

Microbicides Development Programme (MDP) update June 2008

IDMC recommend MDP301 Phase III trial to continue

The Independent Data Monitoring Committee (IDMC) for the Microbicides Development Programme (MDP) met on 4th June 2008 for a routine periodic review of the data collected to date on the MDP301 trial of the candidate microbicide PRO 2000/5, and updated since its last meeting on 8th February 2008.

After reviewing all the available data, the IDMC recommended that the trial should continue to compare the 0.5% concentration of PRO 2000/5 gel with placebo, as recommended in its February review. They congratulated the investigators and all those involved in the conduct of the trial at the sites on the excellent way in which the withdrawal of the 2% gel has been handled. The MDP Trial Steering Committee (TSC) met on 11th June 2008 and accepted the recommendation of the IDMC.

The IDMC will continue to monitor the trial carefully and will meet again in approximately 6 months time. Safety of the participants continues to be of paramount importance.

Notes

1. 61% of the 22.5 million HIV-infected people in sub-Saharan Africa are female. The highest incidence of new infections is among women. The reasons why HIV is spreading so rapidly among women are complex; they are rooted in the social, cultural and economic context of women's everyday lives and circumstances; and in situations in which women frequently do not have control over sexual relations. Women are also biologically more susceptible to HIV infection than men. Women's vulnerability to HIV infection is increased in conditions of poverty. Microbicides could contribute substantially to efforts to provide women with more choice in methods to protect themselves and to reduce rates of HIV infection.

2. The scale of the global epidemic of HIV remains staggering. An estimated 33 million people worldwide currently live with the virus. New infections continue and in 2007 alone there were an estimated 2.5 million new infections – i.e. over 6800 persons infected every day (UNAIDS, 2007). HIV infection is still the leading cause of death in Sub-Saharan Africa with 1.6 million deaths last year. In the absence of a viable vaccine there is a need to intensify efforts in other areas and vaginal microbicides are a promising bio-medical intervention for the prevention of HIV infection.

3. The Microbicides Development Programme (MDP) is an Afro-European partnership to develop vaginal microbicides for the prevention of HIV transmission. MDP is coordinated jointly by Imperial College, London, and the Clinical Trials Unit of the UK Medical Research Council. Partner institutions in Africa are University Teaching Hospital, Lusaka, Zambia; Medical Research Council Uganda Virus Research Institute, Entebbe; African Medical and Research Foundation and National Institute for Medical Research, Mwanza, Tanzania; the Africa Centre for Health and Population Studies, KwaZulu Natal, South Africa; South African Medical Research Council, Durban; and the Reproductive Health and HIV Research Unit, Department of Obstetrics and Gynaecology, University of Witwatersrand, Johannesburg, South Africa. In Mozambique, there are two new MDP sites at the rural Manhiça Health Research Centre and at Mavalane Hospital in the urban capital of Maputo. European partners include the London School of Hygiene and Tropical Medicine, St. George's Hospital, London, and the Universities of York, Southampton and Barcelona. Clinical sites are located in South Africa, Tanzania, Uganda, Zambia and Mozambique. The aim of the partnership is to identify candidate microbicides that perform well in laboratory assessments and take them into human clinical trials from Phase I to Phase III, and on to licensing where appropriate. Another major objective of MDP is to develop the capacity of African researchers and research institutions. The Programme is funded by the UK Department for International Development (DFID) and the Medical Research Council (MRC) and is currently running a

large Phase III trial of a particular microbicide, PRO 2000/5, which it is hoped will block the entry of HIV and other sexually transmitted pathogens into human cells.

4. Microbicides are substances, formulated as gels or creams, which are being developed to offer protection against HIV and other sexually transmitted infections (STIs) when applied to the vagina or rectum before intercourse (although the current PRO 2000/5 gel formulation is designed for intravaginal use only). The compounds being tested as microbicides work in a number of ways: by killing or otherwise immobilizing the virus; by interfering with the initial infection process (PRO 2000/5 would work in this way); or by preventing the infection from taking hold after it has entered the body. Ideally, an eventual microbicide would combine these mechanisms for extra effectiveness.

5. The various microbicides currently being tested differ from each other in terms of their active ingredients, formulation, and mechanisms of action. Hence, the results of any one particular microbicide cannot be extrapolated to other microbicides.

6. The MDP Phase III clinical trial of PRO 2000/5 is overseen by an Independent Data Monitoring Committee whose members have no involvement in running the trial and no financial interest in its outcome. The Committee meets routinely to review data emerging from the trial and monitor the safety of participants. The Committee is chaired by Professor Sir Alasdair Breckenridge, an expert on safety of medicines and Chairman of the UK Medicines and Healthcare products Regulatory Agency. Other members are Professor Catherine Hill, Head of Department, Service of Biostatistics and Epidemiology, Institute Gustave-Roussy, France; Professor Florence Mirembe, Former Head of Obstetrics and Gynaecology at Mulago Hospital, Kampala, Uganda; and Dr Isaac Malonza, Deputy Country Director (Kenya) of JHPIEGO, an international health organization affiliated with The Johns Hopkins University in Baltimore, Maryland USA, and former Head of the Microbicides Desk of the World Health Organisation.

The trial initially consisted of three arms, testing a 2% concentration of PRO 2000/5, a 0.5% concentration of PRO 2000/5 and a placebo.

In 2007, the Committee met on 10 January, 12 March, 18 June and 29 November. On 8 February 2008, they reviewed data collected by treatment arm (high strength, low strength, placebo) on 7,735 women and found there was no more than a small chance of showing protection against HIV infection from 2% PRO 2000/5 compared to placebo gel. They therefore recommended that no further gel should be prescribed to women allocated to the 2% PRO 2000/5 arm of the trial but that the 0.5% and placebo gel arms should continue. The MDP Trial Steering Committee met on 11 February 2008 and accepted the recommendations of the IDMC. Women in the 2% PRO 2000/5 gel arm were asked to return any unused PRO 2000/5 gel supplies. They have also been invited to attend the clinic every three months until they have completed their week 52 visit. None of the MDP investigators apart from the Trial Statistician have seen the data by treatment arm, as this could jeopardise the integrity of the trial.

7. MDP has built a vigorous multicultural and multidisciplinary research network ready to undertake future work of comparable importance and complexity. Years of working collegially have built cohesiveness, efficiency and mutual trust among the scientists, clinical staff, data managers, and other professionals and support staff comprising this Afro-European and pan-African clinical trial network, as well as sound relationships with surrounding communities. MDP has also achieved significant improvements in African laboratory capacity and other research infrastructure, as well as upgrading and reinforcement of professional capacity at its African research sites.

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