Letter of Amendment # 3 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 3.0, October 13, 2015
DAIDS Document ID: 11964
IND # 122,744

Final Version of LoA # 3: November 7, 2016

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.

Some of the information contained in this LoA impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing participants of the contents of this LoA.

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

Several sections of the protocol (outlined below) have been updated per data from the ViiV Healthcare-sponsored ÉCLAIR study that was presented as an oral abstract at the HIV Research for Prevention (HIVR4P) conference in Chicago, Illinois, USA, on October 19, 2016. The data showed that in ÉCLAIR, which randomized US-based men to three sequential intramuscular injections of 800 mg of CAB LA or placebo (administered as 2 x 400 mg) every 12 weeks, approximately 17% of the study population on active drug had detectable cabotegavir drug levels at 52 weeks after the last injection of cabotegravir. Levels ranged between 29 and 105 ng/ml. These levels are between the lower limit of assay quantitation (25 ng/ml) and 1 x PA-IC_{90} (166 ng/ml) Available data prior to the analysis of these new data indicated that detectable drug could persist up to 52 weeks after final injection. Additionally, some extraneous text also has been removed, and a minor grammatical error is corrected.

IMPLEMENTATION

Revision 1 Table of Contents

The following Appendix has been added to the Table of Contents:

APPENDIX XIV: SAMPLE HPTN 077 PARTICIPANT LETTER/INFORMATION SHEET FOR PARTICIPANTS IN COHORTS 1 AND 2

Revision 2 Overview of Study Design and Randomization Scheme

For participants who have already completed the study or remain in the study but do not agree to consent to the additional visits included in this letter of amendment, the overview of the study design and randomization scheme included in Version 3.0, dated October 13, 2015 apply.

For participants who remain in the study and consent to the additional visits included in this letter of amendment, the following revisions to the overview of the study design and randomization scheme will apply:

For Cohort 1, starting at Week 65, the updated visit schedule is: Week 65, 77, ~~81~~, **89, 101, and 105**

For Cohort 2, starting at Week 65, the updated visit schedule is: Week 65, 77, ~~85~~, **89, 101, and 109**

Revision 3

For participants who have already completed the study or remain in the study but do not agree to consent to the additional visits described in this letter of amendment, the duration of their follow-up of 52 weeks after the final injection remains unchanged.

For participants who remain in the study and consent to the additional visits described in this letter of amendment, the previously described duration of 52 weeks of follow-up after the final injection is changed to 76 weeks of follow-up after the final injection. All references to this language in the following sections changes "~~52~~ weeks" to "**76** weeks":

- Schema: Under Study Duration and Secondary Objectives
- Section 2.2: Secondary objectives
- Section 2.4.2: Study Duration
- Section 7.1: Review of Study Design
- Section 7.1.2: Secondary Endpoints
- Section 7.3: Accrual, Follow-Up, and Retention
- Section 7.5: Blinding
- Appendix X: Risk Assessment and Mitigation Strategy

Revision 4 Section 1.2.4 Pharmacokinetics

The third and sixth paragraphs in this section are impacted by this change and are included below:

744LA dosing:

Following a single IM or SC injection of 744LA, plasma drug concentrations increased rapidly over the first week, followed by a general trend to plateau for the remainder of the 12-week follow-up period. ~~GSK1265744 was detected in plasma up to 48 weeks.~~ **Data from the ÉCLAIR study (which administered three serial injections of 800 mg 744LA every 12 weeks [as 2 x 400 mg IM at each injection]) have shown that in some individuals (14 out of 83, 17%), 744LA was detectable in plasma at 52 weeks post last injection (ref R4P abstract). The 744LA concentrations in these study participants ranged from 29-105 ng/ml; these values fall between the lower limit of quantitation (LOQ) of 25 ng/ml and 1 x PA-IC$_{90}$ (166 ng/ml) [60].** ~~When the dose was administered as two equally divided injections, total drug release was increased so that C_{max} was greater than dose proportional and there was a more pronounced decay in drug concentrations over time. However, overall extent of exposure ($AUC_{0-\infty tau}$) was similar. Following single dose 744LA administration, mean absorption-limited apparent terminal phase half-life ranged from 21 to 50 days, reflecting elimination from the depot site (absorption from depot site) rather than the elimination from the systemic circulation.~~

The rationale for extended follow-up in this study ~~(52 weeks after last injection)~~ is two-fold: The first is to assess safety events during the prolonged interval during which drug levels have been demonstrated to be detectable in blood plasma in order to best characterize the safety profile of 744LA. The second is to characterize in detail any HIV infections that might occur during a period of declining blood plasma drug levels, including viral resistance profiles and response to antiretroviral therapy treatment.

Revision 5 Section 1.4 Clinical Experience to Date – GSK1265744

The only item impacted in this section is contained in Footnote "h" under Table 2: Cumulative GSK1265744 Exposure Estimates from Phase 1 through Phase 2b Clinical Studies Up To 01 July 2015

h. Detectable CAB concentrations can remain for up to 52 weeks **or longer** following the last CAB injection

Revision 6 Section 5.15 Tail Phase Visits: Both Cohorts – Week 53, 65, 77

The title of this section is changed as follows:

Tail Phase Visits: Both Cohorts – Week 53, 65, 77, **89, 101**

Revision 7 Section 5.16 Final Visit: Cohort 1 – Week 81; Cohort 2 – Week 85

The title of this section is changed as follows:

Final Visit: Cohort 1 – Week ~~81~~ **105**; Cohort 2 – Week ~~85~~ **109**

Revision 8 Section 5.28 Pharmacokinetics

Cohort 1: Blood samples will be collected during the oral lead-in phase of the study for determination of plasma concentrations of GSK1265744 following oral dosing. Blood samples for PK analysis will also be collected starting on the first day of the first injection phase prior to the injection and every visit thereafter. At each injection visit a blood sample will be collected prior to the injections at Weeks 5, 17 and 29, and one-week post-injection at Weeks 6, 18, and 30, and at week 41. The sample collected 12 weeks following each injection will serve as the pre-dose sample for the subsequent dosing interval (except for after the 3rd injection visit, i.e., the sample will be collected, but will not serve as a pre-dose sample because injections will be completed after the 3rd injection). Two additional samples will be collected 4 and 8 weeks after the first injection (Weeks 9 and 13), and one additional sample will be collected 6 weeks following the second and third injections (Weeks 23 and 35). **Refer to the Schedule of Procedures and Evaluations (Appendix I) and SSP Manual for sample collection** ~~when PK samples will be collected during the oral phase at Week 2 and 4, and every 12 weeks at Weeks 35, 53, 65, 77 and 81 until participants reach 52 weeks post-third injection~~ (these collections are modified for participants who receive less than three injections [see Appendices II and III]).

Cohort 2: Blood samples will be collected during the oral lead-in phase of the study for determination of plasma concentrations of GSK1265744 following oral dosing. Blood samples for PK analysis will also be collected starting on the first day of the first injection phase prior to the injection and every visit thereafter, as indicated in Appendices IV-VIII. At each injection visit a blood sample will be collected prior to the injections at Weeks 5, 9, 17, 25, and 33. The sample collected 4 or 8 weeks following each injection will serve as the pre-dose sample for the subsequent dosing interval (except for after the 5rh injection visit, i.e., the sample will be collected, but will not serve as a pre-dose sample because injections will be completed after the 5th injection). Two additional samples will be collected 1 and 4 weeks after each of the four injections, beginning with the Week 9 injection (Weeks 10, 13, 18, 21, 26, 29, 34, 37). Additionally, a single PK sample will be obtained 1 week after the Week 5 loading dose (Week 6). **Refer to the Schedule of Procedures and Evaluations (Appendix IV) and SSP Manual for sample collection** ~~PK samples also will be collected during the oral phase at Week 2 and 4, and at follow-up phase visits (week 41, 53, 65, 77 and 85) until participants reach 52 weeks post-fifth injection~~ (these collections are modified for participants who receive less than five injections [see Appendices V-VIII).

Revision 9 Section 9.2 Stored Specimens

The fourth paragraph in this section (first paragraph under the "Pharmacology" subheading) is impacted by this change and depicted below.

Pharmacology

Plasma samples for drug levels will be collected beginning at Week 2 through and including the last study visit **for each cohort**~~at Week 81 (Cohort 1) and Week 85 (Cohort 2)~~. These samples will **be** collected from all participants, although PK testing may be limited to a subset of the samples.

Revision 10 Section 11.0 REFERENCES

Reference # 60 is added to the section.

60. ECLAIR Study of Cabotegravir LA Injections: Characterization of Safety and PK During the "PK Tail" Phase. Ford S; Stancil B; Markowitz M, et al. HIV Research for Prevention, Chicago, IL, USA, October 17-21, 2016. Abstract OA12.06LB.

Revision 11 APPENDICES I-VIII: Schedules of Procedures and Evaluations

Note: The Schedule of Procedures and Evaluations depicted below display the updated visit schedule with two additional visits (76 weeks of follow-up following the last injection). Participants that have completed the study prior to the inclusion of the two additional visits or who did not consent to the two additional visits will complete 52 weeks of follow-up following the last injection (as designed prior to the implementation of this letter of amendment). Only the top row of each appendix is impacted by this change and is depicted below.

Appendix I: Schedule of Procedures and Evaluations – For Participants Who Complete All Three Injections in Cohort 1

	Screen	Oral Phase			1-WEEK WASHOUT	Injection And Tail Phase Follow-up								
		Day 0 Enr	Week 2 Safety	Week 4 Post Oral Drug		Week 5 First Injection	Week 6, 9, 13 Safety	Week 17 Second Injection	Week 18, 23 Safety	Week 29 Third Injection	Week 30, 35 Safety	Week 41 Primary Endpoint	Week 53, 65, 77, 89, 101 Tail Phase	Week ~~81~~ 105 Final Visit

Appendix II: Schedule of Procedures and Evaluations – For Participants Who Complete Two Injections Only in Cohort 1

	Injection And Tail Phase Follow-up								
	Week 5 First Injection	Week 6, 9, 13 Safety	Week 17 Second Injection	Week 18, 23 Safety	Week 29 Follow Up	Week 41 Follow Up	Week 53 Follow Up	Week 65, 77, 89 Follow Up	Week ~~69~~ 93 Final

Appendix III: Schedule of Procedures and Evaluations – For Participants Who Complete One Injection Only in Cohort 1

	Injection And Tail Phase Follow-up						
	Week 5 First Injection	Week 6, 9, 13 Safety	Week 17 Follow Up	Week 29 Follow Up	Week 41 Follow Up	Week 53, 65, 77 Follow Up	Week ~~57~~ 81 Final Visit

Appendix IV: Schedule of Procedures and Evaluations – For Participants Who Complete All Five Injections in Cohort 2

	Screen	Oral Phase			1-WEEK WASHOUT	Injection And Tail Phase Follow-up											
		Day 0 Enr	Wk 2 Safety	Week 4 Post Oral Drug		Wk 5 1st Inj	Wk 6 Safety	Wk 9 2nd Inj	Wk 10, 13 Safety	Wk 17 3rd Inj	Wk 18, 21 Safety	Wk 25 4th Inj	Wk 26, 29 Safety	Wk 33 5th Inj	Wk 34, 37 Safety	Wk 41 1º Endpt	Wk 53, 65, 77, 89, 101 Tail	Wk 85 109 Final Visit

Appendix V: Schedule of Procedures and Evaluations – For Participants Who Complete Four Injections Only in Cohort 2

	Injection And Tail Phase Follow-up									
	Week 5 First Injection	Week 6 Safety	Week 9 Second Injection	Week 10, 13 Safety	Week 17 Third Injection	Week 18, 21 Safety	Week 25 Fourth Injection	Week 26, 29 Safety	Week 41, 53, 65, 77, 89 Follow Up	Week ~~77~~ 101 Final

Appendix VI: Schedule of Procedures and Evaluations – For Participants Who Complete Three Injections Only in Cohort 2

	Injection And Tail Phase Follow-up							
	Week 5 First Injection	Week 6 Safety	Week 9 Second Injection	Week 10, 13 Safety	Week 17 Third Injection	Week 18, 21 Safety	Week 29, 41, 53, 77, 89 Follow Up	Week ~~69~~ 93 Final

Appendix VII: Schedule of Procedures and Evaluations – For Participants Who Complete Two Injections Only in Cohort 2

	Injection And Tail Phase Follow-up							
	Week 5 First Injection	Week 6 Safety	Week 9 Second Injection	Week 10, 13 Safety	Week 27 Follow Up	Week 41 Follow Up	Week 53, 65, 77 Follow Up	Week ~~61~~ 85 Final Visit

Appendix VIII: Schedule of Procedures and Evaluations – For Participants Who Complete One Injection Only in Cohort 2

	Injection And Tail Phase Follow-up							
	Week 5 First Injection	**Week 6 Safety**	**Week 9 Follow Up**	**Week 13 Follow Up**	**Week 27 Follow Up**	**Week 41 Follow Up**	**Week 53, 65, 77 Follow Up**	**Week ~~57~~ 81 Final Visit**

Revision 12 APPENDIX XIV: Sample HPTN 077 Participant Letter/Information Sheet for Participants in Cohorts 1 and 2

Note: This is a new letter to inform participants of the new data included in this letter of amendment and to consent to continuing in the study and to the additional visits.

APPENDIX XIV: SAMPLE HPTN 077 PARTICIPANT LETTER/INFORMATION SHEET FOR PARTICIPANTS IN COHORTS 1 AND 2

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

(HPTN 077)

Version 3.0
October 13, 2015
DAIDS Document ID: 11964

Sponsored by: Division of AIDS, United States (US) National Institute of Allergy and Infectious Diseases, US National Institutes of Health. Study products are provided by ViiV Healthcare

Dear HPTN 077 Participant:

The purpose of this letter is to share with you some new information from another study called ÉCLAIR. The other purpose is to ask if you would be willing to be followed in this study for two more visits, for an additional approximately 6 months.

ÉCLAIR is very similar to this study, and was conducted in the United States in men only. The study was completed February 2016. It used the same dose (30 mg) of the pill-version of GSK 1265744 for 4-weeks, and the same injectable form of the drug in the amount of 800 mg. The shots were given every 12 weeks at three time points. The purpose of that study was the same as this one, to test whether the drug is safe and how people respond to it.

Other studies have shown that the GSK 1265744 stays in the body for as long as a year. That's why in the original HPTN 077 protocol, we asked you to stay in the study for a year after your last shot, so we can test how much is in your body over the course of a year. New information from the ÉCLAIR study showed that some people in that study, about 14 out of 83 people (17%), still had low levels of the drug in their body one year after the last shot. Since they had no more study visits after that, we do not know how much longer the drug stayed in the bodies of those 14 people. It is important to remember that for most people, the drug was no longer in their body one year after the last shot.

The study investigators think it is important to find out how long the drug lasts in the body after the last shot. Because of this, in HPTN 077, we would like to ask you to stay in the study longer to help us answer this question.

We would like to add two visits over six additional months before your final visit. The procedures at each new visit are exactly the same as what is currently scheduled at the Week 77 visit. Your final visit remains unchanged except that it will occur 6 months later.

We will continue to update you on any new information, including side effects that we see in this study and other on-going studies, and if those side effects appear to have come from the drug.

The HPTN 077 study team wants you to continue in the study even if you do not agree to these extra visits. Your continued participation in HPTN 077 is, as it has always been, entirely voluntary.

If you have any questions now or later about the information provided in this letter, you may ask the study staff or contact [*site to insert name*] directly. We will do our best to answer any questions or concerns that you may have.

Your participation in the HPTN 077 will lead to important discoveries that will hopefully lead to better prevention methods for protection against HIV infection. Thank you for participating in HPTN 077.

Sincerely,

[Insert name and contact information of site/Investigator of Record]

If you have read this letter, or have had it read and explained to you, and understand the information, please sign your name below.

_____ I agree to continue to take part in this study and to participate in the extra visits.

_____ I agree to continue to take part in this study but do not agree to participate in the extra visits.

_____ I do not agree to continue to take part in this study.

_____	**_____**
Participant Name (print)	**Participant Signature and Date**
_____	**_____**
Study Staff Conducting Consent Discussion (print)	**Study Staff Signature and Date**

Witness Name (print) **Witness Signature and Date**

(As appropriate)