Date: March 2, 2007

Reference: LETTER OF AMENDMENT #2 for IMPAACT/PACTG P1056 (Version 1.0, IND# 71,844, dated 2/3/06), LOA#1 dated 2/21/06 and Clarification Memo #1, dated 4/4/06.

“A Phase I/II Comparative Pharmacokinetic Study of the Fixed Dose Combination (FDC) of Stavudine (d4T), Lamivudine (3TC) and Nevirapine (NVP) as GPO-VIR® Pediatric Chewable Tablets versus the Individual Liquid Formulations in HIV-infected Children ≥ 6 Months to< 13 Years of Age in Thailand”

To: IMPAACT/PACTG PIs & Study Coordinators at Sites Eligible to Participate in P1056

From: IMPAACT/PACTG P1056 Protocol Team

THE FOLLOWING INFORMATION IMPACTS THE IMPAACT/PACTG P1056 STUDY AND MUST BE FORWARD TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. THIS MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

PLEASE FILE THIS LETTER AND ANY IRB/EC CORRESPONDENCE IN YOUR REGULATORY FILE AND OTHER PERTINENT FILES. YOU ARE NOT REQUIRED TO SUBMIT THESE DOCUMENTS TO THE PROTOCOL REGISTRATION OFFICE UNLESS THE CHANGES RESULT IN A CHANGE TO THE INFORMED CONSENT FOR YOUR SITE.

This Letter of Amendment (LOA) is being issued with the approval of the Regulatory Affairs Branch of the Division of AIDS. This LOA provides for an update in the Risk list for the Pediatric Tablet, now known as GPO-VIR® S7, and supplemental grading guidelines for the laboratory parameter total amylase, and local value for pancreatic amylase ULN to be used for Stage I and II, and changes to the protocol for Direct Observation of Therapy (DOT) in the 72 hours prior to the PK Study Days for Stage II.

This LOA will apply to both Stages (I and II) to provide additional information on one of the study drugs, and clarify the toxicity management of hyperamylasemia. The following (in bold) are the specific changes to IMPAACT/PACTG P1056, Version 1.0, 02/03/06:

1. P1056 Cover page, Foreword and throughout the protocol: Due to the network change, update all references to PACTG with “IMPAACT”. Delete references to GSK, as they are not providing pharmaceutical support (per CM#1).
• Second paragraph, is changed to read, “All subjects will be enrolled at eligible IMPAACT/PACTG sites in Thailand.

2. P1056 Roster changes:
• Data Manager: Laura Smith (name change) lsmith@fstrf.org
• Community representative: (ICAB) replace Vinnie DiPoalo with Rungnapa Panitrat, PhD, rxp_35@yahoo.com
• Laboratory Data Coordinator: replace Mary Dobson with Ken Braun, braun@fstrf.org
• Pharmaceutical Company Representative: Delete Cristina Pharo, GSK

3. Section 3.0-Study Design: The second sentence is changed to "For Stage I the study is limited to specific sites in Thailand (Mahidol University/Siriraj Hospital and Queen Sirikit National Institute of Child Health, Bangkok); for Stage II, it is limited to IMPAACT eligible sites in Thailand.

4. Section 5.0: Nomenclature update: GPO has designated the “GPO-VIR® Pediatric tablet” [d4T 7 mg/3TC 30 mg/NVP 50 mg] as “GPO-VIR® S7”.

5. Section 6.24 Hyperamylasemia: The second paragraph has been changed to read “Upon presentation of Grade 3 or 4 total amylase, the blood sample should be fractionated and the pancreatic fraction should then be used to determine the toxicity management. The toxicity grades for total amylase will be calculated using the local laboratory ULN and will be graded according to the table below.

P1056 Supplemental Laboratory Table:

<table>
<thead>
<tr>
<th>LABORATORY PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEMISTRIES (Standard International Units as per Local Laboratory)</td>
<td>&gt;1.0-1.5 x ULN</td>
<td>&gt;1.5-2 x ULN</td>
<td>&gt;2.0-5.0 x ULN</td>
<td>&gt; 5.0 x ULN</td>
</tr>
</tbody>
</table>

For purposes of this protocol the upper limit of normal for pancreatic amylase is defined as 37% of the ULN for total amylase. Pancreatic amylase will be graded according to the relationship to ULN (as determined above) and graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 [December 2004], http://rcc.tech-res-intl.com.”

6. Informed consent: Delete the last section of page 12 entitled “Fixed Dose Combinations (FDCs) of the above drugs” and page 13, and replace with the following:

Fixed Dose Combinations (FDCs) of the above drugs

GPO-VIR® S30, tablets
Government Pharmaceutical Organization (Thailand), updated February 2005 and 
GPO-VIR® S7  (Nevirapine, Lamivudine and Stavudine combination tablets) 

These combinations of the above drugs are produced only in Thailand and GPO-VIR® 
S30 is approved by the Thai FDA (S7 approval pending the outcome of P1056).

As combinations of lamivudine, stavudine and nevirapine, these combination tablets 
include the risks for all of these drugs that are listed above.

An additional risk of the GPO-VIR® S7 tablet is the risk of an allergic reaction 
(including bronchial asthma) to the tartrazine dye included in it.

FOR STAGE II

Add the following to the roster page and also the “Notification Box” on pg. 44 : “For Stage II, 
Site 8252 QSNICH is ineligible under IMPAACT. Additional Eligible sites in Thailand are 
as follows:

MAIN UNIT #8351 and Research Coordinating Center for site # 8356 
Institut de Récherche pour le Développement (IRD), Program for HIV Prevention and 
Treatment (PHPT) 
29/7-8 Samlan Road, Soi 1 Prasing, 
Muang Chiang Mai 50200 
Tel: +660 538 14633-8, Fax: +660 538 14269 
Dr. Marc Lallemand, marc@phpt.org, Dr. Gonzague Jourdain, gonzague@phpt.org, 
Pra-oronsuda Sukrakanchana (Nid), praoronsuda@phpt.org.

SUBUNIT # 8356
Chonburi Regional Hospital, Chonburi 
69 M 2 Sukumvith T. Ban Suan 
Muang Chonburi 20000 Thailand 
Pediatrician: Dr. Suchat Hongsiriwan, suchat845@hotmail.com

IMPAACT CRS, Chiang Mai University CTU [Formerly PACTU# 20101 at Research 
Institute for Health Sciences (RIHES)] 
Virat Sirisanthana, M.D. (IMPAACT CRS PI) 
Research Institute for Health Sciences (RIHES)] 
Chiang Mai University, 110 Intavaroras Road, 
Chiang Mai, 50200 Thailand 
Tel: 66 5389 4138 
Fax: 66 5322 1849

Study team for P1056 
Linda Aupribul, M.D., Principal Investigator, lindaa@rihes-cmu.org
This section of the LOA will apply to **Stage II** of the protocol. It is being issued to provide clarification to eligible sites regarding the requirement for “admission to the hospital” for the 72 hours prior to the PK study, since many descriptions of Stage II, refer to Stage I, (pgs. 27, 28, 29).

**In reference to Stage II:** Please change sentences containing the phrases “admitted to the hospital” or “hospitalized”….prior to the PK study” to:

“**Documentation of Direct Observation of Therapy (DOT) by a clinical study staff member, prior to the PK study.**”

The term “admission” as used in the protocol is not meant to be restrictive or infer inpatient status (as in the US), but rather to reflect host country clinical care practices (outpatient and inpatient). The intent of the protocol is to ensure 100% adherence to the study regimen in the 72 hours preceding the PK study, through Direct Observation of Therapy (DOT) and proper documentation by a clinical study staff member, and is so stated in the eligibility criteria to move to Step 2. “Admission to the hospital” was intended to facilitate eligibility for the PK study and ensure that participants did not miss any doses.

For Stage II (n=32), the children and their families or caregivers will agree to hospitalization for the 12-hour PK study days (Day 28 and 56), but are concerned about missing school and flexibility, in the 72 hours prior to the PK study.

For Stage II, in cases where coming to the clinic/hospital for the specified DOT time periods on Day 25, 26, 27 and Day 53, 54, 55, (prior to the 1st and 2nd intensive PK Study Days respectively), presents undue hardship to the family/caregivers, the clinic study staff may consider an alternate arrangement to provide a visit to the home where the clinical study staff representative directly observes the child taking the study medications at the required times and then records this DOT appropriately, in the 72 hour period preceding the PK Study Day.

The following (**in bold**) are the specific changes to IMPAACT/PACTG P1056, Version 1.0, 02/03/06:

**For Stage II:**

1. Section 3.2 Adherence Assessments and Adherence Assistance, pg. 31: “An intensive PK study will be done at the end of this four week period (Day 28), including **documentation of DOT by a clinical study staff member, prior to the PK study** to ensure adherence, which will begin on Day 25.”

Under STEP 2: Cross-over Regimen (Weeks 5-8)…“A second intensive PK study will be done at the end of this four week period (Day 56), with **documentation of DOT by a clinical study staff member, prior to the PK study** on Day 53, in the same manner as outlined in Step 1.”
2. Inclusion criteria 4.17-“willingness to be hospitalized for the **12-hour intensive PK Study**” (pg. 32).

3. Section 6.321-PK Study Management, Eligibility (pg. 53) “100% adherence to the ARV regimen in the 72 hours prior to the PK study. Subjects will have **documentation of DOT by a clinical study staff member**, prior to the PK study days. See Section 9.0-Pharmacology Plan for PK Study details.”

4. Section 9.21-PK Evaluation (pg. 63), Bullet: “**Documentation of DOT by a clinical study staff member**, prior to the PK study to ensure 100% adherence to the study treatment regimen.”

   Under 1st Intensive PK study: “On Day 11 (Stage I) and Day 25 (Stage II) subjects will be **monitored** for DOT for the 72 hours prior to the first PK study.” Under 2nd Intensive PK Study: “On Day 25 (Stage I) and 53 (Stage II) of the study, subjects will again be **monitored** for DOT and documentation of the doses prior to the second PK study.”

5. Appendix II –Schedule of Evaluations for Stage II

   Lab column: Replace Q and S with “L”.

   (footnote 3); *Subjects will be **monitored and documentation of DOT by a clinical study staff member, will be done** 3-4 days prior to the PK study.”

   (footnote 11), Delete Q and S and replace with “L=Local Laboratory certified to perform the assay”.

6. Appendix III-(pg 3 of 3) under Hospital Admissions: “Children will be monitored beginning on study Day 11 and 25 (Stage I) and **Day 25 and 53 (Stage II)** to implement DOT for the critical time period prior to the start of the **12 hour PK study**…..”

7. Appendix IV-Virology: Designated Laboratory/Contact Person-Add “**Also for Stage II:** Nicole Ngo-Giang-Huong, PHPT-IRD Laboratory, Faculty of Associated Medical Sciences, Department of Clinical Microbiology, 6th Floor, Chiang Mai University, Chiang Mai, 50200, Phone: +66 53 894431, FAX: +66 53 894220, e-mail: nicole@phpt.org , LDMS code: 251.

8. Appendix VII-Informed Consent (pg. 4 and 5 of 17) “If your child has taken all the study drugs the right way, for **3-4 days** your child will be admitted to the hospital for the **12 hour** special blood tests (called a pharmacokinetic study, or PK study for short). Your child will be in the hospital for this **PK study day**. The study staff will make sure your child takes the study drugs the right way during the **monitoring period** and hospital stay. **While in the hospital**, your child will have the **12 hour PK study** done to measure the study drugs in his/her blood.”

   pg 15 of 17 under Confidentiality: Change to "Your child's records may be reviewed by the (insert the name of the participating site) IRB/EC, US Food and Drug Administration (FDA), Thai FDA, Thai Ministry of Public Health (MOPH), National Institutes of Health
(NIH), study staff, study monitors, the drug company supporting the study (GPO) and their designees”.

9. Appendix VIII-Patient Information Handout. 3rd bullet: “Home visits/phone calls may be needed to make sure that the study medication is taken on schedule. If it is taken as directed, the clinical staff will document this several days before children will be admitted to the hospital for the actual 12 hour PK study.”

This information will be added to the next version of the protocol. Please contact the protocol team at actg.teamp1056@fstrf.org if you have any questions.

This Letter of Amendment (LOA) will be available from the IMPAACT Website (http://impaact.s-3.com). The username is: impaact and the password is: cure (all lower case). Select Protocol Specific Web Page (P1056), and LOA #2 dated 3/2/07 under Current Protocol Related Documents.

Thank you for your participation in IMPAACT/PACTG P1056. The P1056 Protocol Team