

Trials Watch: Microbicides late clinical development

This Product Watch provides microbicides advocates with basic information about the products that are entering late clinical development – either Phase II, IIB or III. These trials are designed to evaluate effectiveness in preventing HIV and to assess local safety, acceptability, and adherence. For more information on clinical trials in general, visit http://www.global-campaign.org/clinical_testing.htm. For more information on other candidate microbicides and trials, consult the Alliance for Microbicide Development’s Database at www.microbicide.org

Since the field is continually changing, this Product Watch will be updated as products move through the pipeline and additional information becomes available. The latest version will always be at www.global-campaign.org/download.htm. Please send your input and updates to info@global-campaign.org.

Candidate Product Developer Trial investigator	Trial Design	Start Dates # of trial participants Location	How it works	Preliminary lab findings about contraception ¹ & STI protection ²	What form is it in? What is it made from?
PRO 2000 0.5% formulation (naphthalene sulphate polymer) Indevus Pharmaceutical, Inc. Microbicide Development Programme, UK Medical Research Council www.mdp.mrc.ac.uk	Phase III 2 arm studies for one formulation (0.5%) of PRO 2000 ³ Three arm study: 1. standard prevention package + comparator gel 2. standard prevention + PRO2000 5%	Enrollment started in March 2006 9673 participants in South Africa, Tanzania, Uganda, Zambia	Entry and fusion inhibitor PRO 2000 binds to viruses and bacteria to prevent them from binding to and infecting healthy cells.	May be contraceptive but dose-dependent HIV gonorrhoea HSV	Clear gel .5% formulation PRO2000 is a synthetic long-chain molecule made of repeating units of naphthalene sulphate. For vaginal use, it is formulated as a water-based gel.

¹ Note that these are only preliminary expectations.

² Laboratory testing has shown action against these viruses and bacteria, but they will not necessarily be included as secondary endpoints in these trials.

³ This trial originally included dextrin-2-sulphate (Emmelle) but this product was excluded from the final design of the Phase 3 trial.



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DEVELOPMENT

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Tenofovir Gel Gilead Sciences CAPRISA www.caprisa.org CONRAD FHI LIFElab / DST	Phase 2B started in 2007. Two-arm study: 1. standard prevention package + tenofovir gel 2. standard prevention package + placebo gel.	Enrollment started in 2007 in South Africa. 1250 participants in South Africa (Durban and Vulindlela) Results are expected in 2010.	Replication inhibitor Tenofovir works by preventing the pathogen from replicating once it has entered cells Women will be provided with a supply of single-use, pre-filled applicators according to their randomisation and will be given instructions to apply a first dose of the assigned study product within 12 hours prior to coitus and insert a second dose as soon as possible within 12 hours after coitus. They will be advised to use only two doses of gel in a 24-hour period.	Not contraceptive	Clear gel This gel consists of 1% tenofovir (also known as PMPA). Tenofovir is the active ingredient in Gilead's oral antiretroviral drug Viread™ (tenofovir disoproxil fumarate) which is used as an anti-HIV treatment.

Microbicides Trial Results

Trial Results -- Since 2005, effectiveness trials for four other candidate microbicides have been completed or closed for different reasons. More information is available at the websites listed below or at the Global Campaign's trial updates page: <http://www.global-campaign.org/trial-closures.htm>

HPTN 035 (BufferGel® & PRO 2000) - On 9th February 2009, the US National Institutes of Health announced promising results of a multi-site clinical trial of two candidate microbicides. The study (HPTN 035) was conducted between February 2005 and September 2008 and enrolled 3,099 participants in South Africa, Malawi, Zambia, Zimbabwe and the USA. HPTN 035 evaluated the safety and effectiveness of BufferGel® and PRO 2000 (0.5 percent dose) for

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preventing male-to-female sexual transmission of HIV. The trial found that women who were offered PRO 2000 gel plus condoms had 30% fewer HIV infections than those offered only condoms or condoms plus a placebo gel. The other candidate microbicide tested, BufferGel, did not reduce HIV risk among women. For more information, please go to <http://www.global-campaign.org/HPTN-035.htm>

Cellulose Sulfate - Two trial investigators: Family Health International, www.fhi.org and CONRAD www.conrad.org

At the end of January 2007, the Data Safety and Monitoring Boards (DSMB) of CONRAD met and based on a review of preliminary data, recommended that the Phase III trial of the candidate microbicide Cellulose Sulfate (CS) in Benin, India, Uganda and South Africa be discontinued. Early data suggest that CS may be contributing to an increased risk of HIV infection. Scientists are struggling to figure out exactly what this means given that 11 earlier safety trials had not revealed any safety concerns. Erring on the side of safety, the Family Health International DSMB recommended that the CS trial underway in Nigeria be closed as well, although review of the Nigerian data by that trial's DSMB found no evidence of increased risk. We now know that CS gel is not effective against HIV infection. The results of the CONRAD study do suggest that the use of CS gel might increase a woman's susceptibility to HIV infection. Therefore, CONRAD and FHI made the right decision to stop the study immediately, based on the interim results.

Savvy (C-31G) Biosyn, Inc. / Family Health International www.fhi.org

In November 2005, an independent data-monitoring committee reviewed results from an arm of the study in Ghana that showed that the incidence of HIV (how often people became HIV positive) was so low in the trial area, that the study would not be able to determine whether using SAVVY gel could actually reduce the rate of transmission of HIV. The study in Nigeria was also halted in August 2006, when an independent data monitoring committee decided, looking at the available data, that it was unlikely that SAVVY had a protective effect against HIV transmission. The Nigerian data also showed that a few more women who were using SAVVY became infected with HIV than women using the placebo. The difference between the two arms was so small, however, that it is really impossible to tell whether it occurred simply by chance or whether SAVVY use actually increased women's risk of infection. Once the possibility of chance differences between the two arms is taken into account, it is clear that neither the Ghanaian data nor the the results from Nigeria can tell us definitely whether SAVVY had any effect on HIV transmission or not. These data are still being analysed to see if any further insight into the effect (or lack of effect) of the product can be gathered.

Both studies do, however, confirm that women participating in trials have lower rates of HIV infection than similar women in their communities. This may be due to the other HIV prevention services that are implemented during trials, such as the promotion and provision of free condoms.

Carraguard (Developed and tested by the Population Council – www.popcouncil.org)

On 18 February 2008, the Population Council, an international non-profit research institution, posted results on their Phase 3 trial of Carraguard, a microbicide candidate developed as an odorless, clear gel made from carrageenan, a derivative of seaweed. The Population Council tested Carraguard's effectiveness in a study conducted between 2004-2007 that enrolled 6,202 women participants in South Africa. Trial results showed that the product was safe and acceptable to women, but did not reduce their risk of acquiring HIV.

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