Letter of Amendment #1 for:

IMPAACT P1026s
Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum

IND # 64,535
DAIDS ES # 10040

Letter of Amendment Date: 14 December 2016

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT P1026s study and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, this LoA is to be implemented immediately. Study sites must submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1026s.

If the IMPAACT P1026s protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

Summary of Modifications and Rationale

The following modifications are included in this LoA:

- One of the three tenofovir alafenamide fumarate (TAF) antepartum arms for HIV-infected pregnant women not on tuberculosis treatment has been corrected for consistency with the formulations of this drug that are currently approved by the United States Food and Drug Administration (FDA). These formulations are as follows:
    - Genvoya® – TAF 10 mg co-formulated with elvitegravir and emtricitabine
    - Odefsy – TAF 25 mg co-formulated with rilpivirine and emtricitabine
    - Descovy ®– TAF 25 mg co-formulated with emtricitabine (may be taken with or without cobicistat or ritonavir boosting)

- Instructions for collection of vaginal secretions have been updated.
- Disallowed medicines for the newly added TAF arms have been updated.
- Other minor updates, clarifications, and corrections have been incorporated.

Implementation

Detailed modifications of the protocol text are shown below in general order of appearance in the protocol. Deletions in the protocol text are indicated by strikethrough, and additions are indicated in bold.

1. Protocol Team Roster:

Protocol Data Manager
~~Adriane Hernandez~~
Benjamin Johnston
Phone: 716-834-0900 x7404
E-mail: johnston@fstrf.org

Elise Tjaden, MPH
Phone: 716-834-0900 x7272
Email: tjaden@fstrf.org

Laboratory Data Manager
~~Amy Gonzalez, BS~~
Katelyn Hergott, MPH, MSW
Phone: 716-834-0900 x7212
Email: hergott@fstrf.org

Investigators
~~Nantasak Chotivanich, MD~~

Jullapong Achalapong, MD.
Site Principle Investigator
Obstetrics &Gynecology Department
Chiangrai Prachanukroh Hospital
1039 Sathanpayaban Rd., Muang
Chiang Rai 57000 Thailand
Tel: +66 (0) 53 711 300 Fax: +66 0 53 713 044 Mobile: +66 0 81 950 0707
Email: jullapongachalapong@gmail.com

2. Schema:

Study Arms, Antiretrovirals (ARVs) without tuberculosis (TB) Treatment (10 Arms): HIV-infected pregnant women ≥ 20 weeks gestation NOT on tuberculosis treatment receiving one or more of the following ARV drugs/drug combinations (sixth bullet point):

- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 800/100 mg b.i.d. until 30 weeks gestation; then 800/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 900/100 mg b.i.d. until 30 weeks gestation; then 900/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- dolutegravir 50 mg q.d.
- tenofovir alafenamide fumarate (TAF) 25 mg q.d. without cobicistat or ritonavir boosting
- tenofovir alafenamide fumarate (TAF) 10 mg q.d. with cobicistat
- tenofovir alafenamide fumarate (TAF) ~~10~~ **25** mg q.d. with **cobicistat or** ritonavir **boosting**
- elvitegravir/cobicistat 150/150 mg q.d.
- darunavir/cobicistat 800/150 mg q.d.
- atazanavir/cobicistat 300/150 mg q.d.
- Participants outside of Thailand only: efavirenz 600 mg q.d.

3. Section 3.11, Enrollment Procedures, Maternal Antepartum Enrollment (during pregnancy):

Pregnant women who meet the eligibility criteria, as specified, in Section 4.1 will enroll in P1026s prior to or at the time of pharmacokinetic sampling. The initial PK sampling visit ~~must~~ **should** occur within 5 days of participant enrollment. **If the PK visit cannot be done within 5 days contact the protocol team for permission to perform the sampling visit after 5 days**. See Appendix I-A through I-C for a complete description of the procedures to be performed for each study arm, and Section 10 Data Collection Requirements, for a description of data to be collected.

4. Section 3.21, Genital Tract Viral Load and Drug Concentrations, last sentence (added):

   HIV-infected pregnant women not on TB drugs will have vaginal samples for ARV concentrations obtained at the second and third trimester and the 6-12 postpartum PK sampling visits. Samples will be obtained pre-dose and at 1, 2, and 4 hours after dosing. Samples for drug concentrations will be obtained with the soft plastic aspirator without speculum placement or by another appropriate technique and can be collected by the participant or by a clinician. Samples will be stored and batch shipped for testing. Since target drug concentrations for vaginal samples have not been determined, real time testing and reporting of vaginal specimen results to the sites will not be done. A single vaginal swab will also be obtained without speculum placement for viral load testing once during each PK visit. No vaginal specimens will be collected if contraindicated by a pregnancy complication such as placenta previa or premature rupture of membranes. **Also, no specimens should be collected from women who are menstruating or have vaginal bleeding.**

5. Section 3.4, Intrapartum Pharmacokinetic Sampling, 2nd sentence:

   A single maternal specimen will be drawn at the time the cord is clamped**, unless it is medically contraindicated, in which case it can be obtained as soon as possible**.

6. Section 4.1, Maternal Inclusion Criteria:

   4.111 HIV-infected pregnant women ≥ 20 weeks gestation NOT on tuberculosis treatment receiving one or more of the following ARV drugs/drug combinations (sixth bullet point):

- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 800/100 mg b.i.d. until 30 weeks gestation; then 800/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 900/100 mg b.i.d. until 30 weeks gestation; then 900/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- dolutegravir 50 mg q.d.
- tenofovir alafenamide fumarate (TAF) 25 mg q.d. without cobicistat or ritonavir boosting
- tenofovir alafenamide fumarate (TAF) 10 mg q.d. with cobicistat
- tenofovir alafenamide fumarate (TAF) ~~10~~ **25** mg q.d. with **cobicistat or** ritonavir **boosting**
- elvitegravir/cobicistat 150/150 mg q.d.
- darunavir/cobicistat 800/150 mg q.d.
- atazanavir/cobicistat 300/150 mg q.d.
- Participants outside of Thailand only: efavirenz 600 mg q.d.

5. Section 7.0, Disallowed Medicines:

   7.1 NRTIs

   For tenofovir alafenamide fumarate, **the following medicines are disallowed:** ~~no medicines are disallowed.~~

- **Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin**
- **Antimycobacterials: rifabutin, rifampin, rifapentine**
- **Herbal products: St. John's wort (Hypericum perforatum)**
- **Protease inhibitors: tipranavir/ritonavir**

7.3 PIs, 10th Bullet:

- Neurleptic**: lurasidone,** pimozide

7.33 Ritonavir, 2nd Bullet:

- **Antifungal: voriconazole**

7.4 Integrase Inhibitors, 15th Bullet:

- Neuroleptic: **lurasidone**, pimozide

7.6 Combined Oral Contraceptives (COCs) and Etonogestrel Implant, 1st and 6th Bullets:

- Anticonvulsants: barbiturates, phenytoin, carbamazepine**,** felbamate, oxcarbazepine, topiramate
- Psychostimulants**:** ~~;~~ modafinil

6. Appendices IA, IB, I-AMR, IC, ID, II and III, Schedules of Evaluations:

— Appendix IA, footnotes 9 and 13

9. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System. **The PK sampling visit can be performed more than 5 days after enrollment with permission from the protocol team.**

13. Draw at the time the cord is clamped**, unless it is medically contraindicated, in which case draw can be obtained as soon as possible**.

— Appendix IB, Schedule of Evaluations for Women on ARV Medicines with Tuberculosis Treatment, footnotes 8, 12 and 14:

8. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System. **The PK sampling visit can be performed more than 5 days after enrollment with permission from the protocol team.**

12. Draw at time the cord is clamped**, unless it is medically contraindicated, in which case, the draw can be obtained as soon as** possible. For this arm, collection of maternal delivery sample can be omitted if there are circumstances that prohibit collection (i.e. delivery at non-study facility, delivery during non-business hours).

14. For participants treated with any injectable TB medication the audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the **P1026s Protocol Specific Web Page at http://impaactnetwork.org/studies/P1026s.asp** ~~LPC~~ for additional information.

— Appendix IC, Schedule of Evaluations for HIV-Uninfected Women with Tuberculosis Treatment, footnotes 6 and 10:

6. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5

days after enrollment using the Subject Enrollment System. **The PK sampling visit can be performed more than 5 days after enrollment with permission from the protocol team.**

10. For participants treated with any injectable TB medication the audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the **P1026s Protocol Specific Web Page at http://impaactnetwork.org/studies/P1026s.asp** ~~LPC~~ for additional information.

— Appendix I-D, footnote 12:

12. The participant must be on the ARV of interest for at least 2 weeks prior to the initial PK sampling and not using any hormonal contraceptive method during that time. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System. **The PK sampling visit can be performed more than 5 days after enrollment with permission from the protocol team.**

— Appendix I-AMR, Title:

ADDITIONAL MONITORING REQUIREMENTS FOR WOMEN ON DRV/**r** AND LPV

— Appendix II, Schedule of Evaluations for Infants, footnote 9:

9. Only for infants of mothers treated with any injectable TB medication. The audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the **P1026s Protocol Specific Web Page at http://impaactnetwork.org/studies/P1026s.asp** ~~LPC~~ **for additional information.**

— Appendix III, Maternal Intensive PK Sampling Schedule for ARV Medicines, Tuberculosis Treatment and Hormonal Contraceptives, row 8:

tenofovir alafenamide fumarate ~~10~~ **25** mg q.d. with **cobicistat or** ritonavir **boosting**	24 hour sampling during optional 2nd trimester, during 3rd trimester and 6-12 weeks postpartum