

HIV Prevention Trials Network

Protocol 050: Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel

AMENDMENT #1

29 May 2002
IND # 55,690

Summary of Revisions

- The inclusion criteria of the protocol have been revised to expand the CD4+ cell count criterion.
- The exclusion criteria of the protocol have been revised to exclude participants receiving antibiotic therapy for malaria.
- The procedures and statistics section of the protocol are revised to delete the Initial Acceptability Questionnaire.
- The procedures section of the protocol is revised to specify that vaginal swab specimens are to be taken from the lateral vaginal wall, and dried smears are to be prepared in duplicate.
- The procedures section of the protocol is revised to include the study burden assessment.
- The procedures sections of the protocol and sample informed consent forms are revised to allow sites to conduct specified enrollment procedures on study Days –1 and 0 for participants in the PK sub-cohort.
- The definition of non-adherence has been expanded.
- The treatment-dose allocation has been simplified to enroll participants in sequential order by cohort across sites.
- The protocol version number, date and table of contents are updated. Other administrative and typographical clarifications and corrections have been incorporated throughout the protocol and sample informed consent forms as needed.

Prior to implementing the procedures described below, the HPTU will submit this amendment, the corresponding protocol version 2.0, and an updated local study informed consent form to its Institutional Review Board (IRB). The Division of AIDS Regulatory Affairs Branch will submit this amendment to the Food and Drug Administration for inclusion in the study Investigational New Drug application.

Upon receipt of IRB approval, protocol registration with the DAIDS Regulatory Operations Center, and activation by the HPTN CORE, the following protocol modifications, indicated by ~~strike through~~ and **bold** text, will be implemented:

1. In the Protocol Team Roster:

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2. In the protocol Schema:

Study Duration: Accrual will require ~~eight~~ **11** months. Each participant will be followed for up to 21 days. Acceptability interviews will be convened within four weeks after the completion of product use and follow-up. Therefore the entire study should be completed within ~~40~~ **13** months.

3. In protocol Section 2.4.2, ninth paragraph:

The acceptability of PMPA gel will be assessed via questionnaires and group or individual interviews. At their study Enrollment Visits, female participants will complete a Behavioral Assessment pertaining to their past use of vaginal products. ~~and their past sexual history. and an Initial Acceptability Assessment regarding their likelihood to use a product with characteristics similar to those of PMPA including method of delivery, applicator characteristics, potential discomfort, and effectiveness to prevent HIV. The Initial Acceptability Assessment will allow the investigators to determine whether women with poor initial acceptability of a product with characteristics of PMPA gel are more likely than others to show poor adherence to the study protocol or to drop out of the study.~~ At Day 14, female participants will complete a Follow-up Acceptability Assessment regarding their perceptions of PMPA gel including applicator, vehicle and use-associated factors, **as well as a Study Burden Assessment, regarding their perceptions of study visits, procedures and incentives.** The male sexual partners of participants in cohorts B and D also will complete a questionnaire regarding their perceptions and experiences with PMPA gel, **as well as a Study Burden Assessment, regarding their perceptions of study visits, procedures and incentives.**

4. In protocol Section 2.4.3, last paragraph:

The Protocol Safety Review Team will hold ~~bi-weekly~~ **regularly scheduled** teleconferences to identify trends or emerging patterns in the AE data that may impact the continuation of enrollment and product use in all cohorts.

5. In protocol Section 2.5, first paragraph:

At their **study Day 0** Enrollment Visits and on study Day 13, these participants will apply the first daily dose of PMPA gel at the study site and undergo phlebotomy for serum collection and PK analysis immediately prior to dosing then again at 0.5, 1, 2, 4, 6, 8, 12 hours on both visits.

6. In protocol Sections 3.3 and 3.4, third bullet:

- have a CD4+cell count ~~=200/mm³~~; **of at least 200/mm³ at the time of study screening, based on testing performed by study staff, together with at least one documented CD4+ cell count of at least 200/mm³ in the six months prior to screening.**

7. In protocol Section 3.5, seventh bullet:

- have received a course of antibiotic therapy ~~(other than treatment for malaria)~~ in the 14 days prior to enrollment,

8. In protocol Section 4.5.1, third paragraph, add the following text:

As well, participants who experience an AE that requires permanent product discontinuation, but completed daily administration at the assigned frequency on the days preceding the AE will be considered adherent.

9. In protocol Sections, 5.1.1.1, 5.1.2.1, 5.1.3.1, 5.1.5.1, 5.1.6.2, sub-bullets of the primary bullet that reads: Perform pelvic examination including:

- collection of swab specimen from the ~~anterior or lateral fornix~~ **vaginal wall** for:
 - ~~one~~ dried smear (smear specimen **on two slides** and allow to air dry);

10. In protocol Sections 5.1.2.1 and 5.1.5.1 sub-bullets of the primary bullet that reads: Perform pelvic examination including:

- collection of sno-strip ~~and CVL~~ for HIV viral load (cohorts C and D only)
- **collection of CVL for HIV viral load and resistance testing (cohorts C and D only)**

11. In protocol Sections 5.1.2.1, and 5.1.5.1 bullet regarding collecting blood specimens:

- Collect blood specimens for hematology, liver and renal function (all participants), HIV RNA PCR and **resistance testing** at CL (cohorts C and D only)

12. In protocol Sections 5.1.2.2, and 5.1.5.2 bullet beginning with Conduct CBC:

- Conduct CBC, blood chemistries, liver and renal function tests (all participants) and RNA PCR **and HIV resistance testing** (cohorts C and D only)

13. In protocol Section 5.1.2:

Enrollment Visit - Baseline (Day 0 Non-Pharmacokinetic Participants; Day -1 and/or Day 0 Pharmacokinetic Participants Only)

Participants who are found to be presumptively eligible at their Screening Visit will complete Enrollment Visits 3 to 5 five days post-menses, and within 42 days after the Screening Visit. Participants who do not complete an Enrollment Visit within 42 days of screening must repeat the entire Screening Visit.

All participants will receive their screening test results at their Enrollment Visit. For those whose test results meet the study eligibility criteria, the procedures below will be undertaken in a step-wise manner to confirm eligibility. As was the case at the Screening Visit, procedures will be discontinued if ineligibility is determined at this visit.

Participants in the PK sub-cohorts may complete all Enrollment Visit procedures EXCEPT administering the first dose of PMPA gel and collecting PK blood samples on study Day -1 and/or study Day 0.

14. In protocol Section 5.1.2.1, fourth bullet:

- Conduct Behavioral ~~and Initial Acceptability~~ Assessments.

15. In protocol Sections 5.1.2.2 and 5.1.5.2, add:

Note: Plasma will be stored for HIV drug resistance genotyping. Resistance testing will be performed on selected samples as described in Section 7.4.4.

16. In protocol Section 5.1.3.1, after the tenth bullet add:

Note: Blood specimens will be collected at the Day 2 or 3 Visit only if the Day 7 visit for the participants in the B, C and D cohorts is omitted.

17. In protocol Section 5.1.2.1, eleventh bullet:

- For Pharmacokinetic study participants collect blood specimens at baseline (Time 0). Have participant administer first dose of PMPA gel. Collect PK **blood** samples at 0.5, 1.0, 2, 4, 6, 8, and 12 hours post dosing (**Day 0**).

18. In protocol Section 5.1.5.1, before the last bullet add:

- **Administer Study Burden Assessment (Cohorts A and B only).**

19. In protocol Section 5.1.6.2, before the last bullet add:

- **Administer Study Burden Assessment (Cohorts C and D only).**

20. In protocol Section 5.1.7, second paragraph:

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff or require additional study supplies. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported experience clinically and provide or refer the participant to appropriate medical care. All AEs associated with genital symptoms will be evaluated according to the pelvic exam procedures described for the **Day 2 or 3 and/or** Day 7 Follow-up Visit in Section 5.1.3. Diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

21. In protocol Section 5.1.9, third paragraph:

Group interviews will be conducted with ~~three~~ **at least two** ~~to five~~ and **as many as eight** study participants and will take place approximately two to ~~four~~ **six** weeks following completion of a study regimen. Group discussion will be analyzed to assess acceptability, discomfort and perceived costs of microbicide use.

22. In protocol Section 5.1.10, last two paragraphs:

Male sexual partners will be given a staff-administered questionnaire within four weeks following completion of a study regimen to collect quantitative **follow-up** acceptability **and study burden** data in addition to the individual interview.

Male sexual partners will be given a staff-administered questionnaire within ~~four~~ **six** weeks following completion of a study regimen to collect quantitative follow-up acceptability and study burden data in addition to the individual interview.

Individual interviews will be conducted either in a face to face setting or by phone and also will be carried out within ~~four~~ **six** weeks following completion of a study regimen. Responses will be analyzed to gain in depth information on microbicide acceptability beyond that obtained with the structural questionnaires.

23. In protocol Section 7.3, second paragraph:

Up to 32 women will be recruited per site. In step one, two women from each of the three sites will be recruited in A_1 . If two or more of these six women experience SAEs judged to be related to product use, four women from each of the three sites will be recruited in cohort V in order to test the vehicle. ~~If fewer than two participants from these six experience SAEs related to product use, in step two, six women from each of the three sites will be recruited and will be sequentially allocated in two blocks of size three according to a 1:1:1 allocation i.e., first woman in A_1 , second woman in A_2 , and third woman in A_3 . In step three, if fewer than two participants within each of the first three cohorts (i.e. A_1 , A_2 , and A_3) experience SAEs related to product use, eight women from each of the three sites will be recruited and will be sequentially allocated in two blocks of size four according to a 1:1:2 allocation i.e., first woman in A_2 , second woman in A_3 , and third and fourth woman in A_1 . If fewer than two participants from these six experience SAEs related to product use, in step two, six women from each of the three sites will be recruited and will be sequentially allocated in one block of size six according to a 2:2:2 allocation i.e., the first two available women at each site will be enrolled in A1, the next two available women at each site will be enrolled in A2, and the next two available woman at each site will be enrolled in A3. In step three, if fewer than two participants within each of the first three cohorts (i.e. A1, A2, and A3) experience SAEs related to product use, eight women from each of the three sites will be recruited and will be sequentially allocated in one block of size eight according to a 2:2:4 allocation i.e., the first two available women at each site will be enrolled in A2, the next two available women at each site will be enrolled in A3, and the next four available women at each site will be enrolled in A4. Finally in step four, if fewer than two participants within each of the last three cohorts (i.e., A_2 , A_3 , and A_4) experience SAEs related to product use, eight women, four for cohort B and 4 for cohort C, from each of the three sites will be recruited. After enrollment for B and C is completed, four women from each of the three sites will be recruited in cohort D.~~

24. In protocol Section 7.4.5.1, second paragraph:

Questionnaire data will be tabulated and ~~cross-tabulated~~ to summarize group data regarding ~~initial perceptions of the acceptability of PMPA gel. (perceived preference for product characteristics, perception concerns).~~ **the acceptability of PMPA gel.** ~~Participants' preferences at enrollment will be compared with acceptability after having used PMPA gel.~~ Comparisons will be made examining acceptability data obtained on abstinent and sexually active women. Open-ended response data will be summarized for each site and across sites.

25. In protocol Section 7.4.4:

To assess the effect of product use on cervico-vaginal of HIV, change in the number of copies of HIV RNA from the Baseline visit to the Day ~~21~~ **14** visit will be analyzed in the two HIV-infected groups. In addition the change in the number of copies of HIV RNA will be compared between the sexually active and the sexually abstinent women.

To assess the effect of product use on genotypic resistance on HIV, detectable HIV in cervico-vaginal secretions and plasma ~~will be analyzed for genotypic resistance patterns in the two HIV-infected groups.~~ **from the baseline and Day 14 Visits will be analyzed for the presence of drug resistance mutations in the two HIV-infected groups from baseline and Day 14 Visits. Genotyping will be performed retrospectively. Results from individual patients will not be used in clinical management.**

26. In protocol Appendix I - Clinical Evaluations - Female Participants:

Titles, third column:

Enrollment **Day -1⁴**/Day 0

First column, row 10:

Observe participant apply first dose of study product⁴

First column, row 12:

Conduct Behavioral, ~~and~~ **Follow-Up** Acceptability **and Study Burden** Assessments

First column, row 16:

Collect blood specimens for PK^{1, 4} (Cohorts A₂, B, C, and if necessary D)

Third column, row 12:

Behavioral ~~and Initial~~

Fourth column, row 13:

if indicated

Fifth column, row 12:

*

Seventh column, row 12:

~~Final~~ **Follow-Up all cohorts**
Study Burden A/B

Eighth column, row 12:

Study Burden C/D

Footnotes:

¹Specimens for the first 6 participants in PK study cohorts will be collected at the **Day 0 Enrollment** and the **Day 13 Follow-up Visits**. The schedule for the

specimen collection is as follows: 0.0, 0.5, 1, 2, 4, 6, 8, 12 hours on both days and 24 hours post dosing on day 14 only.

⁴ All Enrollment Visit procedures EXCEPT administering first dose of PMPA gel and collecting PK blood specimens may be completed on study Day -1 for PK sub-cohort participants.

26. In protocol Appendix I – Clinical Evaluations - Male Participants:

First column, row 10:

Conduct ~~Final~~ **Follow-Up** Acceptability and **Study Burden** Assessments.

27. In protocol Appendix II – Laboratory Evaluations:

First column, row 13

Viral Load/**Resistance**^g

First column, row 15

Viral Load/**Resistance**^g

First column, row 16

Plasma archive^{g,h}

First column, row 17

Serum archive^{g,h}

Second column, row 13

HIV-RNA/**HIV genotyping**

Seventh column, title:

Enrollment Day 0 (**Day -1 PK only**)

Eighth column, title:

Follow-up 42-78 Hour ~~Day 2 or 3~~

Seventh column, row 10:

✕

Day 0 only

Footnotes:

^g **Plasma will be collected and stored for HIV drug resistance genotyping. Resistance testing will be performed on selected samples as described in section 7.4.4**

^{g,h} Stored at local repository and to be destroyed at the end of the study – one year from final participant's completion of follow-up (across sites)

*** To be collected if the Day 2 or 3 Hour Visit replaces the Day 7 Visit

28. In the female sample informed consent forms, Cohorts A, B, C and D, the last two paragraphs of the Enrollment Visit Section of the Procedures Section:

You will begin using the PMPA Gel as directed on the day of the Enrollment Visit, then return here in 2 to 3 days for a follow-up visit.

The participants in this group who have joined this study and who have also agreed to join the PK Study will have blood drawn, 40 mL (or 3 tablespoons) over 12 hours as explained in the PK Study consent form. **Your Enrollment Visit may take place over two days.**

~~You will begin using the PMPA Gel as directed on the day of the Enrollment Visit, then return here in 2 to 3 days for a follow-up visit.~~

29. In the pharmacokinetic consent form, in the second paragraph of the Procedures Section:

At your Enrollment Visit, in addition to the main study procedures that you already consented to, you will insert your first dose of PMPA Gel at the clinic. Then your blood (about 5 mL or 1 teaspoon per draw) will be drawn 8 times over the next 12 hours. **Your Enrollment Visit for the main study and PK study may take place over 1 or 2 days. The study staff will tell you whether your Enrollment Visit will be scheduled for 1 day or 2 days.**

? One Day Enrollment Visit

? Two Day Enrollment Visit

(Study staff to check appropriate box for visit schedule)

30. In the pharmacokinetic consent form, in the second paragraph of the Costs To You Section:

You will be reimbursed for your time and effort in this study. You will receive (insert site-specific amount of money) for each of the two sets of blood draws. You will receive (insert site-specific amount of money) per visit if you are asked and return for the ~~24~~ **48** and ~~48~~ **72** hour blood draws.

31. In the female sample informed consent forms, Cohorts A, C, and V the Other Requirements Section of the Procedures Section, first sentence:

~~While you are in this study you must not do the following:~~

You must not do the following starting 48 hours (2 days) before your Enrollment Visit and during the entire time while in the study:

after the first paragraph add:

You must not use spermicides or condoms lubricated with spermicides starting 7 days before your Enrollment Visit and during the entire time while in the study.

after the fourth paragraph add:

If you miss or skip an application on one or two days, the study staff may ask you to continue using the gel for one or two days to make up for the days that were missed.

32. In the female sample informed consent forms, Cohorts B and D, the Other Requirements Section of the Procedures Section first paragraph:

~~While in this study you must not do the following:~~

You must not have vaginal sex during the 48 hours (2 days) before your Enrollment Visit.

You must not do the following starting 48 hours (2 days) before your Enrollment Visit and during the entire time while in this study:

after the first paragraph add:

You must not use spermicides or condoms lubricated with spermicides starting 7 days before your Enrollment Visit and during the entire time while in the study.

after the fourth paragraph add:

If you miss or skip an application on one or two days, the study staff may ask you to continue using the gel for one or two days to make up for the days that were missed.

33. In the female sample informed consent forms, Cohorts B, C and D, in the first paragraph of the During the Study Section of the Procedures Section:

You will be given tubes of PMPA Gel with applicators and instructions on how to use them. Two different strengths of the gel will be tested in this study. You will put about 4 mL (1 teaspoon) of the gel into your vagina once or twice a day for 14 days. The strength you use, and whether you use it once or twice a day, will depend on information gathered from women who have finished their part of the study before ~~joining you~~ **join** the study.

34. In the female sample informed consent forms, Cohorts A , B, C, D and V, in the first paragraph of the Day 2 or 3 Follow-Up Visit Section of the Procedures Section:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel and whether you had any medical problems or discomfort since your last visit. ~~You will also give blood (about 20 mL or 4 teaspoons) for testing to check on your overall health, liver, and kidneys.~~ You will have a pelvic exam. Unless a problem is seen on the pelvic exam, the lens will not be used at this visit.

35. In the female sample consent form, Cohort V, last paragraph in the Risks and/or Discomforts Section:

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that others may learn of your participation here, and think that you are infected with HIV, or at "high risk" for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. ~~There also is a risk to your privacy if you are known by someone else in taking part in the group interview.~~

36. In the male sample informed consent form, Cohort B, Risks and /or Discomforts Section, second paragraph:

~~It is not known what effect PMPA Gel could have on the HIV virus, for example there may be a risk of becoming infected with a more active or resistant type of HIV virus even if condoms are used. It is not known what effect of PMPA Gel could have on the disease condition in HIV-infected people.~~

37. In the female sample consent forms Cohorts A, B, C, D and V, Pregnancy Section, third paragraph:

If you become pregnant during the study you should tell your study doctor or nurse right away. You will stop using PMPA Gel and the study clinician will discuss your choices with you. **The study clinician will contact you every three months during pregnancy, and every three months for one year after the baby is born so that we can find out about your health and your baby's health.**

38. In the female sample consent forms Consents C and D, Other Requirements Sections, before the last paragraph:

Samples of your blood and vaginal fluids will be tested for resistance to see if the HIV virus in your body shows resistance. Resistance is when changes in the HIV virus make the medications that treat HIV stop working or not work as well against the virus.