Section 6. Study Product Considerations for Non-Pharmacy Staff

6 Introduction

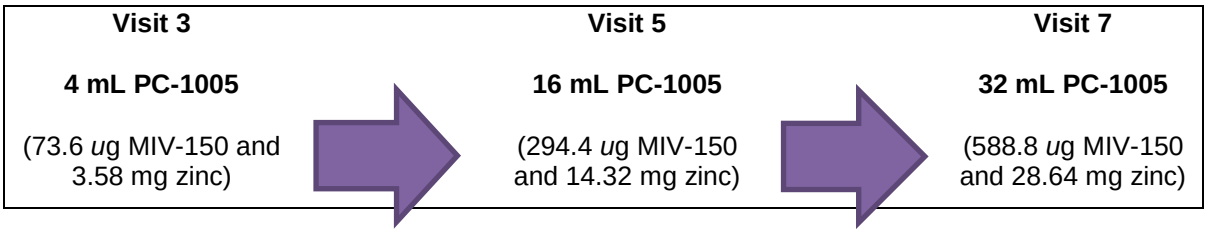
This section provides information and instructions for non-pharmacy staff (i.e., clinic staff) related to the receipt, transport and administration of PC-1005 Associated instructions for pharmacy staff are provided in the *MTN-037 Pharmacy Study Product Management Procedures Manual*, which is available to each site Pharmacist of Record (PoR) by the MTN LOC Pharmacist. Please refer to Section 11 (Counseling Considerations) of this SSP manual for product use instructions and counseling.

6.1 Study Product Regimen

Participants will receive escalating doses of PC-1005 rectally administered by clinic staff in the clinic at 3 visits. Approximately 12 participants (6 per site) will each receive three single escalating doses of the rectal gel: 4mL at Visit 3; 16 mL at Visit 5; and 32 mL at Visit 7 (see Figure 6.1). The study gel will be dispensed in a BD ™ Luer Lok ™ syringe with a red cap and a rectal tip for administration.

Figure 6-1

MTN-037 Study Product Regimen



Approximately 24 hours after each dose, a safety evaluation will be performed. If there are no safety issues identified following a two to six-week washout period, the next dose will be administered in the clinic per clinical management guidelines as outlined in Section 9 of the protocol.

6.2 Prescription Completion and Dispensing PC-1005

MTN-037 PC-1005 Prescription (Appendix 6-1) will be produced as two-part no carbon required (NCR) forms. A bulk supply of prescriptions will be provided to the Pharmacist of Record (PoR by MTN LOC Pharmacy. Sites will identify the individual responsible for receiving the prescriptions and for contacting the MTN LOC Pharmacist should additional prescriptions be needed during the study.

A new prescription will be required for each study gel dose volume (Visit 3, 5, and 7) administered to the participant.

Although the procedures listed in the protocol for each visit must be completed, at a minimum, all of the following procedures must be conducted prior to dispensing study product:

- Rectal exam and, if indicated, physical exam, pelvic exam and/or male genital exam
- AE assessment and reporting, and review of any unresolved AEs (verbal report of symptoms is acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product)
    - A participant with a current AE Grade 2 or higher judged to be related to study product may not receive the next study gel dose; PSRT consultation is required.
- For females: pregnancy testing and contraceptive counseling.
- Product use instructions, as needed

In Clinic (procedures C1-C5):

C1. Complete an MTN-037 Prescription accordingly (at Visit 3, 5 and 7). Record CRS Name, DAIDS Site ID and PTID. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form prior to recording his/her initials beside these boxes.

C2. Indicate the dosage of PC-1005 needed for the visit.

C3. The middle section of the prescription must be completed by a study staff member designated in the site's Delegation of Authorities (DoA) Log as an authorized prescriber of study product. This person also must be listed as an investigator (either the Investigator of Record or Sub-Investigator) on the current FDA Form 1572.

C4. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow (clinic) copy in the participant study notebook.

C5. Deliver the white (pharmacy) original prescription to the study pharmacy.

In Pharmacy (procedures P1-P4):

P1. Upon receiving the completed MTN-037 Prescription, the pharmacist will review the document for completion and accuracy. If pharmacy staff identifies possible errors on the original prescription, (s)he will return the original prescription to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original prescription and the yellow copy. An identical signed and dated note explaining the corrections should be recorded on both copies, on the same date, by the same person. Corrections to original study prescriptions should only be made by an authorized prescriber and fully documented in the participant's chart notes.

P2. The pharmacy staff will prepare the syringe (applicator) with the requested dose of PC-1005. The PoR will label the applicator in accordance with US and local requirements. Labeling will include the PTID of the participant for whom the product was prepared.

P3. The pharmacist will review the procedure for preparing the applicator for use in the clinic with study staff who picks up the dose from the pharmacy. (See Appendix 6.2)

P4. The labeled applicator and rectal tip will be dispensed per instructions in the MTN-037 Pharmacy Study Product Management Procedures Manual and in accordance with the site pharmacy SOP(s).

6.3 PC-1005 Request Slip

MTN-037 PC-1005 Request Slips (Appendix 6-3) will be produced as two-part no carbon required (NCR) forms. A bulk supply of slips will be provided to the PoR by MTN LOC Pharmacy.

The MTN-037 PC-1005 Request Slip is used by clinic staff to communicate to the study pharmacist that an additional applicator is needed, a clinical hold is in place, a participant is resuming study product after a hold, or if a participant has been permanently discontinued, is refusing the gel or completed the study.

Double-check the accuracy of all entries and then separate the two parts of the completed slip. Retain the yellow copy in the participant study notebook and deliver the white original to the pharmacy. If corrections are needed, the same corrections must be made separately on both the white original sheet and the yellow copy. An identical signed and dated note explaining the corrections also should be recorded on both sheets, on the same date, by the same person.

6.3.1 Resupply

A single gel applicator may be needed if the applicator dispensed has become unusable (i.e. dropped on the floor) – this should be rare. Clinic staff will complete the PTID check the RESUPPLY box on the PC-1005 Request Slip. Indicate which dose (4, 16, or 32 mL of PC-1005) is being requested. The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order study product for participants during follow-up. Clinic staff comments may also be provided if needed.

6.3.2 Product Hold/Resume

Product hold following a completed prescription sent to pharmacy:
If the pharmacist receives the prescription and prepares a dose and a study clinician determines that a participant should temporarily hold study product use due to safety reason(s) (e.g., an adverse event), mark the "HOLD" box on the PC-1005 Request Slip. Record the reason for the hold on the adjacent "Reason" line. It is not necessary to complete any new slips at subsequent visits in which the

hold is still in effect. Once a product hold is resolved an authorized prescriber will need to complete a new request slip from the site clinic marked "RESUME." For the specific dose that was held, only clinic staff members who are authorized prescribers may mark the "RESUME" box. In all other circumstances, the slips are not required to be signed by an authorized prescriber; however site-specific pharmacy regulations may be more stringent than these requirements. All sites must comply with local requirements.

Product hold prior to a prescription completed:
If a prescription has not yet been completed and the study clinician determines that a participant should temporarily hold study product use due to safety reason(s) (e.g., an adverse event), it is NOT necessary to complete the Request Slip marked "HOLD". Once the hold is resolved the clinician should complete the prescription for the gel dose requested and send to the pharmacy.

6.3.3 Permanent Discontinuation of Study Product

If a study clinician determines that a participant should permanently discontinue study product use due to safety reason(s) (e.g., HIV infection), mark the "PERMANENT DISCONTINUATION" box on MTN-037 PC-1005 Request Slip. Record the reason for the permanent discontinuation on the "Reason" line provided. Once a permanent discontinuation is in effect, the site pharmacist will not dispense any further study product to that participant. Future slips will no longer be completed at the participant's remaining study visits.

6.3.4 Participant-Initiated Decline of Study Product

If a participant decides on his/her own to stop using study gel, and refuses to be re-supplied further study product, mark the "PARTICIPANT DECLINE" box on MTN-037 PC-1005 Request Slip. Complete the slip and mark "PARTICIPANT DECLINE" at each subsequent visit that the participant refuses study product. If the participant declines product use, the PSRT should be notified.

6.3.5 Scheduled and Early Terminations

When a participant has completed his/her study participation, whether a scheduled or early termination, mark the "PRODUCT USE PERIOD COMPLETE" box on the MTN-037 PC-1005 Request Slip. This serves as a notification to the site pharmacist that the participant will no longer be requiring any additional study product dispensations. The Product Discontinuation CRF should also be completed at this time. Participants who complete all three study gel doses as scheduled should have these product discontinuation procedures done at Visit 8.

6.4 Study Gel Chain of Custody

Study gel will be dispensed from the pharmacy to an authorized clinic staff member who will then deliver the applicator(s) to the clinic for administration. The site must designate its Chain of Custody (dispensing method) for study product in MTN-037 standard operating procedures (SOPs) for product dispensing and re-supply. These SOPs should be developed with input from both pharmacy and clinic staff. They must be approved by the MTN LOC Pharmacist prior to study activation and may only be modified after consultation with the MTN LOC Pharmacist.

The MTN-037 Record of Receipt of Site-Specific (see Appendix 6.4) must be used to document dispensing of all study product from pharmacy staff to clinic staff. Pharmacy staff will complete the top section (CRS Name, DAIDS Site ID) and the first four columns on the Record of Receipt. When receiving PC-1005 from the pharmacy, clinic staff will verify the PTIDs, confirm the applicators received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

Clinic staff are responsible for controlling access to the gel applicators dispensed into their custody and ensuring that the applicators are administered to the participants for whom they were dispensed. Clinic staff also must document administration of the PC-1005 to designated participants in the participants' chart notes or other source document. If the gel applicator dispensed for a participant is not administered to the participant, clinic staff will document this in the participant's study chart and return the applicator to the pharmacy as soon as the participant's visit is completed.

6.5 Study Gel Use Instructions

Detailed instructions are provided in Appendix 6-4.

6.6 Study Product Returns

If an applicator is dispensed from the pharmacy and not administered, it must be returned to the pharmacy prior to the clinic closing the same day.

6.7 Prohibited Medications

Reported use of the following medications is prohibited during study participation:

- PEP and PrEP
- Use of rectally-administered products, and any products containing N-9
- CYP3A inhibitors and inducers. A listing of these specific prohibited agents is provided in Appendices 6-6 and 6-7. It is important to note that single dose oral fluconazole for the treatment of vaginal fungal infections is permitted.
- Anticoagulants or blood-thinners (such as heparin, Lovenox®, warfarin, Plavix® [clopidogrel bisulfate])

Participants will be counseled to abstain from using aspirin (greater than 81 mg) and other non-steroidal anti-inflammatory drugs (NSAIDS) within 72 hours prior to and following a PK sample collection visit. Should a participant report taking any of the medications noted above, which may increase risk of bleeding, or report the use of rectal products within 72 hours prior to biopsy collection, the visit should be rescheduled within the visit window, if possible. If it is determined that rescheduling the visit within the window is not possible, the visit may proceed at IoR discretion after proper participant counseling has occurred.

6.8 Study Gel Complaints

During the study, a problem or concern may be observed with a gel vial or applicator. A problem may be noted by the pharmacy staff, clinic staff, or the participant. These complaints may be about the dosage form (gel), packaging (vial, syringe, cap, rectal tip), or other aspects of the study product. Clinic staff should make thorough record of complaints of participants and clinic staff. The clinic staff member will notify (via email) the site PoR and other designated site pharmacy staff of the study product complaint. This notification should include as much detail as possible and pictures (if necessary). The following information should be provided in the email:

- PTID
- date of the observed issue
- date that the issue was reported
- date gel applicator was dispensed
- did an adverse event occur
- description of the nature of the issue
- any other details deemed necessary

The site PoR will forward (via email) this information to the MTN LOC Pharmacist. If the complaint/issue is concerning an unused gel, then the unused gel vial or applicator should be quarantined in the pharmacy. If the complaint/issue is concerning used gel/used syringe/applicator, then the clinic staff should document in a communication to the pharmacy and /or provide a photo describing the issue (if available).

Appendix 6-1

MTN-037 PC-1005 PRESCRIPTION

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	
DAIDS Site ID:	

Participant ID: ☐☐☐ – ☐☐☐☐☐☐

Did the participant provide written informed consent for enrollment into MTN-037? YES ☐ NO ☐ Clinic Staff Initials: _____

PC-1005 DOSAGE (Check one):

☐ **4 mL** ☐ **16 mL** ☐ **32 mL**

PC-1005

Sig: Insert entire content of one (1) applicator of PC-1005 into rectum as directed.

Quantity: Dispense one (1) applicator of the dosage of PC-1005 indicated above.

Authorized Prescriber Name *(please print)*:_____

Authorized Prescriber Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Version 1.0: 22JAN2018

Pharmacy

Appendix 6-2
Record of Receipt of Site-Specific PC-1005

CRS Name:	DAIDS Site ID:

PHARMACY STAFF				CLINIC STAFF/COURIER/RUNNER/PARTICIPANT			
Date/Time Dispensed by Pharmacy dd-MMM-yy (hh:mm) *24-hr clock*	PTID	Dosage 4, 16, or 32mL of PC-1005	RPh Initials	PTID (Verify PTID)	Date/Time Received by Clinic Staff dd-MMM-yy (hh:mm) *24-hr clock*	Clinic Staff/ Runner	Comments

Appendix 6-3
MTN-037 PC-1005 REQUEST SLIP

MTN-037 PC-1005 REQUEST SLIP

Participant ID: ☐☐☐–☐☐☐☐☐☐

Instructions: Mark the box that corresponds to the appropriate pharmacy action being requested. If ordering gel after a hold, the "RESUME" box must be marked. For "RE-SUPPLY" and "RESUME" indicate the gel dose. Once slip is completed, deliver white original (labeled "Pharmacy") to the pharmacy. File yellow copy (labeled "Clinic") in the participant's study notebook.

☐ **RE-SUPPLY PC-1005** → **Check one:** ☐ **4 mL** ☐ **16 mL** ☐ **32 mL**

☐ **HOLD** → **Reason:** _____

Pharmacy: Do not dispense further PC-1005 to the participant until another MTN-037 PC-1005 Request Slip marked "RESUME" with authorized prescriber signature is received.

☐ **RESUME PC-1005** → **Check one:** ☐ **4 mL** ☐ **16 mL** ☐ **32 mL**

Pharmacy: Only an authorized prescriber can indicate RESUME.

☐ **PERMANENT DISCONTINUATION** → **Reason:** _____

Pharmacy: Do not dispense any further PC-1005 to this participant.

☐ **PARTICIPANT DECLINE** → **Pharmacy: Do not** dispense at this visit. Participant is refusing PC-1005.

☐ **PRODUCT USE PERIOD COMPLETE** → **Pharmacy: Do not** dispense any further PC-1005 to this participant.

Clinic Staff Name *(please print)*: _____

Clinic Staff Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Version 1.0: 22JAN2018

Pharmacy

Appendix 6-4

Instructions for Clinic Administration of PC-1005

1. The pharmacist will dispense the requested applicator (4, 16 or 32 mL) of gel which will be labeled for the participant. The pharmacist will also provide a small amber zip bag containing the tip for rectal administration.

2. When the dose is ready to be inserted, remove the red cap (twist off from the end of the applicator) and discard.

3. Remove the rectal tip from the bag and **secure it with a twist** on the end of the applicator.

4. A small amount of study provided lubricant may be used on the rectal tip for ease of insertion.

5. Holding the barrel of the applicator, completely insert the rectal tip slowly and gently into the anus of the participant.

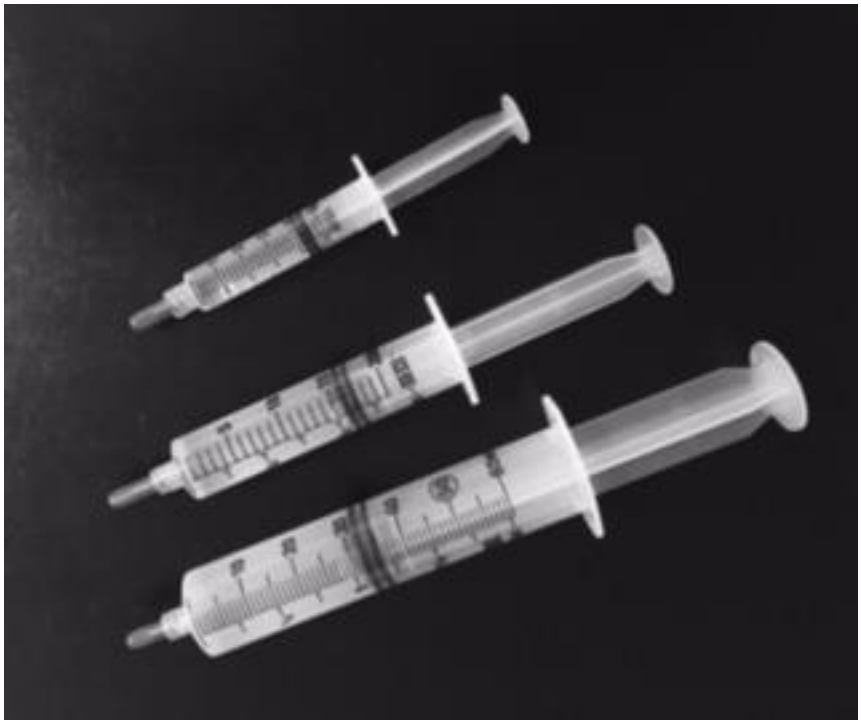
6. Once the tip is completely inserted into the anus, gently push the plunger to expel all of the gel from the applicator.

7. After the plunger has been pushed all the way into the barrel, gently slide the rectal tip out of the anus.

8. Applicator and rectal tip should be discarded in the biohazardous waste container, per institutional guidelines.

Appendix 6-5

Gel Syringes with Red Cap (Applicator)



Rectal tip with Amber Zip Bag

Appendix 6-6

CYP3A4 Inhibitors to Avoid

Strong Inhibitors **≥ 5-fold increase in AUC or > 80% decrease in CL**	**Moderate Inhibitors** **≥2 but < 5-fold increase in AUC or 50-80% decrease in CL**	**Weak Inhibitors** **≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL**
Antibiotics: clarithromycin, telithromycin Antidepressants: nefazodone Azole Antifungals: ketoconazole, itraconazole, posaconazole, voriconazole Pharmacokinetic Enhancers: cobicistat Protease Inhibitors: ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, boceprevir, telaprevir Reverse Transcriptase Inhibitors: delavirdine Vasopression Receptor Antagonists: conivaptan	Antiarrhythmics: dronedarone Antibiotics: erythromycin, ciprofloxacin Antiemetics: aprepitant Antineoplastics: imatinib Azole Antifungals: fluconazole, miconazole Calcium Channel Blockers: verapamil, diltiazem Protease Inhibitors: atazanavir, darunavir/ritonavir, fosamprenavir	Antiandrogens: bicalutamide Antianginals: ranolazine Antiarrhythmics: amiodarone, quinidine Antibiotics: azithromycin Antidepressants: fluoxetine, fluvoxamine Antihyperlipidemics: atorvastatin Anti-inflammatory (asthma): zileuton Antineoplastics: nilotinib Antituberculars: isoniazid Anxiolytics: alprazolam Calcium Channel Blockers: amlodipine, felodipine Herbal Supplements: ginkgo biloba, goldenseal Histamine H2 Antagonists: cimetidine, ranitidine Immune Suppressants: cyclosporine Platelet Aggregation Inhibitors: cilostazol Protease Inhibitors: tipranavir/ritonavir

Appendix 6-7

CYP3A4 Inducers to Avoid

Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
Anticonvulsants/Mood Stabilizers: phenytoin, carbamazepine Anticonvulsants/Barbiturates: primidone Antituberculars: rifampin Barbiturates: phenobarbital, butalbital Glucocorticoids: dexamethasone Herbal Supplements: St. John's wort^ Protease Inhibitors: tipranavir (alone)	Antibiotics: nafcillin Antihypertensives: bosentan Antituberculars: rifabutin CNS Stimulants: modafinil Reverse Transcriptase Inhibitors: efavirenz, etravirine, nevirapine	Anticonvulsants: oxcarbazepine, rufinamide Antidiabetics: pioglitazone CNS Stimulants: armodafinil Glucocorticoids: prednisone Herbal Supplements: echinacea^ Protease Inhibitors: amprenavir

^The effect of St. John's wort and echinacea varies widely and is preparation-dependent.

AUC: Area under the curve in a plot of concentration of drug in blood/systemic circulation versus time. AUC (from zero to infinity) represents the total drug exposure over time.
CL: Clearance