HIV Prevention Trials Network

Letter of Amendment # 2 to:

HPTN 083-01

HPTN 083-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A Sub-study of HPTN 083

DAIDS Study ID: 38654

Version 3.0, dated 2 July 2021

Date of Letter of Amendment: 17 February 2022

LETTER OF AMENDMENT SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study."

Signature of Investigator of Record

Date

Name of Investigator of Record
(printed)

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The following information impacts the HPTN 083-01 study and must be forwarded to all responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) as soon as possible for their information and review. This Letter of Amendment (LoA) must be approved by all responsible IRBs/ECs before implementation.

The information contained in this LoA *does* impact the informed consent forms (ICFs).

Upon receiving final IRB/EC approval for this LoA, sites should implement the LoA immediately. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). As part of the registration package, sites must submit the Letter of Amendment Investigatory Signature Page, signed and dated by the Investigator of Record. 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 the LoA and any IRB correspondence should be retained in the site's regulatory files.

If the full HPTN 083-01 protocol is amended in the future, the changes in this LoA will be incorporated into the next version.

Summary of Revisions and Rationale

1. **SCHEMA:** A new secondary objective for potential exploratory analyses has been added.
2. **Section 1.2:** A new CAB Investigator's Brochure (IB) was released, so this information has been updated.
3. **Section 1.10:** Changed reference to FDA approval of CAB LA, since it was recently FDA approved in December 2021.
4. **Section 2.2:** A new secondary objective for potential exploratory analyses has been added.
5. **Section 4.1.2:** Changed reference to FDA approval of CAB LA, since it was recently FDA approved in December 2021.

6. **Section 7.2.2:** A new secondary objective for potential exploratory analyses has been added.
7. **Section 12.7 (Appendix VII, Main ICF):** Changed reference to FDA approval of CAB LA, since it was recently FDA approved in December 2021.
8. **Section 12.8 (Appendix VIII, Self-Consent):** Changed reference to FDA approval of CAB LA, since it was recently FDA approved in December 2021.
9. **Section 12.10 (Appendix X, Main Adolescent Interview ICF):** Changed reference to FDA approval of CAB LA, since it was recently FDA approved in December 2021.
10. **Section 12.11 (Appendix XI, Self-Consent Interview ICF):** Changed reference to FDA approval of CAB LA, since it was recently FDA approved in December 2021.
11. **Section 12.13 (Appendix XIII, Parent/Guardian Interview ICF):** Changed reference to FDA approval of CAB LA, since it was recently FDA approved in December 2021.

Deletions to the protocol text are indicated by ~~strikethrough~~; additions are indicated in **bold**.

Revision 1: SCHEMA

Secondary Objectives:

- **Additional exploratory analyses may be performed using laboratory and clinical data from the study, including analysis of HIV drug resistance among participants with confirmed HIV infection.**

Revision 2: Section 1.2 Overview of Oral CAB and CAB LA

The majority of information contained in this section of the protocol is a summary of information provided in the CAB Investigator's Brochure (IB) V~~11~~**12**.0 Effective Dated **12 January 2022** ~~February 2021~~, unless otherwise noted.

Revision 3: Section 1.10 Rationale for use of Oral Run-in Prior to Injectable Dosing

1.10 Rationale for use of Oral Run-in Prior to Injectable Dosing

The CAB LA formulation has a PK decay rate that exposes the injected individual to detectable levels of CAB for a year or more after an injection (see Section 1.5.2 of the protocol). In order to maximally identify any acute toxicity prior to administration of a non-dialyzable, non-removable depot injection, a five-week lead-in period of daily oral (short acting) CAB will be employed. This lead-in period will be evaluated with serial safety assessments prior to injectable administration. The current plans for product labeling ~~should FDA approval be granted~~ include an oral lead-in strategy when adequate safety is established after four weeks of oral drug exposure. The 5-week exposure in this study is designed to provide un-interrupted study product coverage while awaiting return of the Week 4 safety laboratory assessments.

Revision 4: 2.2 Secondary Objectives

2.2 Secondary Objectives

- **Additional exploratory analyses may be performed using laboratory and clinical data from the study, including analysis of HIV drug resistance among participants with confirmed HIV infection.**

Revision 5: Section 4.1.2 Injectable Suspension

The CAB study product (oral and LA injectable) being tested in this study **was** ~~is investigational and not yet~~ approved by the US FDA for the ~~treatment or~~ prevention of HIV-1 infection **in adults and adolescents weighing at least 35 kg in December 2021**. Further information on the study product is available in the IB, which will be provided by the DAIDS Regulatory Support Center (RSC).

Revision 6: Section 7 Statistical Considerations

7.2.2 Secondary Endpoints

- **Additional exploratory analyses may be performed using laboratory and clinical data from the study, including analysis of HIV drug resistance among participants with confirmed HIV infection.**

Revision 7: Section 12.7 APPENDIX VII: INFORMED CONSENT FOR PARENTS/LEGAL GUARDIANS AND ASSENT FOR ADOLESCENT PARTICIPANTS AGES 14 – AGE OF MAJORITY

WHAT IS THIS STUDY ABOUT?
In this study, we want to know if it is safe and acceptable for adolescents who do not have HIV to take an anti-HIV drug called cabotegravir (CAB). We would also like to look at the tolerability, or side effects, of CAB. CAB is a new drug that **was recently (December 2021) approved by the ~~FDA~~**~~is still being studied and is not yet approved by the FDA~~, or U.S. Food and Drug Administration, **for the prevention of HIV in adults and adolescents weighing at least 35 kg**~~and is therefore considered experimental~~. ~~Other studies showed that CAB can treat people who have HIV infection and it has recently been shown as a way to prevent HIV infection.~~ The only other ways to prevent getting HIV from sex is to use condoms and/or take one of two PrEP pills, called Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada® or generic) or Tenofovir Alafenamide/Emtricitabine (Trade name: TAF/FTC, Descovy®), every day. But some people have a hard time remembering to take a pill every day, so it is a good idea to have other HIV prevention options. With CAB, people would get injections every 8 weeks and would not have to remember to take a pill every day. It is important that we learn what happens when adolescents use CAB for HIV prevention and whether it is safe and acceptable.

Revision 8: Section 12.8 APPENDIX VIII: INFORMED CONSENT FOR ADOLESCENT PARTICIPANTS ABLE TO CONSENT FOR THEMSELVES (SELF-CONSENT) AND PARTICIPANTS WHO REACH THE AGE OF MAJORITY

WHAT IS THIS STUDY ABOUT?
In this study, we want to know if it is safe and acceptable for adolescents who do not have HIV to take an anti-HIV drug called cabotegravir (CAB). We would also like to look at the tolerability, or side effects, of CAB. CAB is a new drug that **was recently approved** ~~is still being studied and is not yet approved~~ by the FDA **(December 2021)**, or U.S. Food and Drug Administration. ~~Other studies showed that CAB can treat people who have HIV infection, and it has recently been shown as a way to protect people from getting HIV. First, we must study if CAB is safe for people who do not have HIV.~~ CAB comes in the form of a pill and also as an injection. ~~CAB pills and injections are not yet approved for the treatment or prevention of HIV infection by the United States Food and Drug Administration (FDA) and are therefore considered experimental. Recently, the FDA asked for more information about how the CAB pills and injections are manufactured and agreed that studies that investigate CAB should continue while they complete their review.~~

Revision 9: Section 12.10 APPENDIX X: INFORMED CONSENT FOR ADOLESCENT INTERVIEW FOR PARENTS/LEGAL GUARDIANS AND ASSENT FOR ADOLESCENT PARTICIPANTS AGES 14 – AGE OF MAJORITY

About the interview
The main study is being done to find out if it is safe and acceptable for adolescents who do not have HIV to take an ~~experimental~~ HIV drug called cabotegravir (CAB) as PrEP to prevent HIV. The interview portion will ask young men what they like and do not like about getting CAB injections. We will also ask questions to find out what makes some adolescents more or less interested in starting PrEP. Finally, we will ask about difficulties you had getting CAB injections and things that made that easier.

Revision 10: Section 12.11 APPENDIX XI: INFORMED CONSENT FOR ADOLESCENT INTERVIEW FOR ADOLESCENT PARTICIPANTS ABLE TO CONSENT FOR THEMSELVES (SELF-CONSENT) AND PARTICIPANTS WHO REACH THE AGE OF MAJORITY

INTRODUCTION
About the interview
The main study is being done to find out if it is safe and acceptable for adolescents who do not have HIV to take an ~~experimental~~ HIV drug called cabotegravir (CAB) as PrEP to prevent HIV. The interview portion will ask adolescents what they like and do not like about getting CAB injections. We will also ask questions to find out what makes some adolescents more or less interested in starting PrEP. Finally, we will ask about difficulties you had getting CAB injections and things that made that easier.

Revision 11: 12.13 APPENDIX XIII: INFORMED CONSENT PARENT/GUARDIAN INTERVIEW FOR PARENTS/LEGAL GUARDIANS

INTRODUCTION

About the interview

The main study is being done to find out if it is safe and acceptable for adolescents who do not have HIV to take an ~~experimental~~ HIV drug called cabotegravir (CAB) as PrEP to prevent HIV. This interview will ask parents/guardians questions to find out what it is like to have a child getting CAB injections and things that made that easier. We will also ask young people what they like and do not like about getting CAB injections.