Section 6. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff (i.e., clinic staff) related responsibilities regarding blinding, transport, receiving the MTN-026 gel from pharmacy (dispensation of gel from pharmacy staff to clinic staff), and delivery of the study gel to study participants (provision of gel from clinic staff to study participant). Associated instructions for pharmacy staff are provided in the MTN-026 Pharmacy Study Product Management Procedures Manual, which will be made available to each MTN CRS Pharmacy by the MTN LOC Pharmacist. Please refer to Section 10 (Counseling Considerations) of this SSP manual for product use instructions and guidance on study product adherence counseling.

6.1 Responsibilities and Obligations with Regard to Blinding

MTN-026 Investigators of Record (IoRs), and by delegation all MTN-026 study staff, are responsible for maintaining the integrity of the study's blinded design. Each participant is randomized (2:1) to the specific study product (dapivirine 0.05% gel or HEC universal placebo gel, respectively) to be used rectally. The identify of specific study product to which each participant is assigned is double-blinded, meaning that neither study participants nor study staff

will be provided information on the identity of the specific study product. During the study implementation period, the SDMC (SCHARP) statisticians will be the only protocol team members unblinded to participant treatment assignment via study randomization.

As described in section 12 of this manual (Data Collection), designated clinic staff will randomize study participants in the study database. Site pharmacy staff — who are excluded from ascertaining primary and secondary study endpoints – will have on-line access (via Medidata) to blinded, coded information indicating the specific study gel to which a participant has been assigned.

Blinding will be maintained throughout the study and until all study endpoint data have been verified and are ready for final analyses. There are no circumstances under which it is expected that unblinding a participant's study product assignment will be necessary to protect the safety of that individual. In the event that study staff becomes concerned that a participant may be put at undue risk by continuing use of study product, the IoR may permanently discontinue product use by the participant. However, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow- up and/or clinical management of the participant.

6.1.1 Emergency Unblinding Process

During the trial, an IoR/designee may request that a participant's study product regimen assignment be provided (unblinding), if it is essential to protect a participant's safety. To request the unblinding for a specific participant, the following steps are required:

1. IoR/designee must contact the MTN-026 Protocol Safety Review Team (PSRT) (mtn026psrt@mtnstopshiv.org).
2. If the PSRT rules that unblinding is required, the PSRT will send the unblinding e-mail request (with "Unblinding Request" entered in the Subject line) to the Protocol Statistician (Elizabeth Brown; erbrown@fhcrc.org), and cc: the IoR/designee from the site so that the statistician can send the information to the correct person at the site. The MTN PI and co-PI should also be copied on this request from PSRT.
3. The Protocol Statistician will provide the study product assignment to the IoR/designee and will then notify the following: MTN PI and Co-PI, PSRT, the protocol management team and protocol chairs, MTN Regulatory and the Fred Hutchinson Cancer Research Center IRB that this has occurred.
4. The site IoR/designee must notify the local IRB in an expedited manner of this occurrence of unblinding.

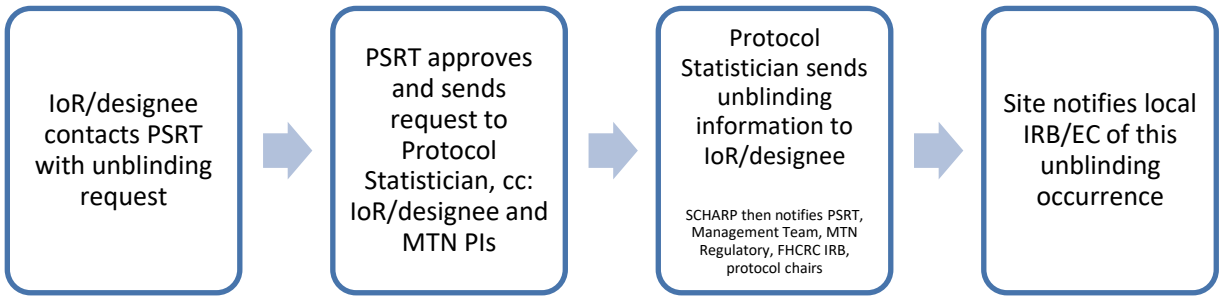

Figure 6-1. Flow Chart of Emergency Unblinding Process

6.2 Randomization Assignment

The MTN Statistical Data Management Center (SDMC) will generate and maintain the study randomization scheme.

Study randomization will occur via the Medidata web-based system, as described in Section 12 (Data Collection) of this manual. After clinic staff have randomized a participant, designated pharmacy staff will have on-line, restricted access (via Medidata) to blinded, coded information that will indicate to the site pharmacist which gel applicator to dispense to the participant. Clinic staff will not have access to this information. Clinic staff will complete a study prescription and send the original part to designated site pharmacy staff, as described in section 6.3 below, to notify the site pharmacist that the participant has been randomized and needs to be dispensed study gel.

6.3 Prescription Completion and Dispensing Study Gel at Visit 3

Participants are randomized (2:1, respectively) to receive a single dose of dapivirine 0.05% gel or HEC universal placebo gel rectally, followed by seven daily doses of the same product administered under direct observation in the clinic.

Prescriptions (Appendix 6-1) will be produced as two-part no carbon required (NCR) forms. A bulk supply of prescriptions will be provided to the clinic staff 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.

After recording CRS Name, CRS ID, PTID, and other details on the prescription, clinic staff will separate the two sheets of the form, and the white original will be delivered to the pharmacy. The yellow copy (bottom) will be retained in the participant's study notebook in the clinic. Only one prescription will be used for each participant. A prescription must be signed by an authorized prescriber as designated on FDA Form 1572. Corrections to the study prescriptions should only be made by study staff authorized to complete the original prescription. The same corrections should be made separately on both the original white sheet and the yellow copy. A signed and dated note explaining the corrections if needed also should be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

Study gel will be dispensed directly to study staff on behalf of the participant, upon receipt of an original, written study prescription that is signed by an authorized prescriber. The pharmacist will dispense one (1) prefilled gel applicator at Visit 3 (single dose, direct observed, rectal gel dosing visit). This one gel applicator is for administration at that visit for directly observed dosing in the clinic.

In Clinic (procedures C1-C5):

C1. At Visit 2 (Enrollment Visit), the Eligibility Criteria eCRF and Randomization eCRF must be completed by clinic staff for a participant to be enrolled/randomized into the study. A participant is considered officially enrolled after the completion of the Randomization eCRF, as evidenced by the appearance of a randomization date and time on this eCRF.

C2. Complete an MTN-026 Prescription accordingly (at Visit 3). 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.

C3. The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties 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-P3):

P1. At Visit 2, designated site pharmacy staff will receive an email Medidata alert that the participant was enrolled/randomized into the study. This communication will be printed and filed in the pharmacy binder.

P2. Upon receiving the completed MTN-026 Prescription (at Visit 3), 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. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes 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 pharmacist will then log into the study database and, using the PTID recorded on

the prescription, navigate to the participant's Pharmacy Dispensation eCRF to determine the study product sublot code to which the participant was randomized.

P3. Pharmacy staff will dispense the study product for participants per instructions in the MTN-026 Pharmacy Study Product Management Procedures Manual and in accordance with the site pharmacy SOP(s).

6.4 Study Gel Request Slip – Visit 7-Visit 13

The MTN-026 Study Gel Request Slip (Appendix 6-2) is used by clinic staff to communicate to the study pharmacist the following:

- To request a single applicator at Visit 7 for the participant to take home for as-needed home dosing in the event that they are unable to attend a clinic visit.
- To request a single gel applicator for direct observed doses in the clinic (Visit 7-13).
- To request a single gel applicator for another reason. Reasons could include: (1) as-needed home dose was lost, stolen, damaged, etc; (2) study product complaint noted for as-need home dose or clinic dose. Use IoR discretion and document.
- NOTE: If the participant uses his/her one as-needed home dose of study gel, he/she will not be provided another home dose if this action is requested by the participant.

The request slip will be produced as two-part no carbon required (NCR) sheets. The top white form is the original (pharmacy), and the bottom yellow form is the copy (clinic). Bulk supplies of the slips are available from the MTN LOC Pharmacist and will be supplied to clinic staff. Sites will identify the individual responsible for receiving the slips and for contacting the MTN LOC Pharmacist should additional request slips be needed during the study. Clinic staff will complete the PTID, visit number, RESUPPLY for 1 or 2 gel applicators, and comments if necessary. 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.

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. A signed and dated note explaining the corrections also should be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

6.5 Study Gel Management Slip

The Study Gel Management Slip (Appendix 6-3) is provided to the research site staff by the MTN LOC Pharmacist and is completed by the clinic staff. It is to be used by the clinic staff to formally communicate to the site pharmacy when there is a permanent discontinuation, participant decline, or if a participant is no longer in the study.

The request slip is a two-part NCR paper document. The top white is the original (pharmacy) and the bottom yellow is the copy (clinic). 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. A signed and dated note explaining the corrections also should be recorded on both sheets. Identical corrections and notes

should be recorded on both copies, on the same date, by the same person.

6.5.1 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. 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. A Treatment Discontinuation CRF must also be completed by clinic staff.

6.5.2 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-026 Study Gel Management 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.

6.5.3 Scheduled and Early Terminations

When a participant has completed his/her study participation, whether a scheduled or early termination, mark the “PRODUCT USE PERIODS COMPLETED” box on the MTN-026 Study Gel Management Slip. This serves as a notification to the site pharmacist that the participant will no longer be requiring any additional study product dispensations. A Treatment Discontinuation and Study Discontinuation CRF should also be completed by clinic staff.

6.6 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 either direct observed administration or home use (1 applicator only). The site must designate its Chain of Custody (dispensing method) for study product in MTN-026 standard operating procedures (SOPs) for product dispensing and re-supply during MTN-026. These SOPs should be developed with input from both pharmacy and clinic staff. They must be approved by the MTN Pharmacist prior to study activation and may only be modified after consultation with the MTN Pharmacist.

6.6.1 Dispensing from the Pharmacy to Clinic Staff

To dispense study product to clinic staff who will then deliver the product to participants, prescriptions and study product request slips are expected to be delivered to the pharmacy by clinic staff or a runner. Upon receipt of a correctly completed and signed prescription or study product request slip, the PoR will prepare the requested quantity of study product as documented on the prescription or slip.

The MTN-026 Record of Receipt of Site-Specific Study Gel must be used to document dispensing of study product to clinic staff. For the Record of Receipt, pharmacy staff will complete the top section (CRS name, CRS ID) and the first four columns in the body of the record. When receiving

study product from the pharmacy for a given participant, clinic staff will verify and record the PTID in the designated column, confirm the quantity of study product dispensed, as documented by the site pharmacist, and complete the remaining two columns in the body of the record. 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 site pharmacy.

Clinic staff is responsible for controlling access to the study products dispensed into their custody and ensuring that the products are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the study products to the designated participants in the participants' study charts. Delivery may be documented in chart notes or on other source documents used for this purpose. If all study products dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the study products to the pharmacy as soon as the participant's visit is completed or as soon as it is known that the participant will not be completing his/her study visit on the scheduled date.

6.7 Study Gel Use Instructions – Rectal Administration

Participants will undergo daily directly observed rectal gel dosing in the clinic. Study Staff will administer one pre-filled applicator of gel, at Visit 3. After a wash out period, study staff will insert gel or participant will be instructed to insert one pre-filled applicator of gel into the rectum daily for seven (7) consecutive days, as close to the same time each day as possible. Clinic staff will instruct the participant to use a small amount of the study-provided lubricant on the outside of the applicator for ease of rectal insertion. The clinic will maintain a supply of the lubricant (4 mL packets), which will be provided by the MTN LOC pharmacist. One packet should be given for each applicator for rectal use. The clinic will also receive 4 oz. tubes of the lubricant for use during study-related procedures. The Directly Observed Dosing Log should be completed by clinic staff to document the visit, date and time the gel application was observed.

At Visit 7, the participant will be given one dose of gel (and one packet of lubricant) to use at home in the rare event that he/she is unable to come to the clinic. The Product Dispensation and Returns (For Non-Observed Home Dose) should be completed by clinic staff to document when the product was provided. If a participant is not able to come to the clinic for a directly observed rectal dose, the participant must rectally insert the gel without observation as close to the scheduled time of the directly observed dose, unless the next dose is estimated to be due within six hours. If the next dose is estimated to be due within six hours, the dose should be skipped. If the dose was used at home or was not done, the applicable dose should be documented on the Directly Observed Dosing Log. The next dose will be administered as originally scheduled.

Detailed instructions for rectal gel insertion are found on the MTN-026 Study Implementation webpage. A list of frequently asked questions pertaining to rectal administration is available in Appendix 6-4.

6.8 Prohibited Medications

Certain medications are prohibited during study participation. These include specified CYP3A4 inhibitors and inducers and drugs that can increase bleeding risk, as described below. Additionally, pre-exposure prophylaxis (PrEP) and post exposure prophylaxis (PEP) regimens are

not permitted during trial participation. Medications listed in Protocol Section 9.3 warrant permanent discontinuation of study gel. The PSRT must be consulted if a participant uses other prohibited medication(s). Please refer to Protocol Sections 6.10 and 9.3 and SSP Section 7 for details.

6.8.1 CYP3A4 Inhibitors and Inducers

Dapivirine is a CYP3A4 substrate – it is metabolized by CYP3A4. Study staff must promote the avoidance of CYP3A4 inhibitors and inducers (prescription medications, over-the- counter medications, herbal supplements, and nutritional supplements) via oral, injectable, vaginal or rectal route of administration, since this study is blinded. Appendix 6-5 outlines CYP3A4 inhibitors that participants should avoid using concomitantly in this study. Appendix 6-6 outlines CYP3A4 inducers to be avoided. **NOTE:** single dose oral fluconazole for the treatment of vaginal fungal infections is permitted.

Information in Appendices 6-5 and 6-6 is adapted from:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#4

If drug-drug interaction questions arise during the study that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the MTN-026 PSRT (mtn026psrt@mtnstopshiv.org). Medications with unknown interactions will be dealt with on a case-by-case basis with input from the PSRT, as needed.

6.8.2 Other Prohibited Medications

Study staff will counsel participants to avoid the use of medications that can increase bleeding risk – these include anticoagulants, blood modifier agents, and non-steroidal anti-inflammatory drugs (NSAIDS). Refer to Appendix 6-7 for a list of anticoagulants/blood modifier agents for participants to avoid. Refer to Appendix 6-8 for a list of prohibited NSAIDS. Additionally, the use of hormone therapy, including hormone replacement therapy, and the use of PrEP and PEP are prohibited.

Other prohibited medications and practices can be found in Protocol Section 6.10 and SSP Section 7. If questions about prohibited medications arise during the study that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the MTN-026 PSRT (mtn026psrt@mtnstopshiv.org). Inquiries will be dealt with on a case-by-case basis with input from the PSRT, as needed.

6.9 Study Gel Retrieval

Protocol Section 6.7 specifies the circumstances under which study product must be retrieved from participants. Because each participant is undergoing directly observed dosing of gel in the clinic and only has one gel applicator (for as-needed at home use) in his/her possession during study participation, the need for product retrieval is expected to be rare. When product retrieval is required, retrieval may occur by the participant returning the product to study staff. Only unused gel applicators are to be brought to the pharmacy for quarantine.

When study product is permanently discontinued, the one unused gel applicator (for as-needed at home use) must be returned to the clinic. If the unused gel applicator is not retrieved with 24 hours of discontinuation notification, then the MTN-026 PSRT must be informed.

Study participants will be instructed to return the unused gel applicator at Visit 14: 24 hour PK Visit. In the event that the unused gel applicator is not returned at this visit, site staff will make efforts to encourage participants to return the study product as soon as possible. These efforts must be documented in the participant's chart notes.

If not previously returned, it is expected that participants will returned the unused gel applicator at Visit 16: Final Clinic Visit. The return of the unused gel applicator must be documented by clinic staff on the Product Dispensation and Returns (For Non-Observed Home Dose) CRF. In the event that the unused gel applicator is not returned at this visit, site staff will make efforts to encourage participants to return the study product within 7 days. These efforts must be documented in the participant's chart notes. If study product is not retrieved within 7 days, the MTN-026 PSRT must be notified and a Protocol Deviation Log CRF completed.

6.10 Study Gel Complaints

During the study, a problem or concern may be observed with a gel 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 (overwrap pouch, cap, barrel, plunger), 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:

- 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, and 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 applicator, then the unused gel applicator should be quarantined in the pharmacy. If the complaint/issue is concerning a used gel 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: The MTN-026 Study Gel Prescription

MTN-026 STUDY GEL 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:	
CRS ID:	

Participant ID: ☐☐☐ – ☐☐☐☐☐☐

Did the participant provide written informed consent for enrollment into MTN-026? YES ☐ NO ☐ Clinic Staff Initials: _____

Dapivirine 0.05% or Placebo Gel

Sig: Insert entire contents of one (1) applicator into rectum as directed.

Quantity: Sufficient to last for one plus seven consecutive days of study gel administration. Study gel may be refilled as needed for the duration of the study product administration period.

Authorized Prescriber Name *(please print)*:_____

Authorized Prescriber Signature: _____

Date: ☐☐ ☐☐☐ ☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Once the prescription is completed, deliver white original (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant's study notebook.

Pharmacy: Each participant will receive nine gel applicators.

- Dispense 1 gel applicator at Visit 3.
- Dispense 2 applicators at Visit 7: 1 applicator for direct observed dosing in the clinic and 1 applicator for as-needed home dosing by the participant.
- The remaining quantity of applicators (6 applicators) will be dispensed once daily for the remainder of the direct observed dosing study product administration Visits 8-13.

Appendix 6-2: The MTN-026 Study Gel Request

MTN-026 STUDY GEL REQUEST SLIP

Instructions: Once slip is completed, deliver white original (labeled "Pharmacy") to the pharmacy. File yellow copy (labeled "Clinic") in the participant's study notebook.

Participant ID

☐☐☐ – ☐☐☐☐☐☐

Visit #: _____

☐ **RE-SUPPLY** ⟶ **Pharmacy: Dispense**

Check One:

☐ **2 gel applicators at Visit 7. One applicator for direct observed dosing in clinic and one applicator for as-needed home dosing.**

☐ **1 gel applicator for clinic direct observed dosing at Visits 8-13 or other.***

* If additional applicator is requested provide explanation in comments below.

Clinic Staff Comments:

Clinic Staff Name *(please print)*: _____

Clinic Staff Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Appendix 6-3: The MTN-026 Study Gel Management Slip

MTN-026 STUDY GEL MANAGEMENT SLIP

Instructions: Mark the box that corresponds to the appropriate pharmacy action being requested. Once slip is completed, deliver white original (labeled "Pharmacy") to the pharmacy. File yellow copy (labeled "Clinic") in the participant's study notebook.

Participant ID

			–						

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

Pharmacy: Do not dispense any further MTN-026 study gel to this participant.

☐ **PARTICIPANT DECLINE** → **Pharmacy: Do not dispense –** participant is **refusing study gel.**

☐ **PRODUCT USE PERIOD COMPLETED** → **Pharmacy: Do not dispense** any further MTN-026 study gel to this participant.

Clinic Staff Name *(please print)*: _____

Clinic Staff Signature: _____

Date: | | | – | | | | – | | |

dd *MMM* *yy*

Appendix 6-4: Rectal Gel Use Frequently Asked Questions

1. What is the best position to insert the gel rectally?
   A. Find the position that feels the most comfortable to you. Many people may already have a position that they prefer. If you do not have a preferred position, we recommend that you stand or lie on your side to insert the gel rectally.

2. What should I do if it hurts when I use the applicator to insert the gel?
   A. Before rectal gel application, make sure there is lubricant on the outside of the applicator as inserting a dry applicator may cause discomfort. You should also not force the applicator into the rectum.

3. Where does the gel go to after I put it inside?
   A. The study gel stays in the rectum. It is not likely that some of the gel will leak from the rectum. Sometimes when the gel comes out it looks clear. Sometimes it has a white color, and sometimes it has white clumps. This has been seen in other studies of the gels and it is normal. It is not normal to see a yellow or green discharge from the rectum. If this happens you should contact the study clinic.

4. Can the applicator get lost inside me?
   A. No, the applicator cannot get lost inside you. When you use the applicator, hold it with your fingers about half-way along the barrel, and insert it until your fingers touch your body. Half of the barrel of the applicator should go inside your body. The other half should stay outside the body. Once the contents are inserted, remove the entire applicator and discard.

5. What should I do if I have trouble applying the gel with the applicator?
   A. The applicators should be easy to use rectally. The applicator, when used rectally, should be slightly lubricated with the lubricant provided by the clinic staff. If you have difficulty using the applicators, ask study staff for help, as they may be able to show you different ways that you can insert the gel, which might make it easier.

6. What should I do if I think there is something wrong with an applicator?
   A. If there seems to be something wrong with an applicator (for example, you find it difficult to push the study gel out of the applicator, or if study gel has leaked out, or you think there is some other problem), do not use the applicator. If this occurs during directly observed dosing, immediately alert clinic staff. If this occurs with your at-home dose (as-needed), immediately call the clinic for guidance. Keep the applicator that had something wrong with it and show it to staff or bring it to the study clinic.

7. What happens if I press the plunger too early and most of the gel comes out on my outside? Can I put more in?
   A. If most of the study gel comes out on your outside, let study staff know and they will provide you with a new applicator to use. If you are at home, contact the clinic for guidance.

8. How do I store the one gel applicator that was provided to me for as-needed use?
   A. Store the study gel in a safe, cool, dry place at room temperature and not in the sun and out of reach of children and pets.

9. What happens if the applicator gets wet before I need to use it?
   A. If only the wrapper gets wet, the applicator can still be used. Dry the wrapper off before taking out the applicator. If the applicator itself gets wet, it should not be used, but this might only happen if the wrapper is already open. Contact the clinic for guidance.

10. What should I do if the wrapper is already open when I want to use the gel?
    A. You should only use an applicator with a sealed wrapper, so you should always open the wrapper right before inserting the gel. If you notice an applicator with a wrapper that is not sealed, do not use that applicator and let the study staff know. If you are at home, contact clinic staff. Bring the unused applicator with the open wrapper to the clinic.

11. What should I do if I forget to come to the clinic and use the gel?
    A. If you miss an appointment, you should call the clinic staff. If you aren't able to come into the clinic that day, you should insert the missed dose as soon as possible, unless the next dose is estimated to be due within 6 hours. If the next dose is estimated to be due within six hours, you should skip the missed dose. The next dose should be inserted as originally scheduled.

12. What should I do if I have a reaction to the study gel at home (e.g., unusual itching, stinging)?
    A. Contact the study staff and ask their advice. They might ask you to go to the clinic to be assessed and receive treatment, if needed.

13. Can I use the study gel before oral, anal or vaginal sex?
    A. Participants must abstain from vaginal, rectal, and oral sex 72 hours prior to clinic visits and during the study product use period. Males should abstain from receptive sexual activities for 72 hours after biopsy collection. Females should abstain from sexual activities (both vaginal and rectal) for 7 days following biopsy collection.

14. Can I use tampons at the same time as the gel?
    A. You should not use tampons 72 hours prior to clinic visits, during study gel use, or for 7 days after biopsy collection. If you happen to be on your menses during your gel use, you should use a panty liner, a pad or sanitary napkin if you are able. If you are not able to use a panty liner, a pad or sanitary napkin, and have to use tampons, please notify clinic staff at your next appointment.

Appendix 6-5: 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 6-6: 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

Appendix 6-7: Anticoagulants/Blood Modifier Agents to Avoid

Apixaban (Eliquis)
Clopidogrel sulfate (Plavix)
Dabigatran (Pradaxa)
Dalteparin (Fragmin)
Enoxaparin sodium (Lovenox)
Fondaparinux (Arixtra)
Heparin
Prasugrel (Effient)
Rivaroxaban (Xarelto)
Ticagrelor (Brillinta)
Warfarin (Coumadin)

Appendix 6-8: NSAIDS to Avoid

Aspirin (greater than 81mg/day; Anacin, Ascriptin, Bayer, Bufferin, Ecotrin, Excedrin*)
Choline and magnesium salicylates (CMT, Tricosal, Trilisate)
Choline salicylate (Anthropan)
Celecoxib (Celebrex)
Diclofenac potassium (Cataflam)
Diclofenac sodium (Voltaren, Voltaren XR)
Diflunisal (Dolobid)
Etodolac (Lodine, Lodine XL)
Fenoprofen calcium (Nalfon)
Flurbiprofen (Ansaid)
Ibuprofen (Advil, Motrin,Nuprin)
Indomethacin (Indocin, Indocin SR)
Ketoprofen (Actron, Orudis, Oruvail)
Ketorolac (Toradol)
Magnesium salicylate (Arthritab, Bayer Select, Magan, Mobidin, Mobogesic)
Meclofenamate sodium (Meclomen)
Mefenamic acid (Ponstel)
Meloxicam (Mobic)
Nabumetone (Relafen)
Naproxen, naproxen sodium (Naprosyn, Naprelan, Aleve, Anaprox)
Oxaprozin (Daypro)
Piroxicam (Feldene)
Rofecoxib (Vioxx)
Salsalate (Amigesic, Anaflex 750, Disalcid, Marthritic, Mono-Gesic, Salflex, Salsitab)
Sodium salicylate (various)
Sulindac (Clinoril)
Tolmetin sodium (Tolectin)
Valdecoxib (Bextra)
***Note: some products, such as Excedrin, are combination products. Excedrin contains aspirin, acetaminophen, and caffeine. Aspirin free Excedrin is available.**