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BACKGROUNDER

MTN-004: A SAFETY AND ACCEPTABILITY STUDY OF THE CANDIDATE MICROBICIDE VIVAGEL IN SEXUALLY ACTIVE YOUNG WOMEN

Trial Overview

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. Microbicides are substances designed to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically on the inside of the vagina or rectum. The study, which was launched in July of 2007, paused October 2007, and restarted in July 2008, enrolled 61 women at three sites. Women in the study were randomly assigned to use either VivaGel or one of two placebo gels twice a day for two weeks. The study was conducted to help researchers determine if the product should be advanced for further testing.

MTN-004 was a study of the Microbicides Trials Network (MTN), an HIV/AIDS clinical trials network established by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the National Institute of Mental Health (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). It was conducted at the University of South Florida in Tampa and the University of Puerto Rico in San Juan in a collaboration between the MTN and the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) of NICHD. A third site was at the University of Pittsburgh, a clinical research site affiliated with the MTN. Ian McGowan, M.D., Ph.D., from the University of Pittsburgh and Magee-Womens Research Institute, led the study.

What the Study Found

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

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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

Why this Study Was Important

Women are fast becoming the group 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, 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, according to the most recent information from the U.S. Centers for Disease Control and Prevention.

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 or do not wish to 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.

How the Study Was Conducted

A total of 61 sexually active women aged 18-24 were enrolled and randomly assigned to one of three treatment groups: 22 women received VivaGel; 21 women received the VivaGel placebo and 18 women in the third group received the HEC placebo, sometimes referred to as the "universal placebo." Neither the researchers nor the participants knew their assignment. The participants inserted the vaginal gel twice daily for 14 consecutive days. Researchers assessed the safety of VivaGel (rather than how well it works against HIV infection), comparing it with the VivaGel placebo and the HEC placebo gel, through laboratory tests and regular clinical examinations of study participants. Web-based questionnaires provided 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. Women in the study were provided condoms to be used with each act of sex. Study participation lasted three weeks, including the two-week period that gels were used.

MTN-004 was originally designed as a two-arm study in which 40 participants would be randomly assigned to use either VivaGel or the VivaGel placebo. Seven women were enrolled and completed follow-up in this two-arm study. In order to obtain more comprehensive data about the safety of VivaGel and strengthen the study's conclusions, researchers modified the design of MTN-004 to include the third study group.. The seven women who completed the earlier study are included in the study's total enrollment and final data analysis.

The Candidate Microbicide Studied

The candidate microbicide being studied in MTN-004 was SPL7013 Gel, more commonly known by its brand name VivaGel. 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 Holdings Limited of Melbourne, Australia, 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.

Participant Safety

MTN-004 was designed according to the most rigorous international clinical practices and ethical standards and with the greatest concern for participant safety. A detailed informed consent process ensured that participants understood the procedures, risks and benefits of the study, the voluntary nature of participation, and their option to leave the study, without consequence, at any time.

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.

Funding

MTN-004 was funded by NIAID's Division of AIDS and NICHD. The study product was provided by Starpharma Holdings Limited.

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

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 who are devoted to preventing or reducing the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally.

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