australia. Ian McGowan, M.D., Ph.D., from the University of Pittsburgh and Magee-Womens Research Institute, led the study.

##### **4. Where and when was the study conducted?**

MTN-004 was conducted at two ATN-affiliated sites, the University of South Florida in Tampa and the University of Puerto Rico in San Juan, and at the University of Pittsburgh, an MTN clinical research site. MTN-004 was launched in July 2007 and enrolled the first participants in August 2007. Follow-up of participants was completed in November 2009.

##### **5. What candidate microbicide was studied?**

SPL7013 Gel, known by its brand name VivaGel, was evaluated in MTN-004. The active pharmaceutical ingredient in VivaGel has a unique molecular structure that belongs to a class of compounds called dendrimers, which are large, well organized molecular structures. Researchers believe the active ingredient in VivaGel hampers the ability of HIV to attach to and infect healthy cells. Starpharma is developing VivaGel as a candidate microbicide for the prevention of both HIV/AIDS and genital herpes. Three other Phase I studies of VivaGel have been conducted in which researchers found the gel safe and well tolerated in sexually abstinent women who used gel once or twice a day for up to 14 days and in men who applied gel to the surface of their penis once daily for seven days.

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## **6. Why was the study paused and is this common practice?**

It is not unusual to pause a Phase I study in order to assess early observations. As such, MTN-004 researchers took this cautious approach to ensure the safety of study participants after noticing that many of the women who initially enrolled were experiencing similar signs and symptoms, some of which were likely related to their use of the study products. An interim review of all available data at the time, including laboratory and clinical information, confirmed these signs and symptoms were typical for a Phase I microbicide study. All were minor in nature and resolved completely and rapidly during follow-up. However, the research team opted to continue to pause the study in order to make modifications to allow for the collection of more comprehensive safety data, and thus, strengthen the study conclusions.

## **7. How was MTN-004 originally designed and what was changed?**

MTN-004 was a randomized placebo-controlled Phase I safety and acceptability study. Originally, researchers planned to enroll 40 participants who would be randomly assigned to one of two study groups, with neither the researchers nor the participants knowing their assignment. One group would apply VivaGel twice a day for two weeks, while participants in the other group would apply a VivaGel placebo containing the same formulation but with no active ingredients. The study was subsequently modified to include a third arm and enrolled 61 women, which includes seven women from the earlier two-arm study. After this modification, participants were assigned to either the VivaGel group, the VivaGel placebo group or a group that used the hydroxyethyl cellulose (HEC) “universal placebo.” The HEC gel has been adopted as the standard placebo in many other microbicide trials. As with the original design, women in the study were provided condoms to be used with each act of sex. Researchers assessed the safety of VivaGel, comparing it with the VivaGel placebo and the HEC placebo gel, through laboratory tests and regular clinical examinations of study participants. Web-based questionnaires were used to provide information about the product’s acceptability, such as what participants liked or disliked about using the gel, how their sexual partners felt about its use and how likely they are to use microbicides in the future. Participation in the study lasts three weeks, including the two-week period that gels were used.

## **8. Why was the protocol modified to include a third arm?**

Researchers believed that by adding the universal placebo they would be able to enhance the study’s ability to capture relevant safety data and obtain more useful information for the clinical development of VivaGel as a candidate microbicide.

## **9. What did the study find?**

MTN-004 found that VivaGel was generally well tolerated yet women in the study said it was less acceptable to use than the two placebo gels – a VivaGel placebo, formulated in the same way but without the active ingredient; and a placebo known as hydroxyethylcellulose (HEC), which also contains no active microbicide and was used as an additional comparison. The findings suggest that it may be necessary to consider reformulating VivaGel before moving to further studies.

Symptoms such as vaginal itching, burning or redness were reported most frequently with VivaGel (63.6 percent) compared with the VivaGel placebo (52.4 percent); and the HEC placebo (38.9 percent), although these differences were not statistically significant. In a head-to-head comparison between products, however, women in the VivaGel group had a significantly higher incidence of urological/gynecological side effects compared to the HEC placebo group. It is important to note that none of the women experienced a serious side effect or withdrew from the study due to any kind of side effect. Both VivaGel and the VivaGel placebo caused changes to the vaginal microflora (bacteria and other microorganisms that are important to the health of the vagina), but 14-day use did not result in vaginal infections such as bacterial vaginosis. Women using VivaGel were less adherent to product use than women in the other two groups, with adherence rates 77 percent for VivaGel, 95 percent for the VivaGel placebo and 94 percent for the HEC placebo group. As for acceptability of the gels, 36 percent in the VivaGel group said they would be very likely to use the gel again in the future, while 48 percent of the women in the VivaGel placebo group and 61 percent of those in the HEC placebo group reported they would be likely use those products again.

## **10. What was done to ensure the safety of the participants?**

MTN-004 was designed according to the most rigorous international medical practices and ethical standards. Significant measures were taken to protect the safety and wellbeing of study participants through a multi-tiered

safety review process that included strict national and international procedures for monitoring and reporting. This process included clinicians evaluating participants at the trial sites; a team at the MTN Statistical and Data Management Center (SDMC) that assessed incoming reports on a daily basis; three MTN physicians – two specializing in infectious diseases and HIV and one in obstetrics and gynecology – who reviewed summary reports and any concerns raised by site clinicians or the SDMC; and monthly reviews by a protocol safety review team.

#### **11. What approvals were required to conduct this trial?**

Both the initial design and the amended protocol for MTN-004 underwent extensive and rigorous reviews by NIH, the U.S. Food and Drug Administration (FDA) and each site's Institutional Review Board (IRB). Local IRBs ensure that studies are scientifically valid and ethically conducted and they provide oversight throughout the duration of the trial. In addition, each trial site has a local community advisory board to provide input and oversight around trial activities.

#### **12. Did women participating in the study provide informed consent?**

Written informed consent was obtained from each study participant prior to both screening and enrollment. The process ensured that women understood the procedures, risks and benefits of the study, the need to practice safer sex behaviors regardless of the study treatment group, the importance of adherence, and the potential medical risks associated with study participation. Participants were under no obligation to participate and were aware that they could leave the study, without consequence, at any time.

#### **13. How does this trial differ from other microbicide trials?**

MTN-004 is one of only a few trials that have evaluated a candidate microbicide that belongs to the class of compounds known as dendrimers, unique molecular structures that hold promise for preventing the sexual transmission of HIV and genital herpes.

#### **14. Why was this trial important?**

Women are fast becoming the group being hardest hit by the HIV/AIDS epidemic. Especially alarming is the steady increase in HIV rates among women under the age of 25, a population considered one of today's most vulnerable for acquiring the disease. According to statistics from UNAIDS and the U.S. Centers for Disease Control and Prevention, half of the more than 33 million people living with HIV/AIDS worldwide are women, and among 15- to 24-year-olds with HIV, females account for about 60 percent of the total. In the United States, girls represented 41 percent of AIDS cases reported among people aged 10 to 24. Between 70 and 90 percent of all HIV infections in women are due to heterosexual intercourse. In fact, women are twice as likely as their male partners to acquire HIV during sex, due in part to biological factors that make women more vulnerable. Although correct and consistent use of male condoms has been shown to prevent HIV infection, women often cannot negotiate condom use with their male partners. If proven effective, microbicides could be an approach for many women who cannot simply rely on condoms or abstinence as methods for protecting themselves from HIV.

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More information about MTN-004 and other MTN studies can be found at [www.mtnstopshiv.org](http://www.mtnstopshiv.org).

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