MICROBICIDES DEVELOPMENT PROGRAMME

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EMBARGOED until MONDAY 14 December 2009 - 07:00 GMT

Technical Fact Sheet for Scientists

This Fact Sheet provides a technical summary of the main analysis for MDP 301, and assumes that the reader is familiar with the trial design (please see http://www.mdp.mrc.ac.uk/mdpstudy.html MDP 301 protocol v2.1 08 May 2008).

In brief, the trial was a randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of 0.5% and 2% PRO 2000 gels for the prevention of vaginally acquired HIV infection**.**

Three statistical reports were produced:

- 0.5% PRO 2000 and placebo gel using all the data for participants allocated to 0.5% or placebo gel
- 0.5%, 2% and placebo using data up to 14th February 2008 when 2% PRO 2000 was discontinued
- Centre report using all the data for all three treatment groups combined, including the data collected on women allocated to 2% gel after the gel was discontinued

All analyses were conducted in Stata v10.1 .

Data collected on the second trial number allocated to the participants that enrolled twice in MDP 301 have not been included in the analysis datasets.

Efficacy Datasets

Women that never had a HIV test during follow-up and women who were found to be HIV positive at enrolment are excluded from the efficacy datasets.

The primacy efficacy analysis is a modified intention to treat (MITT):

- Women were censored for pregnancy, so HIV infection detected after a participant interrupted/discontinued gel for pregnancy was excluded
- Women were censored at week 52 so that HIV infection detected after the 52 week visit window closed (58 weeks from enrolment) was excluded

A secondary ITT analysis includes all HIV infections regardless of pregnancy or time.

A planned sub-group analysis was conducted for the primary efficacy analysis according to the consistency of gel use, using the median percentage gel use to divide women into 'consistent' and 'inconsistent' users.

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The percentage gel used at the most recent sex act was calculated for each woman by taking her answer to this question at every visit she attended.

Consistent use was defined by three criteria:

- Attending at least 7 of the possible maximum 13 visits (unless pregnant or HIV sero-converter)
- Reporting gel use at the most recent sex act, at or greater than the median % of attended visits
- Returning at least one used applicator at all visits when gel use was reported at the most recent sex act

Safety Datasets

Systemic safety was assessed through routine laboratory parameters, collected in a sub-set (the first 500 participants enrolled in each of Durban and Johannesburg, and all participants enrolled in Masaka).

The systemic toxicity analysis is based on an increase in grade from baseline due to raised liver transaminases, bilirubin, clotting factors, or decreased platelets.

The local toxicity analysis is based on any grade of genital itching, genital burning, internal erythema, internal epithelial disruption, internal oedema.

All safety analyses are ITT. The primary safety analysis is based on grade 3 or higher clinical or laboratory adverse events.

For all three toxicity analyses, a planned sub-group analysis was performed dividing women according to the level of exposure to gel during the trial, using the median number of returned used applicators to classify women as high or low gel users.

Statistical methods

Analyses were 'time to event', and incidence rates were compared using the hazard ratio (HR) estimated from a Cox Proportional Hazards model.

Results

- 15,818 women were screened
- 9,404 trial numbers were allocated, including 19 women enrolled twice in the trial, so there were 9,385 participants
- 95% returned for at least one HIV test
- 97% returned for a pelvic examination

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- 84% of the maximum possible total women years were available for the primary efficacy analysis which was censored for pregnancy and time. 88% were available for the secondary ITT analysis
- The median percentage gel use reported was 92%

Primary efficacy

- There were 130 new HIV infections in the 0.5%, and 123 in the placebo giving incidence rates of 4.5 and 4.3/100 women years respectively, and a HR of 1.05 (95% CI 0.82 – 1.34; p=0.712)

ITT efficacy

- There were 145 new HIV infections in the 0.5%, and 143 in the placebo giving incidence rates of 4.6 and 4.6/100 women years respectively, and a HR of 1.00 (95% CI 0.79 – 1.26; p=0.993)
- There was no significant difference in efficacy between consistent gel users and inconsistent gel users.
- There were 423 primary safety events in 398 participants.
- There were no differences in primary safety endpoints or local toxicity events between the gel groups, including after stratification by high and low gel use.

In February 2008 when 2% PRO 2000 was discontinued on the recommendation of the Data Monitoring Committee, the findings were:

Primary efficacy

- There were 82 new HIV infections in the 2%, 67 in the 0.5%, and 67 in the placebo giving incidence rates of 4.7, 3.9 and 3.9/100 women years respectively.
- The HR for the 2% to placebo comparison was 1.21 (95% CI 0.88 – 1.68; p=0.239)
- The HR for the 0.5% to placebo comparison was 0.99 (95% CI 0.70 – 1.39.; p=0.940)

ITT efficacy

- There were 86 new HIV infections in the 2%, 70 in the 0.5%, and 77 in the placebo giving incidence rates of 4.7, 3.8 and 4.2/100 women years respectively.
- The HR for the 2% to placebo comparison was 1.11 (95% CI 0.82 – 1.51; p=0.497)
- The HR for the 0.5% to placebo comparison was 0.90 (95% CI 0.65 – 1.24; p=0.525)

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Concluding remarks

Reported adherence was high, based on self reported gel use at the last sex act. Although this is may be an over-estimate, the self-reports were corroborated by the used applicator returns in the trial population, as well as the additional data collected through coital diaries and In-depth interviews in the social science sub-set of 725 participants. Taken together, the data suggest the majority of participants were using the gel consistently. Retention in follow up was also high with over 95% women returning for at least one HIV test, and loss of just over 10% of the maximum women years for the ITT analysis.

In February 2009, Phase II/IIb HPTN 035 trial found that 0.5% PRO 2000 gel reduced HIV incidence by 30% compared to placebo gel in an intention to treat analysis (HR 0.7; 95% CI 0.46-1.08; p=0.10), and concluded that a large trial would be needed to provide definitive evidence regarding efficacy.

The MDP301 result is compatible with the HPTN 035 result, as the results of the latter could be explained by chance, and the HPTN 035 95% confidence interval included the estimates observed in MDP 301 (HR=1.05, and HR =1.00).