Clarification Memo # 1 to:

HPTN 076: Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for Pre-Exposure Prophylaxis (PrEP), Version 2.0, dated 1 October 2014

DAIDS Protocol #: 119844

FINAL Clarification Memo Version: 19 November 2015

Summary of Revisions and Rationale

Rationale

The Study Monitoring Committee (SMC) for HPTN 076 met on 26 October 2015 and recommended the following:

1) "The protocol team should draft a Clarification Memo to reconcile differences in Toxicity Management in the protocol (specifically, Sections 14.1 and 14.2).
2) Participants with Grade 2 ALT/AST AEs [Adverse Events] may restart study drug, after consultation with the CMC [Clinical Management Committee], if levels return to normal within 3 weeks. If the participant experiences a second Grade 2 or higher ALT/AST AE, study drug should be permanently discontinued and the SMC should be notified.
3) Participants with Grade 3 or higher ALT/AST AEs should permanently discontinue study drug.
4) Except as otherwise written in the protocol, non-AST/ALT, RELATED Grade 3 or higher AEs may continue study drug only after CMC consultation."

To adopt SMC recommendation #1, we are submitting this Clarification Memo. Section 6 of the HPTN 076, v2.0, 1 Oct 2014 protocol states "Participants who present with Grade 2 or greater AEs RELATED to study product will not be given an injection. Participants who present with Grade 3 or 4 UNRELATED AEs will not be given an injection unless approved by the CMC." These statements are discrepant with some of the guidance in Section 14, Appendix II, Toxicity Management. The changes made by this Clarification Memo address the SMC recommendation and bring text in Sections 6 and 14 in alignment.

To adopt SMC recommendations #2 and #3, this Clarification Memo includes language to specify that any participant with a Grade 3 or higher ALT/AST AE will be permanently discontinued from study product. It also includes language to indicate that participants with a Grade 2 ALT/AST AE may continue with study product only if ALT/AST returns to normal within 3 weeks AND is approved by the CMC.

To adopt SMC recommendation #4, this Clarification Memo includes language permitting continued study product exposure following a non-ALT/AST RELATED Grade 3 or higher AE only after consultation with and agreement by the CMC.

Summary of Revisions

The HPTN 076 protocol v2.0, 1 Oct 2014 has been updated to reflect the changes listed in this Summary of Revisions and Rationale. All changes made are clearly indicated in the next section, Implementation of the Protocol Modifications.

1) Clarifying text for management of participants with Adverse Events (AEs) was added to Sections 6.0 (Study Procedures) and 14.0 (Appendix II: Toxicity Management).

Implementation of the Protocol Modifications

The procedures clarified in this memorandum have been approved by the Division of AIDS (DAIDS) Medical Officer and are to be implemented immediately upon issuance. IRB approval of HPTN 076 Protocol Clarification Memo #1 to HPTN 076, Version 2.0 is not required by the sponsor; however, sites may submit the Clarification Memo to the responsible IRBs for their information.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in **bold** will be added. Edited text is also highlighted in grey for ease of review.

Revision 1- Related Changes: Text clarifications to Section 6.0

Revision 1, Change 1)

- Section 6.7, Weeks 12, 20 and 28 Visits (Injection Visits), Week 14 Visit (Post-Injection Visit)
- Section 6.8, Weeks 36 and 44 Visits (Injection Visits)

have been revised as follows:

> "NOTE: **In general, ~~P~~p**articipants who present with Grade 2 or greater AEs RELATED to study product will not be given an injection **unless approved by the CMC (see Section 14.0, Appendix II: Toxicity Management for detailed instruction)**. Participants who present with Grade 3 or 4 UNRELATED AEs will not be given an injection unless approved by the CMC."

Revision 2- Related Changes: Text clarifications to Section 14.0

Revision 2, Change 1)

- Section 14.1, Toxicity Management General Guidance, has been revised as follows:

> Grade 2
> **AEs Unrelated to Study Product**
> In general, participants who develop a Grade 2 AE unrelated to study product, and that is not specifically addressed in the Tables below may continue use of the study product per protocol.
>
> **AEs Related to Study Product**
> If the Grade 2 AE occurs during the oral phase and is deemed related to study drug by the IoR, study drug must be discontinued and the CMC must be notified; the participant will not proceed to the injectable phase.
>
> **In general, ~~I~~i**f the Grade 2 AE occurs during the injection phase and is deemed related to study drug by the IoR, the participant must be discontinued from the study product ~~no additional injections will be given~~ and~~,~~ the CMC must be notified**. Guidance in the below tables must be followed. In certain circumstance, with CMC approval, injectable study product may resume.**

Grades 3 and 4

AEs Unrelated to Study Product

In general, participants who develop a Grade 3 or 4 AE unrelated to study product during the oral run-in phase must be discontinued from the study drug and the CMC must be notified. These participants will not receive additional oral study drug or proceed to the injection phase unless approved by the CMC. **Guidance in the below tables must be followed.**

In general, ~~P~~**p**articipants who develop a Grade 3 or 4 AE unrelated to study product during the injection phase will not receive the next injection unless approved by the CMC. **Guidance in the below tables must be followed.**

AEs Related to Study Product

If a Grade 3 or 4 AE occurs during the oral phase and is deemed related to study drug by the IoR, study drug must be discontinued and the CMC must be notified; the participant will not proceed to the injectable phase.

In general, ~~I~~**i**f the Grade 3 or 4 AE occurs during the injection phase and is deemed related to study drug by the IoR, no additional study drug injections will be given**,** ~~and~~ the CMC must be notified **and guidance in the below tables must be followed. In certain circumstance, with CMC approval, injectable study product may resume**.

Revision 2, Change 2)

- Section 14.2.2, Clinical Hepatitis, has been revised as follows:

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Elevations in AST or ALT (New clinical finding or increase from baseline clinical finding only)		
2.5 < 5.0 x ULN (Grade 2)	~~Continue study drug unless participant is symptomatic~~ **Temporarily discontinue study drug**	Participants should have AST/ALT re-checked as soon as possible (ideally within 1 week of the receipt of the results) and then be followed weekly until levels are ≤ 2 x ULN transaminase. The frequency of follow up may be altered at the discretion of the site IoR if deemed to be unrelated to study product following consultation with the CMC. **If ALT/AST levels return to < Grade 1 within 3 weeks of receiving the results, study drug may be resumed with the approval of the CMC.** **If the ALT/AST levels do not return to < Grade 1 within 3 weeks of receiving the results, study drug must be permanently discontinued.** **NOTE: If a participant experiences a second Grade 2 or higher elevation in ALT/AST, study drug must be permanently discontinued and the SMC must be notified.** ~~Study drug may continue at the discretion of the IoR provided the participant is asymptomatic.~~ ~~In the case of symptomatic participants or if thought to be study drug related, study drug will be held temporarily., and management (including resumption of study drug) should be arranged in consultation with the CMC.~~
5.0 < 10.0 x ULN (Grade 3)	~~Discontinue study drug temporarily~~ **Permanently discontinue study drug**	~~Study drug should be temporarily held for any Grade 3 AST or ALT.~~ Participants should have AST/ALT re-checked as soon as possible (ideally within 1 week of the receipt of the results). Participants should then be followed weekly until levels are ≤ 2 x ULN transaminase. **Notify CMC.** ~~Resumption of study drug should be arranged in consultation with the CMC. If improvement to Grade ≤1 cannot be documented within three weeks of receiving the Grade 3 results, study drug must be permanently discontinued.~~ ~~If following a Grade 3 event(s) the participant is permitted to resume study drug, but has an additional event (AST and/or ALT) at a Grade 3 level, the IoR must permanently discontinue the study drug, offer symptomatic treatment (if appropriate), and order any clinically relevant laboratory analyses (per judgment of the IoR).~~