Letter of Amendment # 1 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 # 1: March 30, 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.

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 an 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. An 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 appearing in highlighted ~~strike-through~~ will be deleted.

Summary of Revisions and Rationale

Revisions 1-4: The content of Clarification Memo # 1, dated 04 December 2014, has been incorporated. The content is summarized as: Section 3.1, Inclusion Criteria, correctly indicates that total bilirubin and direct bilirubin should be completed at Screening. Direct bilirubin was inadvertently omitted in the following corresponding sections of the protocol that discuss screening or general procedures: Section 5.1, Section 9.1 and the Schedule of Procedures and Evaluations. Additionally, in Section 6.4.2, only total bilirubin should be reported, and this has been clarified.

Revisions 5 and 6 a and b: The content of Clarification Memo # 2, dated 09 February 2015, has been incorporated. The content is summarized as: Revision 5: In Section 3.1, the word "and" has been changed to "or" to clarify the intent that reporting any one of the sexually transmitted infections listed in the last 12 months will prohibit entry in to the study. Revision 6 a and b: The sponsor of the study, Division of AIDS/NIAID/NIH, on 06 February 2015 released an updated table to grade toxicities that occur in their sponsored studies. The updated table, Version 2.0, dated November 2014, will be used for the entire duration of this study. Sections 6.3 and 6.42 include clarifications regarding this updated table.

Revisions 7 and 8: The sponsor of the study, Division of AIDS/NIAID/NIH, has deemed the use of condoms plus a diaphragm or a cervical cap as inadequate contraception for a study involving the use of a long-acting injectable agent. The choice of this option as an acceptable form of contraception has been removed from Section 3.1 of the protocol and from the sample informed consent.

IMPLEMENTATION

Revision 1 Section 5.1: Screening

Laboratory Evaluations

- HIV testing (see SSP Manual)., including testing for acute HIV infection within 14 days prior to enrollment
- Hepatitis testing: HBsAg, HBsAb, HBcAb, HCAb
- CBC with differential
- Chemistry testing (see Appendix I)
- Liver function testing (AST, ALT, total **and direct** bilirubin, and alkaline phosphatase)
- Syphilis testing
- GC/CT testing (urine for men and either urine or vaginal swab for women)
- Plasma storage
- Urine pregnancy testing (for women of reproductive potential)

Revision 2 Section 6.4.2: Reporting Requirements for this Study

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 of the DAIDS EAE manual, will be used for this study (the definition of an SAE is also included in the manual).

In addition to SAEs, sites will report in an expedited manner the following results (must be both in order to require expedited reporting): ALT≥3xULN AND **total** bilirubin≥2xULN.

These reporting requirements are required for each study participant from enrollment (week 0) until their follow-up in the study ends. After this time, sites must report serious, unexpected, clinical suspected adverse drug reactions if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

The study agents for the purposes of EAE reporting are GSK1265744 30 mg oral tablet or placebo and 744LA injectable suspension (200mg/mL) or placebo (also outlined in Section 4.1.).

Revision 3 Section 9.1: Local Laboratory Specimens

The following types of tests will be performed at the local laboratory:

- HIV testing (see SSP Manual)
- HBV and HCV testing to include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) and hepatitis C antibody (HCV) tests
- CBC with differential and platelets
- Chemistry testing (BUN/urea, Na, K, Cl, CO_2, CPK, creatinine, total protein, glucose, calcium, phosphorous, amylase, lipase, magnesium)
- LFTs (AST, ALT, total **and direct** bilirubin, alkaline phosphatase)
- Fasting lipid profile (total cholesterol, HDL, triglycerides, LDL – calculated or measured (participants should be fasting for at least 8 [preferably 12] hours prior to sample collection)
- Syphilis serologic testing (men and women)
- Urine for GC/CT testing for men and women. (may be replaced with a vaginal swab in women if desired)
- Urinalysis (protein and glucose)
- Urine test for pregnancy*
- Rectal swabs for GC/CT for men and women (for non-US sites, batch and ship to the HPTN LC; for US sites, testing will be performed locally)
- Plasma storage
- Plasma storage for Pharmacology testing
- Sample storage for Pharmacogenomic testing (sites may choose to opt out of this testing if is not acceptable to local regulatory bodies or for other reasons approved by the protocol team)
- Following a positive or reactive HIV test result: HIV viral load, CD4 cell count, HIV resistance testing at a local laboratory (real-time resistance testing for clinical management is optional, at the site's discretion), plasma storage.

Revision 4 Appendix I: Schedule of Procedures and Evaluations. Only the section called "Local Laboratory Evaluations & Procedures" from the Schedule of Procedures and Evaluations is shown below for ease of reference.

	Screening	Oral Phase			1-WEEK	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 Tail Phase	Week 81 Final Visit
LOCAL LABORATORY EVALUATIONS & PROCEDURES														
HIV testing[7]	X	X	X	X		X	X	X	X	X	X	X	X	X
HBV and HCV testing[8]	X													
CBC with differential	X	X	X	X		X	X	X	X	X	X	X		
Chemistry testing[9]	X	X	X	X		X	X	X	X	X	X	X		
LFTs (AST, ALT, total bilirubin, [at screening only, direct bilirubin in addition to total], alkaline phosphatase)	X	X	X	X		X	X	X	X	X	X	X	X	X
Fasting lipid profile[10]		X										X		
Syphilis serologic testing men and women[5]	X									X			X	
Urine/ vaginal swab GC/CT testing men and women[5]	X									X			X	
Rectal swab GC/CT testing[5]		X								X			X	
Urinalysis[11]		X										X		

Revision 5 Section 3.1: Inclusion Criteria

Note: Only the one bullet impacted by this clarification in this section is included below, under "In the last 12 months (at the time of screening):

- No self-reported diagnosis of GC, CT, incident syphilis, bacterial vaginosis, ~~and~~ **or** trichomoniasis

Revision 6a Section 6.3: Adverse Event Definition and Reporting

Note: Only the relevant paragraph from this section is included below, which is the third paragraph in the section.

Study site staff will document in source documents and the appropriate CRF all AEs (Grade 1 and higher) reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, ~~Version 1.0, December 2004 (Clarification dated August 2009).~~ **Version 2.0, November 2014. This version will be used for the entire duration of the study.**

Revision 6b Section 6.4.2: Reporting Requirements for this Study

Note: Only the relevant paragraph from this section is included below, which is the first paragraph under "Grading of Severity of Events"

Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, ~~December 2004, clarification August 2009 (or latest version) must~~ **Version 2.0, November 2014, will** be used **for the entire duration of the study for** determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance.

Revision 7 Section 3.1: Inclusion Criteria

Additional requirements for all women:

Note: Only the second bullet from this section is included here as it contains the change

- If of reproductive potential and participating in sexual activity that could lead to pregnancy, women must agree to use a form of contraception during the trial and for 30 days after stopping the oral study medication or for 52 weeks after stopping the long acting injectable from the list below:
  - ~~Condoms (male or female) with or without a spermicidal agent, PLUS a diaphragm or cervical cap with spermicide~~
  - Intrauterine device (IUD) or intrauterine system (IUS) that meets <1% failure rate as stated in the product label
  - Hormone-based contraceptive

Revision 8 Appendix VII: Sample Screening and Enrollment Informed Consent Form

Note: Only the first two paragraphs under this section are depicted below.

Pregnancy

There are no studies of pregnant women taking the drug being used in this study. If you are pregnant, you are not eligible to be in this study.

If you can get pregnant and are engaging in sexual activity that could lead to pregnancy, you must agree to use a form of contraception (~~condoms with or without a spermicidal agent and a diaphragm or cervical cap with spermicide; or~~ an IUD~~;~~ or **a** hormone-based contraceptive) during the trial. If you stop being in the study during or right after the first part of the study, which is the part where you take the pills only, then you have to be on contraception for 30 days after taking your last pill. If you stay in the study and get injections, then you have to be on contraception for one year after your last shot.