Letter of Amendment # 2 to:

HPTN 077: A Phase IIa Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, GSK1265744, in HIV-uninfected Men and Women, Version 2.0, November 18, 2014, DAIDS Document ID: 11964
IND # 122,744

FINAL Version of LoA # 2: July 6, 2015

The following information impacts the HPTN 077 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) as soon as possible for their information and review. This Letter of Amendment (LoA) must be approved by all responsible IRBs/ECs, as well as other regulatory entities as applicable and per the policies and procedures of the regulatory entities.

The information contained in this LoA does NOT impact the sample informed consent.

Upon receiving final IRB/EC and any other applicable regulatory entity approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

If the HPTN 077 protocol is fully amended in the future, this Letter of Amendment will be incorporated into the next version. Text appearing below in highlighted **bold** will be added and text with a highlighted ~~strike-through~~ will be deleted.

Summary of Revisions and Rationale

Revision 1: The exclusion criterion for ECG has been modified to reflect that abnormal results should be clinically significant, and where there is a question, to refer the case to the CMC for adjudication.

The rationale for this modification is based on additional data provided by the pharmaceutical sponsor regarding cardiac conduction studies that they recently completed, which showed no impact of cabotegravir on QTc or PR interval over a range of doses and routes of administration. The new verbiage serves to clarify the original intent of the exclusion criterion, which was previously ambiguously worded.

Revisions 2a and b: The Toxicity Management section of the protocol is amended regarding guidance for AST/ALT and creatine phosphokinase in order to allow the protocol team's Clinical Management Committee (CMC) to adjudicate clinical cases during the injection phase when CK is $\geq$ Grade 3 and AST/ALT is $\leq$ Grade 3, in the cases of exercise-induced CK abnormalities.

The rationale for this modification is the observation that rates of exercise-induced CK abnormality appear to be quite high in the healthy target population of HPTN 077. Muscle inflammation from exercise (fitness-focused, e.g. cross-fit or other strenuous exercise, or related to activities of daily

living, e.g. walking long distances or carrying heavy objects) is common, and may additionally be accompanied by AST and ALT elevations. Cases observed already in the ÉCLAIR protocol and in HPTN 077 suggest non-relatedness to study product based on temporal association, and are leading to a high level of protocol-related discontinuation, even in the context of study sites providing guidance to participants regarding the effects of exercise on safety monitoring labs. This amendment does not guarantee permission to continue injections in the face of such abnormalities, but allows adjudication by the CMC of the clinical scenario as to the safety of continuing for additional injections. The amendment does not provide changes to the oral phase safety management schema, where the opportunity to make attribution to study product is much more time-limited, and the current level of conservative management remains appropriate.

IMPLEMENTATION

Revision 1 Section 3.2: Exclusion criteria (only the portion related to ECG is depicted)

- Clinically significant cardiovascular disease, including:
  - ECG **(one repeat ECG is allowed during screening; may be performed on the same day)** with:
    - heart rate < 45 or > 100 beats per minute for men, and <50 or >100 beats per minute for women ~~(one repeat ECG is allowed during screening; can be performed on the same day)~~
    - QRS duration >120 msec
    - QTc interval (B or F) > 450 msec
    - evidence of previous myocardial infarction (pathologic Q waves, S-T segment changes (except early repolarization)
    - any **clinically significant** conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree (type II) or higher], Wolf Parkinson White [WPW] syndrome) **(any question of clinical significance should be referred to the CMC for adjudication)**
    - sinus pauses > 3 seconds
    - any **clinically** significant arrhythmia which, in the opinion of the Investigator of Record or designee, will interfere with the safety for the individual participant **(any question of clinical significance should be referred to the CMC for adjudication)**
    - or history of non-sustained (≥3 consecutive ventricular ectopic beats on ECG at screening or entry) or sustained ventricular tachycardia

Revision 2a Appendix VI: Toxicity Management (only the sections of the Toxicity Management section that include changes are depicted)

Guidance on Toxicity Management for Specified Toxicities:

AST/ALT

CONDITION AND SEVERITY[1]	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT[2]
ELEVATIONS in AST/ALT (New clinical finding or increase from baseline clinical finding only)		
Grade 1 and higher	**Oral phase:** A Grade 1 AST/ALT abnormality reported at Week 2, regardless of relatedness to the study product, should be confirmed within one week. Study drug may continue until the confirmatory results are available. If the repeat value is < Grade 1, study drug may continue to Week 4. If the repeat value is Grade 1 or higher, study product should be stopped, and the participant will be prohibited from entering the injection phase of the study, and will be terminated from the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly AST/ALT assessments until they return to < Grade 1. A Grade 2 or higher AST/ALT abnormality reported at Week 2 of the oral phase, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase of the study, and the participant will be terminated from the study. All such cases must be reported to the CMC. In addition, participants will be followed with weekly AST/ALT assessments until they return to < Grade 1 **Injection phase**: The CMC should be notified as soon as possible. For a Grade 1 AST/ALT, the CMC will determine whether further injections may be given in cases where levels are < Grade 1 prior to the next scheduled injection. Unless otherwise specified by the CMC, for Grade 1 and 2 AST/ALT, repeat testing should be performed weekly until levels are < Grade 1. For Grade 2 and higher AST/ALT, study product will be permanently discontinued. For Grade 3 and 4 AST/ALT, repeat testing should be performed as soon as possible, and participants should be followed weekly until levels are < Grade 1. Participants who are permanently discontinued from stud product should continue to be followed on study/off study product, following the appropriate Schedule of Evaluations (based on number of injections received). **Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed attributable to exercise, at the Grade 3 or higher level accompanied by ALT/AST abnormalities of Grade 3 or lower should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT or AST, regardless of CK elevation will prompt permanent discontinuation of study product. All such cases must be reported to the CMC.**	

Revision 2b Appendix VI: Toxicity Management

Guidance on Toxicity Management for Specified Toxicities:

Creatine Phosphokinase (CK or CPK)

CONDITION AND SEVERITY[1]	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT[2]
Creatine Phosphokinase		
Grade 3	Continue study product until repeat test results are available	A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2-4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of products known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained.
Grade 4	Continue study product until repeat test results are available if the elevation is thought to be possibly or probably related to study product.	Grade 4 elevations in CPK should have a repeat assessment after the subject has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study product, study product should be discontinued and the participant should be followed on study/off study product. **(See section on ALT/AST abnormalities for important notes on ALT/AST abnormalities accompanying CK elevations)**