CLARIFICATION MEMO #02 TO:

MATRIX-001

A Phase I Randomized, Placebo-Controlled, Double-Blind Study to Assess Safety, Pharmacokinetics, and Modeled Pharmacodynamics of a Vaginal Insert Containing Tenofovir Alafenamide and Elvitegravir

Cooperative Agreement #7200AA22CA00002

IND # 141,295

Version 1.0 / May 4, 2023

Clarification Memo Date: September 27, 2023

Section 1: Summary of Clarifications and Rationale

The procedures clarified in this Clarification Memorandum (CM) have been approved by the MATRIX Prime-Clinical Trials Hub, MATRIX-001 Protocol Co-Chairs, and MATRIX-001 Product Developer (PD)/Sponsor and are to be implemented immediately upon issuance. IRB/IEC approval of this CM is not required by MATRIX prior to implementation; however, investigators may submit the CM to the IRB/IEC overseeing the study at their site for the IRB/IEC's notification. This CM is official MATRIX-001 documentation and is effective immediately. A copy of this CM must be retained in the PD/Sponsor's and in each study site's Essential Documents file for MATRIX-001. No changes in the sample informed consent form or schedule of visits/procedures are included in this CM.

This document clarifies that the temporary product use hold criteria for a Grade 2 or higher adverse event (AE)/serious adverse event (SAE) where short-term resolution is possible only applies to AEs/SAEs assessed by the Investigator of Record (IoR)/designee to clinically warrant a product hold, and in consultation with the Protocol Safety Review Team (PSRT).

Section 2: Implementation

With the exception of updates to the protocol team roster, text to be deleted is noted below with a ~~strikethrough~~, text to be added is in **bold**, and text in ***bold italics*** is not to be added, but to serve as a clarification of the implementation item in question. This information will be included in the protocol the next time the protocol is updated.

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1. The following clarification applies to Section 9.3 (General Criteria for Temporary Hold and Permanent Discontinuation of Study Product), which states "A participant will be temporarily held from product use by the IoR/designee for any of the following reasons: Grade 2 or higher AE/SAE where short-term resolution is possible… The IoR/designee must consult the PSRT on all temporary product holds instituted at their discretion for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation. If product use is temporarily held/permanently discontinued at IoR/designee discretion, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time."

   The temporary product use hold criteria for a Grade 2 or higher AE/SAE where short-term resolution is possible only applies to AEs/SAEs assessed by the Investigator of Record (IoR)/designee to clinically warrant a product hold, and in consultation with the PSRT.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.