MATRIX-001 Study-Specific Procedures (SSP) Manual
Section 6 – Study Product Considerations for Non-Pharmacy Staff

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6 Introduction

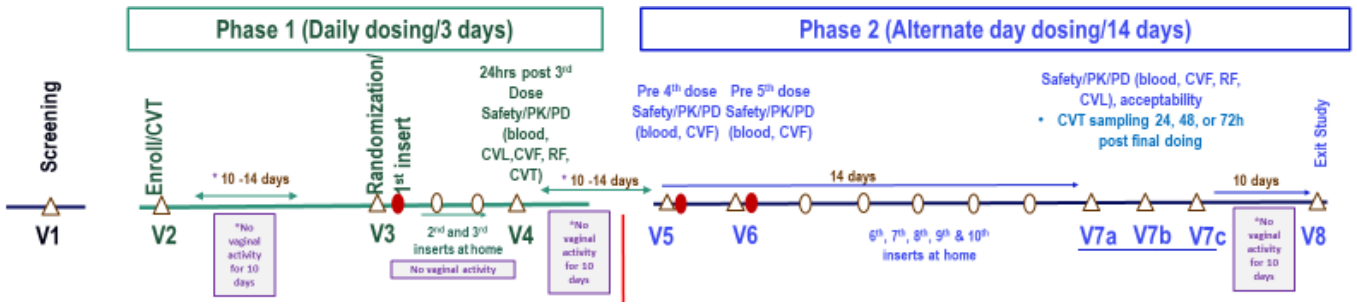
This section provides information and instructions for study staff related to the ordering, transport, delivery and provision of MATRIX-001 study product (vaginal insert) to study participants. Associated instructions for pharmacy staff are provided in the MATRIX-001 Pharmacy Manual, which will be made available to each site Pharmacist of Record (PoR) by the Product Development Team. The PoR is defined by the staff designated to perform this function by the Investigator of Record on the Delegation of Duties Log and on the FDA Form 1572, as required. Pharmacy documents referred to in the SSP are provided but sites may adjust them according to site needs.

6.1 Study Product Regimen

Phase 1
Each study participant will be randomized to receive TAF/EVG or placebo insert for vaginal administration. The insert will be provided by clinic staff in the site clinic for self-insertion at Randomization Visit 3. Participants will be given single doses for each of the second and third daily doses for self-insertion on the 2 days following visit 3.

Phase 2
At Visits 5 and 6, participants will self-insert a single dose in the clinic to start the Phase 2 alternate day dosing. At Visit 6, participants will be given doses 6-10 to insert every other day at home. The total duration of product administration is approximately 4 weeks (depending on menses), including recovery time (10-14 days) post tissue collection at Visit 4.

Figure 1: Study Product Regimen



Randomization Assignment
The FHI 360 Data Management and Statistical Support will generate and maintain the study randomization scheme.

Study randomization will occur via the FHI 360 OpenClinica web-based data system, as described in SSP Section 12 (Data Collection). At Visit 3 (Randomization), after a participant has been confirmed eligible, delegated staff will randomize the participant via OpenClinica. The randomization code along with tissue sampling timepoint post final dose (24, 48 or 72h) will be generated and displayed. After randomizing, staff should either screenshot or print the Randomization report from OpenClinica for the PoR/designee. The printed randomization should be filed in the pharmacy with the prescription (described below). The PoR/designee will be provided with the decode list for proper assignment and allocation of study product according to the randomization code. In the event site is unable to access OpenClinica, please refer to SSP Section 12.1 Data Collection for the process to follow.

6.2 Study Product(s)

MATRIX-001 includes, TAF/EVG and placebo vaginal inserts. The TAF/EVG vaginal insert contains 20 mg tenofovir alafenamide (TAF) and 16 mg elvitegravir (EVG). The placebo vaginal insert will be similar in appearance to the TAF/EVG insert without active pharmaceutical ingredients. Participants will be randomized (1:1) through OpenClinica to receive either TAF/EVG or placebo vaginal inserts. Each participant will receive their assigned vaginal insert to complete a total of 10 doses (3 doses inserted as one dose per day for 3 consecutive days and 7 doses inserted as one dose on alternating days for 14 days).

The inserts will be dispensed from the pharmacy at Visit 3, Visit 5 and Visit 6 using the provided MATRIX-001 Prescription. A separate prescription should be used at each visit. In the event an insert is dropped, participants can visually inspect the study insert for signs of debris and may dry wipe insert and re-attempt insertion. Where required, replacement inserts may be dispensed. If possible, unused inserts should be returned to the study pharmacy for quarantine and destruction. If the insert is not retrievable or able to be returned, documentation is required in Study Product Accountability Log(s) and chart notes as necessary.

The Vaginal Insert Guide is available to help the participant with the administration of the insert and can be found on the MATRIX-001 webpage under Study Documents.

6.3 Prescriptions and Dispensing Study Product

6.3.1 Clinic Procedures

MATRIX-001 prescriptions will be required for each dose administration visit (Visits 3, 5 and 6). In addition, sites may also use their own prescription/study medication order form as required by their institution or local requirements. As this is a double-blind study, neither study staff nor the participant will know what study product the participant has been assigned to use.

Designated clinic staff will complete a study prescription and send to the PoR/designee, as described below, to notify that the participant has been randomized and needs the assigned insert to be dispensed. Alternately, with confirmation from the clinician and if the PoR/designee has OpenClinica access, they can randomize the participant. A separate prescription is completed at each dose administration visit.

- Visit 3: doses 1-3, with 1 dose self-inserted at the clinic and doses 2-3 dispensed for self-insertion over the next 2 days
- Visit 5: dose 4 self-inserted at the clinic
- Visit 6: dose 5 self-inserted at the clinic and doses 6-10 dispensed for self-insertion on alternate days

The completed prescription includes PTID, verification of signed informed consent (at Visit 3 only), and the quantity to be dispensed. If an additional insert is needed (i.e. an insert is dropped on floor), a new prescription is completed to get an additional insert. In the event a dose is dropped and not retrievable, clearly document accordingly.

Phase	Dispensing Visit	Number of Doses to Dispense	Indication
1	Visit 3	3	Daily dose self-insertion
2	Visit 5	1	Self-insertion at visit
	Visit 6	6	Alternate day dose self-insertion

The middle section of the prescription includes the printed name and signature of the authorized prescriber, and date. This section must be completed by a study staff member designated in the site's Delegation of Duties (DoD) 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 form. The prescription template may be updated to comply with local regulations.

A printout or screenshot of the OpenClinica Randomization assignment (with PTID and assigned treatment group visible on same page) should accompany the Prescription. The printout should be filed in the pharmacy with the original prescription.

Sites may opt to provide additional doses (in addition to the required doses in the table above) in order to accommodate for dropped doses or clinic closure. Additional doses must clearly document in the participant's chart and on the prescription. Extra doses must be returned to site if not used and returned product must be documented accordingly on the Pharmacy Accountability Log(s).

6.3.2 Pharmacy Procedures

Prescriptions and printed randomization assignment, as applicable, should be delivered to the pharmacy by clinic staff. Upon receiving the completed MATRIX-001 Prescription, the PoR/designee will review the document for completion and accuracy. If pharmacy staff identify possible errors on the original prescription prior to making a copy, they will request clarification or correction from clinic staff. A decoding list will be provided to the PoR/designee for appropriate dispensing of study product.

The PoR/designee will verify the randomization assignment for the PTID by reviewing the accompanying randomization screenshot/printout. The PoR/designee verification should be documented on the appropriate section of the Prescription. The PoR/designee will print name, sign and date the prescription. The PoR/designee will prepare the requested product as documented on the prescription.

Once the entire MATRIX-001 Prescription is completed, double-check the accuracy of all entries and then make a copy. The original prescription stays with pharmacy, the copy is filed in the participant study chart. If corrections are needed after a copy is made, the same corrections must be made separately on both the original and the copy or a new copy is made with an explanation.

The PoR/designee will prepare and dispense the requested dose(s) of the assigned inserts for participant use per protocol and pharmacy manual. Single inserts may be dispensed in a plastic zip bag while multiple inserts should be dispensed in a secondary plastic bottle. All dispensed items must have a participant label.

6.4 Study Product Prescription

The MATRIX-001 Study Product Prescription is used by clinic staff to communicate to the PoR/designee the number of inserts to be dispensed as well as decisions to hold, discontinue, or resume study product use. The form will also be used to communicate to the PoR/designee if a participant chooses to stop using study product and/or terminate early from the study. In addition to the prescription, any interruption in dosing must be documented in the Product Interruption Form CRF.

Clinic staff will record the PTID on the top of the form. When the form is used to request study product, 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.

6.4.1 Product Hold/Resume

If 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 MATRIX-001 Study Product Prescription. Record the reason for the hold on the adjacent "Reason" line. It is not necessary to complete any new scripts at subsequent visits in which the hold is still in effect. Once a product hold is in effect, the PoR/designee will not dispense any study product to that participant until they receive a new Prescription marked "RESUME". Only clinic staff members who are authorized prescribers may mark the "RESUME" box. The "RESUME" box should only be checked if study product is being ordered and dispensed following a product hold and resumption.

6.4.2 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., grade 4 AE), mark the "PERMANENT DISCONTINUATION" box on the MATRIX-001 Study Product Prescription. Record the reason for the permanent discontinuation on the "Reason" line provided. Once a permanent discontinuation is in effect, the PoR/designee will not dispense any further study product for that participant. Future scripts will no longer be completed at the participant's remaining study visits.

6.4.3 Participant-Initiated Decline of Study Product

If a participant decides on her own to stop using study product, and refuses to be re-supplied with study product, do not mark the "HOLD" box. Instead, mark the "PARTICIPANT DECLINE" box on MATRIX-001 Study Product Prescription. Complete the script and mark "PARTICIPANT DECLINE" at each subsequent

visit during which the participant refuses study product. If the participant changes her mind and later decides to restart study product use, complete the script and mark "RESUME".

6.5 Chain of Custody

6.5.1 Dispensing from the Pharmacy to Clinic Staff

Each vaginal insert will be dispensed from the pharmacy into either a plastic bottle or plastic zip bag with a participant label. The vaginal insert(s) will be dispensed from the pharmacy to an authorized clinic staff member who will then deliver it to the participant or may be dispensed directly to the participant. Each site must develop an SOP on product dispensation and include information on Chain of Custody (dispensing/provision) for study product. The SOP should be developed with input from both pharmacy and clinic staff.

The MATRIX-001 Study Product Accountability Log(s) must be completed to document dispensation of study product to clinic staff for a given participant. Entries should be confirmed by a 2nd person. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All MATRIX-001 Study Product Accountability Log(s) will be retained at the site pharmacy.

Clinic staff are responsible for the study products once dispensed to their custody and for ensuring that the products are provided to the participant for whom they were intended. Clinic staff must document delivery of the study products to a participant in the participant's study chart (i.e. visit checklists, chart notes or on other source documents used for this purpose). In the event study products dispensed for a participant are not provided to/used by 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 clinic staff learn that the participant will not be completing her study visit on the scheduled date.

6.6 Study Product Return

If a vaginal insert is dispensed from the pharmacy and not administered, ideally it should be returned to the pharmacy the same day for quarantine and destruction or if requested, returned to the Product Development Team. If the study product cannot be returned the same day, it must be kept in a secure, locked location and returned the following day. Upon the clinic staff returning the unused study product to the pharmacy, both the clinic staff member and the pharmacist/designee will together complete the designated Study Product Accountability Log(s).

Each time unused study product is returned to the pharmacy, the Study Product Accountability Log(s) will be updated on the PTID line with the date returned, the quantity returned, and receiver initials and date. Comments may be recorded in the designated space, and if additional space is needed, on the back of the record. All Study Product Accountability Log(s) will be retained in the site pharmacy.