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

An International Trial of the Pediatric AIDS Clinical Trials Group (PACTG) Bangkok, Thailand

Sponsored by:
The National Institute of Allergy and Infectious Diseases (NIAID)

Pharmaceutical Support Provided by:
The Government Pharmaceutical Organization (GPO), Thailand
And
GlaxoSmithKline

The U.S. Food and Drug Administration (FDA)
Investigational New Drug (IND) # 71, 844

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Final
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FOREWORD

PACTG P1056 is a collaborative study restricted to international sites in Thailand. It is designed to compare the pharmacokinetics and bioavailability of the new GPO-VIR® pediatric fixed-dose combination (FDC) chewable tablet produced by the Thai Government Pharmaceutical Organization (GPO) with the standard, brand name liquid formulations of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP) in HIV-infected children in Thailand. This generic FDC pediatric formulation, hereafter referred to as “GPO-VIR® Pediatric tablet” is expected to become the first line of therapy for children in the Thai Ministry of Public Health’s Access to Care Program. PACTG P1056 is among the first of the international treatment protocols of the PACTG to use generic anti-HIV drugs.

All subjects will be enrolled at two PACTG sites in Bangkok, Thailand. A Thai point of contact for clinical issues and Expedited Adverse Event (EAE) reporting at each site has been identified (See Team Roster). Pharmacokinetic sample analysis will be done in Thailand, as well.

The sponsor of this study is the Division of AIDS (DAIDS) which holds the IND for this study (71, 844). Pharmaceutical company support and consultation are being provided by GPO and GSK. Subjects in Thailand will be consented and treated as per their country guidelines.

In Thailand, the trial will follow the 1993 Revision of the Ethical Review Committee of the Ministry of Public Health, the Ethical Principles for Medical Research Involving Human Subjects, World Medical Association Declaration of Helsinki (October 2000), and ICH Tripartite Harmonised Guidelines for Good Clinical Practice at Step 4 of the ICH process (1 May 1996) (English and Thai version) [ISBN 974-8044-95-5].
GLOSSARY

3TC  Lamivudine
AE   Adverse event, also adverse experience
ALT  Alanine aminotransferase
ARV  Antiretroviral Therapy
ART  Antiretroviral Therapy
ATC  Access to Care Program
AUC  Area Under the Curve
BSA  Body Surface Area
CBC  Complete Blood Count
CI/F  Clearance
C_max and C_min  Concentration (maximum and minimum)
CRF  Case Report Form
d4T  stavudine
DAIDS (United States) Division of AIDS
DMC (United States) Data Management Center
DOT  Direct Observation of Therapy
DSMB  Data and Safety Monitoring Board
EAE  Expedited Adverse Event
EC  Ethics Committee
FDA (United States) Food and Drug Administration
FDC  Fixed-Dose Combination
GCP  Good Clinical Practice
GPO (Thailand) Government Pharmaceutical Organization
GPO-VIR® (d4T + 3TC + NVP) fixed-dose combination tablet
HAART  Highly active antiretroviral therapy
ICH  International Conference of Harmonization
IND  Investigational new drug
IRB  Institutional Review Board
IUD  Intrauterine device
K_a and K_el  Rate constant (absorption and elimination)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
</tr>
<tr>
<td>LDMS</td>
<td>Laboratory Data Management System</td>
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<tr>
<td>LPC</td>
<td>Laboratory Processing Chart</td>
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<tr>
<td>LFT</td>
<td>Liver function test</td>
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<tr>
<td>MOPH</td>
<td>(Thailand) Ministry of Public Health</td>
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<tr>
<td>NIAID</td>
<td>(United States) National Institute of Allergy and Infectious Diseases</td>
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<tr>
<td>NIH</td>
<td>(United States) National Institutes of Health</td>
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<tr>
<td>NNRTI</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitor</td>
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<tr>
<td>NRTI</td>
<td>Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitor</td>
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<tr>
<td>NVP</td>
<td>Nevirapine</td>
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<tr>
<td>OHRP</td>
<td>(United States) Office for Human Research Protections</td>
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<tr>
<td>PACTG</td>
<td>Pediatric AIDS Clinical Trials Group</td>
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<tr>
<td>PACTU</td>
<td>Pediatric AIDS Clinical Trial Unit</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>PID</td>
<td>Patient Identification Number</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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<tr>
<td>q</td>
<td>Every</td>
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<tr>
<td>QSNICH</td>
<td>Queen Sirikit National Institute of Child Health, Thailand</td>
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<tr>
<td>RCC</td>
<td>(United States, DAIDS) Regulatory Compliance Center</td>
</tr>
<tr>
<td>SADR</td>
<td>Suspected Adverse Drug Reaction</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SES</td>
<td>Subject Enrollment System</td>
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<tr>
<td>SID</td>
<td>Study Identification Number</td>
</tr>
<tr>
<td>$T_{\frac{1}{2}}$ or $t_{1/2}$</td>
<td>Half-life</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>United States of America</td>
</tr>
<tr>
<td>$V_d$</td>
<td>Volume (distribution)</td>
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<tr>
<td>VQA</td>
<td>Virology Quality Assurance</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
PACTG P1056 PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to actg.teamp1056@fstrf.org. Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to actg.teamp1056@fstrf.org. Due to the different time zones all decisions requiring immediate attention, such as emergency clinical care decisions that have to be addressed within 48 hours, will be made by the Protocol Chairs at the Thai sites. A response should generally be received within 24 hours (Monday - Friday). To contact any of the team members directly via fax or telephone, (see contact information below for each team member) from the USA: dial 011 + Country and City Codes + phone number [Codes: Chiang Mai, Thailand 66-53; Bangkok, Thailand 66-2. From all other countries: dial IDD + 1 + Code + Area Code in the USA + Phone Number (USA-IDD=011 and USA Code=1)]. The time difference between U. S. Eastern Standard Time (EST)/Daylight Time (EDT) and Thailand is 12/11 hours ahead. For protocol registration questions, e-mail Protocol@tech-res.com, or call 1-301-897-1707. For Expedited Adverse Event (EAE) questions, e-mail RCCSafetyOffice@tech-res.com or call 1-800-537-9979 or FAX 1-800-275-7619 (US); 1-301-897-1730 or FAX 1-301-897-1710 (International). To order study drug, call the Clinical Research Products Management Center 1-301-294-0741. For randomization or enrollment questions, call the Data Management Center (DMC), 1-716-834-0900.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>SCHEMA</th>
<th>...............................................................................................................................</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 INTRODUCTION</td>
<td>.....................................................................................................................</td>
<td>15</td>
</tr>
<tr>
<td>1.1 Background</td>
<td>...............................................................................................................</td>
<td>15</td>
</tr>
<tr>
<td>1.2 Rationale</td>
<td>...................................................................................................................</td>
<td>23</td>
</tr>
<tr>
<td>2.0 STUDY OBJECTIVES</td>
<td>.............................................................................................................</td>
<td>25</td>
</tr>
<tr>
<td>2.1 Primary Objectives</td>
<td>...........................................................................................................</td>
<td>25</td>
</tr>
<tr>
<td>2.2 Secondary Objectives</td>
<td>.................................................................................................</td>
<td>25</td>
</tr>
<tr>
<td>3.0 STUDY DESIGN</td>
<td>..............................................................................................................</td>
<td>25</td>
</tr>
<tr>
<td>3.1 Stage I</td>
<td>..................................................................................................................</td>
<td>26</td>
</tr>
<tr>
<td>3.2 Stage II</td>
<td>..................................................................................................................</td>
<td>29</td>
</tr>
<tr>
<td>4.0 SELECTION AND ENROLLMENT OF SUBJECTS</td>
<td>.....................................................</td>
<td>30</td>
</tr>
<tr>
<td>4.1 Inclusion Criteria</td>
<td>...........................................................................................................</td>
<td>30</td>
</tr>
<tr>
<td>4.2 Exclusion Criteria</td>
<td>...........................................................................................................</td>
<td>32</td>
</tr>
<tr>
<td>4.3 Allowed Medications</td>
<td>...................................................................................................</td>
<td>33</td>
</tr>
<tr>
<td>4.4 Disallowed Medications</td>
<td>...............................................................................................</td>
<td>33</td>
</tr>
<tr>
<td>4.5 Enrollment Procedures</td>
<td>.................................................................................................</td>
<td>35</td>
</tr>
<tr>
<td>4.6 Co-enrollment Guidelines</td>
<td>.................................................................................................</td>
<td>35</td>
</tr>
<tr>
<td>5.0 STUDY TREATMENT</td>
<td>.....................................................................................................</td>
<td>35</td>
</tr>
<tr>
<td>5.1 Drug Regimens, Administration and Duration</td>
<td>.......................................................</td>
<td>35</td>
</tr>
<tr>
<td>5.2 Drug Formulation</td>
<td>.......................................................................................................</td>
<td>39</td>
</tr>
<tr>
<td>5.3 Drug Supply, Distribution and Pharmacy</td>
<td>...............................................................</td>
<td>40</td>
</tr>
<tr>
<td>6.0 SUBJECT MANAGEMENT</td>
<td>..............................................................................................</td>
<td>41</td>
</tr>
<tr>
<td>6.1 Toxicity Management</td>
<td>...............................................................................................</td>
<td>41</td>
</tr>
<tr>
<td>6.2 Management of Specific Adverse Events</td>
<td>........................................................................</td>
<td>45</td>
</tr>
<tr>
<td>6.3 Study Management Plan</td>
<td>...............................................................................................</td>
<td>51</td>
</tr>
<tr>
<td>6.4 Criteria for Study Discontinuation</td>
<td>...............................................................................................</td>
<td>52</td>
</tr>
<tr>
<td>7.0 EXPEDITED ADVERSE EVENT REPORTING</td>
<td>.............................................................</td>
<td>53</td>
</tr>
<tr>
<td>8.0 STATISTICAL CONSIDERATIONS</td>
<td>...........................................................................</td>
<td>55</td>
</tr>
<tr>
<td>8.1 General Design Issues</td>
<td>...........................................................................................................</td>
<td>55</td>
</tr>
<tr>
<td>8.2 Outcome Measures</td>
<td>...........................................................................................................</td>
<td>56</td>
</tr>
<tr>
<td>8.3 Stratification</td>
<td>...............................................................................................................</td>
<td>57</td>
</tr>
<tr>
<td>8.4 Sample Size</td>
<td>...............................................................................................................</td>
<td>57</td>
</tr>
</tbody>
</table>
8.5 Monitoring ................................................................. 58

9.0 CLINICAL PHARMACOLOGY PLAN .................................................. 61
9.1 Study Design ........................................................................ 61
9.2 Pharmacokinetic (PK) Evaluation ........................................... 62
9.3 Data Analysis ........................................................................ 65
9.4 Evaluable Subjects ............................................................ 66

10.0 HUMAN SUBJECTS ................................................................. 66
10.1 Institutional Review Board/Ethics Committee Review and Informed Consent ... 66
10.2 Subject Confidentiality ........................................................... 67
10.3 Study Discontinuation .......................................................... 62
10.4 Regulatory Authorities ......................................................... 67

11.0 PUBLICATION OF RESEARCH FINDINGS .................................. 68

12.0 BIOHAZARD CONTAINMENT ..................................................... 68

13.0 REFERENCES ........................................................................... 69

APPENDICES

I: SCHEDULE OF EVALUATIONS-STAGE I

II: SCHEDULE OF EVALUATIONS-STAGE II

III: STUDY DRUG ADMINISTRATION PROCEDURES

IV: VIROLOGY COLLECTION, SHIPPING AND STORAGE INSTRUCTIONS

V: IMMUNOLOGY COLLECTION, SHIPPING AND STORAGE INSTRUCTIONS

VI: PHARMACOLOGY COLLECTION, SHIPPING AND STORAGE INSTRUCTIONS

VII: SAMPLE INFORMED CONSENT

VIII: PATIENT INFORMATION HANDOUT
SCHEMA

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

DESIGN: Two stage, Phase I/II, two arm, randomized, open-label, multiple-dose pharmacokinetic cross-over study.

POPULATION: HIV-infected Thai children ≥6 months to <13 years of age, clinically stable on a HAART regimen (NVP + 2 NRTIs) and receiving a maintenance dose of NVP for at least 4 weeks.

SAMPLE SIZE: 8 evaluable children ≥12 to ≤30 kg in weight

STEP 1: Randomization into two treatment arms:

REGIMEN²:

Arm A: Starting regimen: GPO-VIR® Pediatric tablet(s) q 12 hours for two weeks:
• [d4T 7 mg/3TC 30 mg/NVP 50 mg]
(Weeks 1-2)

Arm B: Starting regimen: (liquid formulations) q 12 hours for two weeks:
• d4T (1 mg/kg) + 3TC (4 mg/kg) + NVP (150 mg/m²)

STEP 2: Register into the cross-over regimens:

(Weeks 3-4) Arm A: d4T/3TC/NVP liquid formulations, q 12 hours for two weeks
Arm B: GPO-VIR® Pediatric tablet(s) q 12 hours for two weeks.

NOTE: PK studies will be conducted at the end of Week 2 and Week 4, respectively.

STUDY DURATION:

Maximum of 12 weeks (On treatment + safety follow-up)
Treatment: Minimum of 4 weeks, maximum of 6 weeks
Safety follow-up: 6 weeks

SCHEMA (Cont.)

² Dosing per body weight, for liquid and GPO-VIR® Pediatric tablet. See Table 1, Section 5.1
Provided the study is not stopped in Stage I, (see Section 8.51); the Stage I analysis will include plasma drug levels (d4T, 3TC and NVP) and the initial noncompartmental pharmacokinetic analysis for NVP. See Section 9.3

Stage II will be initiated as soon as the analysis of Stage I is completed.

<table>
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<tr>
<th>STAGE II</th>
<th>SAMPLE SIZE: minimum 30, maximum 44 evaluable children</th>
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STRATIFICATION: Children are stratified by weight, ≥6 to ≤30 kg (n=30-44):

- Group 1: ≥6-8 kg (n=6-8)
- Group 2: >8-16 kg (n=8-12)
- Group 3: >16-23 kg (n=8-12)
- Group 4: >23-30 kg (n=8-12)

STEP 1: Randomization into two treatment arms (as in Stage I)

REGIMEN: Same as Stage I, adjusted for weight (Table 1, Section 5.1):

- Arm A: GPO-VIR® Pediatric tablet(s) q 12 hours for four weeks
- Arm B: d4T, 3TC and NVP liquid formulations q 12 hours for four weeks

STEP 2: Register into the cross-over regimens (as in Stage I):

- Arm A: d4T/3TC/NVP liquid formulations q 12 hours for four weeks
- Arm B: GPO-VIR® Pediatric tablet(s) q 12 hours for four weeks

NOTE: PK studies will be conducted at the end of Week 4 and Week 8, respectively.

STUDY DURATION:

- Maximum of 24 weeks (On treatment + safety follow-up)
- Treatment: Minimum of 8 weeks, maximum of 18 weeks.
- Safety follow-up: 6 weeks
OBJECTIVES:

Primary

1. To compare the bioavailability of d4T, 3TC and NVP in the GPO-VIR® Pediatric tablet formulation with the liquid formulations of d4T, 3TC and NVP in HIV-infected children in Thailand.

2. To estimate the population average exposure to NVP delivered in the GPO-VIR® Pediatric formulation, and to compare this exposure to an adult exposure of therapeutically adequate NVP concentration.

Secondary

1. To describe the pharmacokinetic parameters of d4T, 3TC and NVP in HIV-infected Thai children ≥6 months to <13 years of age in the weight range of ≥6 to ≤30 kg.

2. To evaluate the intra- and inter-subject variability of the pharmacokinetics of d4T, 3TC and NVP when administered as the GPO-VIR® Pediatric tablet(s) and as the individual liquid drug formulations.

3. To describe any adverse drug reactions due to the GPO-VIR® Pediatric formulation and the individual d4T, 3TC and NVP liquid formulations.
1.0 INTRODUCTION

1.1 Background

The number of children infected with the Human Immunodeficiency Virus (HIV) in Thailand continues to rise. Since the initiation of HIV infection and AIDS surveillance in Thailand in 1981, it has been estimated that there are more than one million HIV-infected individuals in the country. By the end of 2000, there were 32,961 HIV-infected children. Approximately 0.8 million pregnancies occur each year with a current seropositivity rate in pregnant women of 1.4%. Given a perinatal transmission rate of 6-25%, 672-2,800 HIV-infected infants are born annually (1).

The Thai Ministry of Public Health (TMOPH) launched an “Access to Care” program in 2000 to provide antiretroviral (ARV) drugs to HIV-infected patients as well as to improve the infrastructure of the medical services in hospitals participating in the program (2). The majority of the ARV drugs being provided are produced by the Thai Government Pharmaceutical Organization (GPO) (www.gpo.or.th). GPO supplies pharmaceutical and medical products to support health service activities throughout the country as a state enterprise under the TMOPH.

In December 2001, GPO-VIR® was registered by the Thai Food and Drug Administration for treatment of HIV infection in adults (3). GPO-VIR®, a fixed-dose combination (FDC) tablet of lamivudine (3TC), stavudine (d4T) and nevirapine (NVP) is available in two formulations, named based upon the dosage of stavudine. GPO-VIR® S30 (for adults, weight <60 kg) contains 30 mg of stavudine, 150 mg of 3TC and 200 mg of NVP. GPO-VIR® S40 (adults ≥60 kg) contains 40 mg of stavudine, 150 mg of 3TC and 200 mg of NVP (4). The two formulations are listed as the first-line ARV drugs in the national treatment guidelines for HIV-infected adults as part of the Access to Care program (1). The GPO-VIR® regimen has reduced ARV costs to the equivalent of $27/person/month. The S30 formulation has been widely used in the HIV-infected pediatric population due in part to the lack of other affordable ARVs and the convenience and advantages of a FDC tablet. A similar pediatric formulation had not been available.

In 2002, the TMOPH launched the National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPHA) with the aim of providing treatment to all Thai patients with HIV infection. The program relies heavily on GPO-VIR® and the use of non-pediatric formulations is encouraged for children. A recent publication on the efficacy of HAART in HIV-infected children participating in the Program concluded that HAART (either NVP or efavirenz...
(EFV), together with 3TC and d4T) using generic drugs and/or adult formulations was safe, effective and feasible (5).

While there are few published studies of the use of GPO-VIR® S30 in children, a recent study of children ages 3-15 years was completed by investigators at Siriraj Hospital, Chiang Mai University, and the University of California San Diego (6). Thirty-five (35) HIV-infected children, who were stable on GPO-VIR® S-30 [30 mg d4T, 150 mg 3TC and 200 mg NVP] for more than 8 weeks, were enrolled. 15 of these children were treatment naïve; four were also receiving indinavir boosted with ritonavir. Children received an observed dose of the scored tablet (½, ¾, or full tablet, according to weight and the NVP dose of 120-200 mg/m², every 12 hours). PK samples were drawn to assess NVP plasma concentrations. In the 34 evaluable subjects (18 female and 16 male) with a median treatment duration of 16.8 (2.7-27.5) months, the median CD4+ count and percentage at baseline was 246 (10-1221) cells/mm³ and 20.3 (1.7-30.2) % at the time of the PK study. The median PK parameters and ranges were: AUC_{(12h)} of 78.4 (50-306.6) h·mcg/mL; C_{min} of 6.0 (2.6-24.4) mcg/mL; T_{1/2} of 25.5 (12.1-105.2) h; NVP clearance of 0.08 (0.02-0.16) L/kg/hr and V_d of 2.95 (2.7-3.2) L/kg (K. Chokephaibulkit personal communication). The GPO-VIR® S30 FDC tablet can be administered to children over 3 years of age and will result in appropriate NVP exposure. Most Thai children receiving this formulation tolerated it well and experienced sustained immunologic benefit.

GPO-VIR® Pediatric tablet

In 2004, the GPO developed a FDC formulation of GPO-VIR® containing d4T (7 mg)/3TC (30 mg)/NVP (50 mg) for pediatric use, and referred to in this protocol as the “GPO-VIR® Pediatric tablet”. It is a chewable, citrus flavored, scored tablet that is taken twice a day (every 12 hours). Initial stability testing was done June 21–August 28, 2004, the preliminary results indicated the required parameters had been met [GPO-personal communication]. GPO provided the P1056 team with final information on February 3, 2006 on product batches manufactured on 1/17/05, 2/12/05 and 8/22/05. The report concluded that based on the accelerated stability testing results up to 6 months, the product meets the requirements for all quality parameters tested at storage conditions up to 6 months in market HDPE bottles. The results of follow up long term stability up to 9 months are within the specification limits [GPO Report]. This formulation has not been studied in children or adults.

1.11 Pharmacokinetic Differences in Children and Adults

Various factors specific to the pediatric population dictate treatment options. First, pediatric dosage is based on age, weight or body surface area (BSA).
Second, developmental changes influence absorption, distribution, metabolism and excretion of drugs as children grow from infancy through adolescence. Finally, pediatric-specific issues influence medication adherence.

Dosage selection of ARVs based upon age alone is relatively inaccurate and not recommended. A dosing method used occasionally for ART therapy and frequently for cancer chemotherapy in children is based upon BSA. This takes into account both the patient’s weight and height. Many physiological parameters such as cardiac output, metabolic rate, hepatic blood flow and glomerular filtration rate, correlate closely with BSA. However, most drugs in pediatrics are dosed based on weight, since this is simpler to measure than BSA and for most drugs functions as a reasonable surrogate. Finally, if pediatric dosages are not well established for certain ARVs, it may be necessary to extrapolate a dosage based upon an adult weight or BSA (7).

Several age-related factors, including gastric acid secretion, gastric emptying time, intestinal transit time and gastrointestinal motility, influence the absorption of drugs in pediatric patients. Body composition varies greatly with age and plays a major role in the distribution of drugs among pediatric patients (8). Total body water (TBW) as a percentage of body weight changes with age. Differences in tissue binding characteristics between infants and adults also affect drug distribution. Altered hepatic enzymatic activity during the postnatal period tends to decrease the metabolism of drugs. Neonatal activity of the cytochrome P450 (CYP) enzyme system approximates 20-70% of adult values. Enzymatic activity increases to adult levels by 6-12 months, exceeds adult levels during 1-4 year of age and then declines to adult levels by the end of puberty (7). Finally, some drugs are handled exclusively or primarily by the kidney, and renal function is the major determinant of pharmacokinetics. The level of renal function in a term neonate approximates one-fifth of adult levels. Glomerular filtration rate approaches adult levels by 6 months of age and maturation of tubular secretory function occurs at approximately 7-8 months of age. Therefore, renal clearance of drugs may be reduced in infants compared with adults. Peak renal function occurs at 3-5 years of life and declines to average adult levels by 18 years of age.

A drug’s formulation can have pronounced effects on the concentration versus time profile. Therefore, it is important to know a drug’s pharmacokinetic disposition after administration of the formulation to be used. Drug administration methods and formulations for the pediatric population need to be taken into account when considering pediatric pharmacokinetics. Medication adherence is an important factor that influences pharmacotherapy. Palatability and ease of taking a particular medication can be problematic with pediatric patients, since adherence is dependent in large part on their caregivers.
1.12 Previous Pharmacokinetic studies of Lamivudine (3TC), Stavudine (d4T) and Nevirapine (NVP)

The nucleoside reverse transcriptase inhibitors (NRTIs), 3TC and d4T, are 3’ modified deoxynucleosides that require intracellular phosphorylation to their triphosphate anabolites to become active. Specific cellular host enzymes are responsible for this process. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) also inhibit the HIV reverse transcriptase, but are non-competitive inhibitors and do not require intracellular activation.

Lamivudine (3TC, Epivir®)

The recommended oral dose of 3TC in pediatric patients 3 months to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice daily) (9). The PK parameters of 3TC have been determined in 55 children (3 months to 17 years) following oral administration of 1, 2, 4, 8, 12 or 20 mg/kg/day given twice daily (10). The median CL/F and terminal half-life were 240 mL/min/m² and 1.7 hours, respectively. Serum concentrations of 3TC at each dosage level were greater than the concentration required to inhibit 50% of the virus (IC50) for virus isolates obtained from patients during the enrollment period. All serum concentrations of 3TC obtained were consistently lower than the corresponding concentrations found in adults participating in a similar study. The 8 mg/kg/day dose produced an AUC12 of 5.2 mg*hr/L and t1/2β of 1.76 hours. The 3TC exposure at this dose is similar to the AUC of 6.1 mg*hr/L seen in adult Phase I studies following administration of 150 mg (11). Another study evaluating PK parameters of 3TC at six dose levels ranging from 0.5-10 mg/kg of body weight in 52 HIV-infected children (6 months to 17.5 years) yielded parameter values similar to those seen in adults (12). The mean clearance of 3TC (± standard deviation) in the children was 0.53 ± 0.19 L/kg/hr and the mean half-life at the distribution and elimination phases were 0.23 ± 0.18 and 2.2 ± 2.1 hours, respectively. 3TC was rapidly absorbed after oral administration with a bioavailability of 66 ± 25%. Elimination of 3TC occurs through renal excretion. Adult patients with severe renal impairment experience >90% reduction in 3TC clearance (13). In pediatric patients, when 3TC clearance was normalized to body weight, a significant correlation was noted between age and clearance. However, clearance normalized to BSA was age-independent. The intracellular 3TC triphosphate (TP) concentrations correlate more closely with efficacy than serum 3TC concentrations. However, intracellular 3TC-TP concentrations demonstrate tremendous inter-patient variability and are not strongly correlated with plasma concentrations (11),
The conclusion from the available data in pediatric studies of 3TC is that dosage based upon body weight is adequate for treatment of children after 3 months of age. Please refer to the Epivir® Package Insert for complete prescribing information.

Stavudine (d4T, Zerit®)

The recommended oral dosage of d4T in pediatric patients weighing <30 kg is 1 mg/kg twice daily (15). Pediatric patients weighing >30 kg and <60 kg should receive the recommended adult dose of 30 mg twice daily, and children >60 kg in weight should receive the recommended adult dosage of 40 mg twice daily.

A Phase I/II study evaluated d4T pharmacokinetics in 37 children (7 months to 15 years) following dosage of 0.125, 0.25, 0.5, 1, 2, 4 mg/kg/day in two divided doses given intravenous and orally (16). PK parameters were similar for intravenous and oral administration across all doses studied. At dosages of 1 and 2 mg/kg/day, the t1/2β was 1.11 and 1.13 hours, the maximum concentration (Cmax) was 0.44 and 1.1 mg/L. Oral bioavailability ranged from 61-78%. The clearance of d4T decreases with increasing renal impairment. PK properties of d4T were similar to adults and children, except that children required twice the dose per unit body weight to achieve a comparable Cmax. Please refer to the Zerit® Package Insert for complete prescribing information.

Nevirapine (NVP, Viramune®)

The labeled NVP dose for treatment of HIV infection in pediatric patients 2 months to 8 years of age is 4 mg/kg once a day for the first 14 days followed by 7 mg/kg twice daily per the Package Insert (17). Patients 8 years and older should receive 4 mg/kg once daily for 2 weeks followed by 4 mg/kg twice daily. However, several of the pediatric NVP clinical trials were conducted using NVP at 120-200 mg/m² twice daily and some clinicians prefer this dosage as it produces more consistent drug concentrations across pediatric age groups (17), (18), (19), (20), (21), (22), (23) and (http://www.aidsinfo.nih.gov), access either the pediatric treatment guidelines or the drugs link, and specify nevirapine. The following information is taken from the Viramune® package insert (revised January 11, 2005).

NVP is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in
12 healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma NVP concentrations of 2 ± 0.4 µg/mL (7.5 µM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, NVP peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough NVP concentrations of 4.5 ± 1.9 µg/mL (17 ± 7 µM), (n = 242) were attained at 400 mg/day.

NVP tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions.

Pharmacokinetic profiles for HIV-infected female and male subjects were obtained in Boehringer Ingelheim (BI) Study 1100.1090, a trial that included PK profiling for 8 women and 35 men receiving a NVP dose of 200 mg po BID. At steady state, the $C_{max}$ was 6.0 µg/mL (standard deviation 1.1), 12 hour AUC was 60.6 µg*hr/mL (SD 12.7), and $C_{min}$ 4.0 µg/mL (SD 0.8) (21).

Elimination of NVP is via oxidative metabolism by enzymes of the CYP3A and CYP2B6 families. The CYP enzyme system is active at very low levels in neonates but reaches adult activity within several months. It then exceeds adult levels during 1-4 years of age and declines to adult levels by the end of puberty. NVP induces its own metabolism such that clearance after two weeks of therapy is much higher and the half-life shorter than following the first dose of NVP (20), (21).

There are limited data available for NVP pharmacokinetics in HIV-infected children. A Phase I study was conducted to examine the pharmacokinetics, safety and antiretroviral activity of NVP in HIV-infected children (22). The results of the study, which showed more rapid oral clearance in children compared with that for adults, prompted the investigators to increase the NVP dosage in children <9 years of age in order to attain target steady-state concentrations. More recently Verweel et al. examined their retrospective results of nevirapine use in children and concluded that higher doses (at or over 300 mg/m²/day) appeared to achieve more satisfactory virologic results without additional toxicity (23). Please refer to the Viramune® Package Insert for complete prescribing information.
GPO-VIR® FDC tablet

There have been several GPO-VIR® S30 and S40 efficacy and safety studies done in Thailand (24), (25), (26). A 52-week cohort study in Siriraj Hospital included 101 ARV-naïve HIV-infected adults (GPO, Abstract, XV International AIDS Conference, July 11-16, 2004, Bangkok). Using intent to treat (ITT) and on-treatment (OT) analyses, this prospective study found that 80% and 97% of the patients had viral loads <400 copies/mL at week 24. At week 52, 59/101 (58%-ITT) and 59/76 (78%-OT) had viral loads <50 copies/mL, respectively. When using a viral load cut-off of 400 copies/mL, 72% (ITT) and 96% (OT) of the patients had less than this value at week 52. Approximately 20% of the patients discontinued therapy due to adverse events thought to be related to treatment with GPO-VIR®. Five patients had rash; four had fever with rash and one had fever. Two patients had rash with elevated liver enzymes (i.e. >5 times upper limit of normal (ULN)); four had symptomatic lactic acidemia and one had seizure (25).

A retrospective review included 115 ARV-naïve and 31 ARV-experienced patients treated at Bamrasnaradura Institute. The review period was 48 weeks. On-treatment analysis found that 97% of the ARV- naïve and 100% of the ARV-experienced patients had viral loads <50 copies/mL. Due to adverse events, 8% of patients discontinued ART and 6% changed their ARV drug regimen. Adverse events included: rash (1.4%), peripheral neuropathy (2.7%), lactic acidosis (2%), hepatitis (1.7%), lipodystrophy (0.7%) and both peripheral neuropathy and lactic acidosis (0.7%) (26).

Another study involved a three month, OT analysis of 39 ARV-naïve and 35 ARV-experienced patients. Patients with a CD4+ count ≤100 cells/mm³ prior to treatment had a greater increase in CD4+ than those with a count >100 cells/mm³ (111 vs 72 cells/mm³), respectively (27).

1.13 Previous safety studies of NVP

The safety of NVP has been assessed in more than 2,800 patients in clinical trials (28). The experience from clinical trials and clinical practice has shown that the most serious adverse reactions are clinical hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Fatalities due to these serious adverse events have been reported. The most common clinical toxicity of NVP is rash, with NVP-attributable rash occurring in 17% of
adult patients receiving combination regimens in Phase II/III controlled studies. Thirty-seven percent (37%, n=252) of patients treated with NVP experienced rash compared with 20% (n=255) of controls treated with either ZDV + ddI or ZDV alone. Severe (Grade 3) or life-threatening (Grade 4) skin toxicity (Stevens-Johnson syndrome) occurred in 7.6% of NVP-treated patients compared with 1.2% of controls.

A recent clinical trial found that concomitant administration of prednisone use was associated with an increase in the incidence and severity of rash during the first 6 weeks of NVP therapy. Therefore, use of prednisone to prevent NVP-associated rash is not recommended, per the Viramune® Package Insert (revised January 11, 2005).

Rashes were usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. The majority of rashes occurred within the first 6 weeks of therapy. Severe rashes occurred most frequently within the first 28 days of treatment; 25% of the patients with severe rashes required hospitalization; and one patient required surgical intervention. Overall, 7% of patients discontinued NVP due to rash.

In clinical trials, the overall risk of clinical hepatitis with NVP treatment is approximately 1%. There have been reports of severe, life threatening and in some cases, fatal hepatotoxicity in patients treated with NVP. These have led to the issuance of several warnings by the FDA. A letter dated September 22, 2004 reads as follows:

“Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in patients treated with VIRAMUNE®. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Women, and patients with higher CD4 counts, are at increased risk of these hepatic events. Women with CD4 counts >250 cells/mm³, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk of these events. Patients with signs or symptoms of hepatitis must discontinue VIRAMUNE® and seek medical evaluation immediately. (See WARNINGS).

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE®. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe
skin reactions or hypersensitivity reactions must discontinue VIRAMUNE® and seek medical evaluation immediately. (See WARNINGS).

It is essential that patients be monitored intensively during the first 18 weeks of therapy with VIRAMUNE® to detect potentially life-threatening hepatotoxicity or skin reactions. The greatest risk of severe rash or hepatic events (often associated with rash) occurs in the first 6 weeks of therapy. However, the risk of any hepatic event, with or without rash, continues past this period and monitoring should continue at frequent intervals. In some cases, hepatic injury has progressed despite discontinuation of treatment. VIRAMUNE® should not be restarted following severe hepatic, skin or hypersensitivity reactions. In addition, the 14-day lead-in period with VIRAMUNE® 200 mg daily dosing must be strictly followed.”(19).

Symptoms of clinical hepatitis include fatigue, malaise, anorexia, nausea, jaundice, alcoholic stools, liver tenderness or hepatomegaly. Acute hepatotoxicity has progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, prolonged PTT, or eosinophilia. Hepatic dysfunction may be isolated or associated with signs of hypersensitivity. NVP-related hepatotoxicity can occur in asymptomatic individuals with normal LFTs prior to NVP therapy. Increased AST or ALT levels before the start of ART and/or a history of hepatitis B or C infection are associated with a greater risk of hepatic adverse events. Most serious hepatic events occurred during the first 12 weeks of NVP treatment. However, approximately one-third of cases occurred later in treatment.

1.2 Rationale

It has been well proven that combination therapy using ARVs from at least two classes is superior to monotherapy and dual-NRTI therapy. ARV drug combinations containing NVP were more effective than single drugs in suppressing replication of an HIV-1 isolate in peripheral blood mononuclear cell cultures (28). Synergistic antiretroviral interactions were observed in dual-drug combinations of NVP with 3TC or d4T (29). An important factor affecting the exposure of ARVs, and thereby therapeutic response, is ARV adherence. A common reason for poor adherence is pill burden. A combination fixed dose drug approach appears to be an attractive strategy to improve adherence and in turn, therapeutic response.
Specific PK studies of this GPO-VIR® Pediatric tablet in HIV-infected Thai children are needed. Since the pediatric dosing of these three agents changes at different rates during childhood, no dosing regimen exists with the fixed ratio d4T/3TC/NVP that will result in exactly the same dose that is recommended with the standard single drug formulations. However, as mentioned above, there is controversy about the optimal dosing scheme for NVP in children. For this reason, and since there is stronger correlation between NVP plasma concentrations and clinical response than with either 3TC or d4T plasma levels and response, the dosing strategy for the GPO-VIR® Pediatric tablet is designed to achieve plasma NVP concentrations associated with therapeutic success.

In addition to assuring that the GPO-VIR® Pediatric formulation in this protocol results in therapeutic drug exposure, it will be important to know if the bioavailability differs from the standard liquid formulations. While bioequivalence between the original single drug and the GPO-VIR® Pediatric tablet component is not necessary, there will be individual instances where children will need to be switched from one formulation to the other. Therefore, it is clinically important to determine the PK parameters of this new formulation in comparison to the individual ARV drug components which have been studied in greater detail. Since PACTG P1056 will be generating pharmacokinetic data on the GPO-VIR® Pediatric formulation, adding a cross-over component to assess the pharmacokinetics of the single drug formulations is an efficient way to determine relative bioavailability of the formulations. A cross-over study will also minimize inter-patient variability.

CD4+ and viral load are measured at the beginning and end of the trial in order to characterize the study population and to guide generalization of the results at the end of the trial. The final values are also included as a safety screen to monitor the biologic consequences of the trial and to guide management in the post-trial period.

The two-stage design is dictated by the fact that the GPO-VIR® Pediatric formulation has not been tested in human beings before. Early data are needed both on possible early toxicity and, perhaps of greater importance, drug exposure in children taking this formulation.

Currently, there are nearly 500 HIV-infected pediatric patients being treated at the Pediatric Infectious Disease clinics at Siriraj Hospital, Mahidol University (PACTG Site 8251) and Queen Sirikit National Institute of Child Health, (PACTG Site 8252) in Bangkok, Thailand. At least 340 of these patients are eligible for free ARVs under the “Access to Care” program of the Ministry of Public Health as well as other sources. The prescribed ARVs are the
recommended doses of GPO-VIR® S30 or the d4T, 3TC and NVP liquid formulations.

Stage I includes only children $\geq 12$ kg so that a 2-week, rather than 4-week cross-over design can be safely implemented (blood volume considerations and the need for multiple samples over a relatively short period of time prevent inclusion of smaller children). A stopping rule has been designed which will maximize the safety of proceeding to Stage II. In Stage II, the cross-over design is lengthened to 4 weeks for two reasons: to permit smaller children to be included; and to allow for longer exposure to the study drugs and therefore more assurance about possible toxicity.

2.0 **STUDY OBJECTIVES**

2.1 **Primary Objectives**

2.11 To compare the bioavailability of d4T, 3TC and NVP in the GPO-VIR® Pediatric tablet formulation with the liquid formulations of d4T, 3TC and NVP in HIV-infected children in Thailand.

2.12 To estimate the population average exposure to NVP delivered in the GPO-VIR® Pediatric formulation, and to compare this exposure to an adult exposure of therapeutically adequate NVP concentration.

2.2 **Secondary Objectives**

2.21 To describe the pharmacokinetic parameters of d4T, 3TC and NVP in HIV-infected Thai children $\geq 6$ months to $< 13$ years of age in the weight range of $\geq 6$ to $\leq 30$ kg.

2.22 To evaluate the intra- and inter-subject variability of the pharmacokinetics of d4T, 3TC and NVP when administered as the GPO-VIR® Pediatric tablet(s) and as the individual liquid drug formulations.

2.23 To describe any adverse drug reactions due to the GPO-VIR® Pediatric formulation and the individual d4T, 3TC and NVP liquid formulations.

3.0 **STUDY DESIGN**

PACTG P1056 is a Phase I/II, two arm, randomized, open-label, multiple-dose comparative pharmacokinetic cross-over study that will be done in two stages. The study
is limited to specific sites in Thailand (Mahidol University/Siriraj Hospital and Queen Sirikit National Institute of Child Health, Bangkok). It will compare the levels of NVP, 3TC and d4T in children receiving the new GPO-VIR® Pediatric tablet to those in children receiving the individual liquid formulations.

Each study stage is divided into two steps. An initial regimen (Step 1) followed by cross–over into the alternate regimen. Advancement into the subsequent step (Step 2) will be dependent on 100% adherence in the 72 hours prior to the PK study. Case Report Forms (CRFs) specific to P1056 and tablet/liquid count will be used to assess subject adherence during this study.

3.1 Stage I

The first stage (Stage I) will provide initial safety data on the study drugs as well as preliminary information on bioavailability and the therapeutic adequacy of the two regimens. Stage I is not weight stratified, and the target is 8 evaluable HIV-infected children ≥12 kg to ≤30 kg who have been prescribed a HAART regimen (NVP + 2 NRTIs) and have been receiving a maintenance dose of NVP for a minimum of 4 weeks, in accordance with the Access to Care guidelines (1).

This four week stabilization period is a prerequisite for study entry and is intended to ensure adequate induction of P450 enzymes; clinical stability and likely adequate ARV adherence prior to enrollment and randomization for the pharmacokinetic cross-over study. This period will address concerns about NVP-associated skin rash, which usually occurs within the first six weeks of therapy (17).

To be eligible, children must be considered stable on treatment, (i.e. without acute opportunistic infection and with stable CD4+ cell counts and not considered an “immunological failure” as defined in Section 4.24). Stage I is designed with two-week periods on study drugs before PK studies are performed in order to obtain very early information about the possible toxicity or therapeutic inadequacy of the GPO-VIR® Pediatric tablet(s), a formulation that has not been studied in human subjects before. With the relatively short period between PK studies and the consequent need for relatively large blood volumes over time, only children ≥12 kg in weight will participate in Stage I.

Eligibility will be in accordance with the criteria in Section 4.1 and 4.2. Subject management will include stopping rules and monitoring in accordance with Section 6.0 and 8.0. The PK studies are detailed in Section 9.0. Stage II will be initiated once Stage I analyses are completed.
Adherence Assessments

Each subject’s ARV adherence will be evaluated by tablet count and amount of liquid remaining (i.e. difference in dispensed versus returned number of tablets and liquid study drug bottle weights, converted to an adherence percentage) and the responses to adherence questions on specific CRFs. Subjects will receive their study drugs at entry and any special instructions for administration. Drug administration procedures and adherence measurement procedures will be standardized for all subjects during the study period (see Appendix III). Early intervention, such as a home visit or frequent telephone follow-up, will be implemented, as necessary, to identify any potential adherence problems.

Adherence assessments will be done at screening in order to obtain baseline data and give reasonable assurance of subjects’ qualifications for the study. They will also be done in order to ensure eligibility for the first PK study (Day 14 in Step 1 and Day 28 in Step 2). Subjects will be admitted to the hospital on study Day 11 and 25, respectively, for a period of 3-4 days to verify that the specified criteria, 100% adherence in the past 72 hours, are met. The subject will be ineligible for the PK study if this adherence percentage is not met.

Adherence Assistance

Home visits will be attempted for every accessible subject during their first week of treatment in each of the regimens in the two study steps. Weekly phone follow up will also be used to determine compliance and improve adherence.

STEP 1: Initial Regimens (Weeks 1-2)

Upon entry (Day 0), subjects weighing ≥12 to ≤30 kg will be randomized to one of two treatment arms:

- Arm A: GPO-VIR® Pediatric tablet(s) [d4T 7 mg/3TC 30 mg/NVP 50 mg] orally q 12 hours.
- Arm B: d4T + 3TC + NVP liquid formulations orally q 12 hours. Equivalent doses of individual study drugs to those given in Arm A will be used (see Table 1, Section 5.1)

Study drug dosage will be based on body weight as measured at entry (Day 0). This dose is not expected to change in a two week period, and will not be adjusted for changes in weight. Drug administration is outlined in Section 5.12.
An intensive PK study will be done at the end of this two week period (Day 14). Eligibility for the PK study will be dependent on 100% adherence to the study drugs in the 72 hours prior to the PK study.

Subjects will be admitted to the hospital on study Day 11. During the PK study day, subjects will be required to fast for at least two hours before and one hour after study drug administration, if feasible. Adjustments may have to be made in this schedule, especially in the youngest children. See Section 9.0-Pharmacology Plan for PK study details.

STEP 2: Cross-over Regimen (Weeks 3-4)

Immediately following the PK study in Step 1, there will be a cross-over to the alternate formulations in each treatment arm.

Children in Arm A will be given instructions by the study staff and shown how to take the original liquid formulations while those in Arm B will receive instructions from the staff on how to take the GPO-VIR® Pediatric tablet(s) for the next two weeks. The dosages will be based on the subject’s weight on Day 0.

A second intensive PK study will be done at the end of this two week period (Day 28), with hospitalization on Day 25 to ensure adherence is achieved, in the same manner as outlined in Step 1.

After completing Stage I, all children will resume their pre-study ARVs (unless the treating clinician indicates otherwise).

Stopping rules for Stage I are defined in Section 6.3 - Study Management and Section 8.5 - Monitoring.

Stage II can only be initiated upon the completion of the Stage I analyses. A review of the Stage I results by an external panel may also be required.

PACTG P1056 will observe toxicities through clinical evaluation and laboratory monitoring for the expected 4-6 week treatment duration of Stage I as described in the Schedule of Evaluations in Appendix I. The December 2004 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 will be used. A safety follow-up period of 6 weeks [on study, off-study drugs, but on an ARV treatment] will bring the study duration to a maximum of 12 weeks.

CD4+ cell counts and viral load are measured at screening, entry and the end of Stage I (Day 28) or for early discontinuation, and for safety follow-up. Blood samples for laboratory evaluations (3 mL) will be collected on Day 14, and 28, in
conjunction with the PK studies (14 mL) and for off treatment follow-up, if needed. Schedule timelines may need to be adjusted, for toxicity or PK eligibility (see Section 6.0-Subject Management and Section 9.0- Pharmacology Plan for the respective study details).

If there is any left over plasma from any samples, it will be stored at the Thai sites for future PACTG and MOPH-approved HIV-related studies, in accordance with Thai IRB/EC guidelines.

Children who have participated in Stage I are ineligible for Stage II.

3.2 Stage II

Stage II (30-44 children) is weight stratified and designed with four-week periods on study drugs in order to permit smaller children to be studied, and also to increase data on toxicity over time for the main portion of the study.

Children are stratified by weight, ≥6 to ≤30 kg (n=30-44):

Group 1: ≥6-8 kg (n=6-8)
Group 2: >8-16 kg (n=8-12)
Group 3: >16-23 kg (n=8-12)
Group 4: >23-30 kg (n=8-12)

The sample size is expected to result in a maximum of 44 evaluable children. A minimum of 30 evaluable children is required for adequate statistical evaluation (see Section 8.4).

Adherence assessments and assistance are similar to the procedures described in Stage I. The Stage II Schedule of Evaluations is in Appendix II. Eligibility for the PK studies is the same as described for Stage I. The study steps outlined below for Stage II are the same as those in Stage I, except for length of time.

STEP 1: Initial Regimen (Weeks 1-4)

Upon entry (Day 0), all subjects will be stratified into four dosage groups based on body weight as measured at entry (see Table 1 in Section 5.1).

Subjects in each weight group will be randomized into one of two treatment arms (as described in Stage I):

- Arm A: GPO-VIR® Pediatric tablet(s) orally q 12 hours
• Arm B: \(\text{d}4\text{T} + 3\text{TC} + \text{NVP}\) liquid formulations orally q 12 hours
   Equivalent doses of individual study drugs to those given in Arm A will be used per Table 1, Section 5.1.

The dose will not be adjusted for weight during the study. An intensive PK study will be done at the end of this four week period (Day 28), including hospitalization to ensure adherence, which will begin on Day 25. Eligibility for the PK study, adherence and PK sampling will be as described in Stage I and the PK Plan, Section 9.0.

STEP 2: Cross-over Regimen (Weeks 5-8)

Immediately following the successful completion of the PK study in Step 1, there will be a cross-over to the alternate formulations in each treatment arm. The subject weight at Day 0 will be used to calculate the dose of the alternative regimen. Children in Arm A will switch to the original liquid formulations while those in Arm B will switch to the GPO-VIR® Pediatric tablet(s) for four weeks. A second intensive PK study will be done at the end of this four week period (Day 56), with hospitalization on Day 53, in the same manner as outlined for Step 1.

After completing Step 2, all children will resume their pre-study ARVs (unless the treating clinician indicates otherwise).

PACTG P1056 will observe toxicities through clinical evaluation and laboratory monitoring for the duration of Stage II, (8-18 weeks on study drug treatment and a 6 week safety follow-up period, off-treatment, for a maximum study duration of 24 weeks). The schedule of laboratory and clinical evaluations for Stage II of this study is outlined in Appendix II. Sample collection volumes, storage and PK sampling procedures and evaluability are as described previously for Stage I.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

PACTG P1056 will be site restricted to PACTU 8251 and 8252 in Bangkok, Thailand.

4.1 Inclusion Criteria

4.11 Weight: Stage I: \(\geq 12\) to \(\leq 30\) kg
     Stage II: \(\geq 6\) to \(\leq 30\) kg
4.12 Age: ≥6 months to <13 years old

4.13 A confirmed diagnosis of HIV infection defined as two positive assays from two different specimens from different days supported by documentation from the child’s medical record. At least one of the specified assays must be performed in a certified (DAIDS VQA) laboratory which is approved to perform the assay for protocol testing. The two results may be any combination of the following:

- Children ≤18 months of age: HIV DNA PCR or HIV RNA PCR (>10,000 copies/mL)
- Children >18 months of age: Licensed ELISA with confirmatory Western Blot, gel agglutination test, HIV DNA PCR or HIV RNA PCR (>10,000 copies/mL)

4.14 On a HAART regimen (NVP + 2 NRTIs); receiving a maintenance dose of NVP for at least 4 weeks prior to study entry and taking the current recommended oral dose every 12 hours. Didanosine (ddI) interacts with stavudine (d4T) and is disallowed within 30 days of study entry.

4.15 Females of child-bearing potential must have a negative pregnancy test at entry and must agree to use an adequate method of birth control that has been discussed with the site personnel. Hormonal birth control alone (e.g. pills, shots, or slow release inserts placed under the skin) would not be considered adequate. An effective, medically accepted barrier method of contraception [e.g., female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm, intrauterine device (IUD), others] must also be used during the study. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission. Use of an IUD may increase the risk of pelvic inflammatory disease.

4.16 Demonstrated ability and willingness to swallow/chew study drugs.

4.17 Willingness to be hospitalized for the PK study.

4.18 Parent or legal guardian able and willing to provide written informed consent.

For subjects to be eligible for Step 2, in both Stage I and II, the following requirements must be met:

- Successful completion of the PK study at the end of Step 1
• Females of child-bearing potential must have a negative pregnancy test at entry to Step 2 and must agree to continue to use an adequate method of birth control (as per 4.15).

To continue on Step 2:
• 100% adherence in the 72 hours prior to the PK study

4.2 Exclusion Criteria

4.21 The following laboratory toxicities within 14 days prior to entry:

• For children <2 years of age: Hemoglobin: ≤8 g/dL
• For children ≥2 years of age: Hemoglobin ≤9 g/dL
• Platelets: ≤75,000 mm$^3$
• AST (SGOT) or ALT (SGPT) or ALP: >3 x ULN
• Creatinine: >1 mg/dL
• Any other ≥Grade 3 laboratory toxicity

4.22 Vomiting >Grade 2 within 30 days prior to study entry.

4.23 Diarrhea >Grade 2 within 30 days prior to study entry.

4.24 Documented history of immunological failure defined as:

• For children ≤6 years of age: CD4+ percentage decrease of >30% from previous values within the previous 6 month period
• For children >6 years of age: CD4+ cell count decrease of >30% from previous values within the previous 6 month period.

Previous CD4+ values will be available from the baseline values collected upon entry to the ATC program, as well as from the 6 month follow-up visits recommended in the ATC guidelines.

4.25 Current treatment for an acute serious bacterial, viral, or opportunistic infection.

4.26 History of dose-limiting toxicity requiring treatment discontinuation of any of the study drugs.

4.27 Known hypersensitivity to any of the study drugs that will be assigned in this study.
4.28 Current surgical or medical problem affecting gastrointestinal motility or absorption (e.g., ileus, ulcerative colitis) or liver function.

4.29 Treatment with immune modulators, myelosuppressive, neurotoxic, pancreatotoxic, hepatotoxic or cytotoxic drugs within 30 days prior to study entry, excluding therapeutic vaccines.

4.210 Treatment with experimental drugs for any indication within 30 days prior to study entry.

4.211 Acute hepatitis due to any cause.

4.212 Chemotherapy for active malignancy.

4.213 Pregnancy

4.214 Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator’s opinion, would compromise the outcome of this study.

4.215 Inability or failure to provide a reliable means of contact, (e.g. telephone).

Subjects will be excluded from Step 2, in both Stage I and II, if the following occur:

- History of dose-limiting toxicity requiring treatment discontinuation of any of the study drugs.
- Known hypersensitivity to any of the study drugs that will be assigned in this study.

4.3 **Allowed Medications**

Antiretroviral study drugs as specified in the study drug regimens. Any other medication, prescribed by the child’s physician that is not listed in Section 4.4 will be allowed while on study.

4.4 **Disallowing Medications**

4.41 Didanosine (ddl, [Videx® - Bristol-Myers Squibb]; DIVIR®, chewable buffered tablets, 125 mg, and DIDANOSINE BUFFERED ORAL POWDER (30, 60, 167, 230 and 285 mg)-GPO) interacts with stavudine (d4T) and is disallowed within 30 days of study entry.
4.42 Concomitant medications:

Below is a list of selected concomitant medications. This list is only current as of the date of this protocol. Therefore, whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agents' most recent package inserts, Investigator's Brochures, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Concomitant use of any of the following is disallowed:

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>US Brand Name</th>
<th>Thai Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>Zithromax</td>
<td>Zythromax</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Biaxin</td>
<td>Klacid, Klacid MR, Clarith, Claron, Cri xen, Fascar,</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Sporonox</td>
<td>Candidtral, Icona, Itra, Itracon, Norspor, Spazol, Sporal, Sporlab, Spornar,</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nizoral, Ketoconazole</td>
<td>Diazon, Fungazol, Fungiderm-K, Funginox, Katsin, Kazinal, Kenazol, Kenoral, Ketazol, Ketazon, Ketocine, Ketomed, Ketoconazole, Ketosil, Ketoza l, Manoketo, Masarol, Mizoron, Ninazol, Nizoral, Pasalen, Sporoxyl</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifadin, Rimactane, Rifamate, Rifampicin</td>
<td>Manorificin, Myrin, Myrin-P, Ramfin, Rampicin, Ricin, Ridafour e-200, Rifamcin, Rifampyrid, Ricinis, Rifagen, Rifano, Rifater, Rifinah, Rifam, Rifam-P, Rifamed, Rifadin, Rrifodex, Rimactane, Rimcur e 3-FDC, Rimactazid, Rimecin, Rimstar 4-FDC, RP-Pose, Tibirim,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>US Brand Name</th>
<th>Thai Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine,</td>
<td>Carbato1, Tegretol, Carbama zapine</td>
<td>Antafit, Carbatol, carbazene, Carmap ine, Carpine, Carzepine, Mazepeine, Panitol, Taver, Tegretol, Zeptol- CR</td>
</tr>
<tr>
<td>Phenobarbital,</td>
<td>Donnatal, Phenobarbital</td>
<td>Benera, Gardenal sodium, Menobarb, Neuramizone, Phenobarbital Atlantic, Phenotal</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Dilantin, Phenytoin</td>
<td>Dantoin, Dilantin, Dtoin, Ditomed, Fenitoina Rubio, Pepsytoin-100</td>
</tr>
<tr>
<td>Prednisone (within the first 6 weeks of NVP therapy, prednisone is not recommended to prevent NVP-associated rash per the Viramune® package insert [17])</td>
<td>PredniSONE, Prednisone</td>
<td>(Underlined brand indicates oral administration; all others external application) Denson, Di-Adreson F, Farakil, Inf-Oph, Levoptin simplex, Mysolone-N, Neosolone, Opredson, Polypred, Pred Forte, Pred Mild, Pred-Oph, Prednerson, Prednisil, Prednisil-N, Prednisolone Atlantic, Prednisolone Pharmasant, Unipred</td>
</tr>
<tr>
<td>St. John’s wort (herb)</td>
<td>Hypericum perforatum</td>
<td>St. John’s wort</td>
</tr>
</tbody>
</table>
4.5 **Enrollment Procedures**

Protocol registration must occur through the Regulatory Compliance Center (RCC) Protocol Registration Office. Before subjects can be enrolled in the study, protocol registration materials must be sent electronically to epr@tech-res.com. Prior to implementation of this study, each Thai site must have the protocol document and the consent form approved by the local Institutional Review Board (IRB)/Ethics Committee (EC).

A team-approved Protocol Implementation Plan (PIP), for the Thai sites and sub-units participating in P1056, must be on file with PACTG/DAIDS prior to protocol registration for Version 1.0.

Eligible children who elect to participate and meet study entry criteria will be enrolled according to standard Data Management Center (DMC) procedures, using the Subject Enrollment System (SES). Step 1 will require randomization and registration using the SES. Screening evaluations must be completed within two weeks prior to the start of each stage of the study (Entry Day 0). Step 2 will require registration using the SES.

4.6 **Co-enrollment Guidelines**

Co-enrollment into any other protocols is discouraged. However, if co-enrollment into PACTG 219C (or similar international version) becomes possible, it will be strongly encouraged. If co-enrollment of a subject is considered, approval will be contingent upon the assent of the PACTG P1056 Chair and Co-Chairs.

5.0 **STUDY TREATMENT**

5.1 **Drug Regimens, Administration and Duration**

5.11 Regimen (Stages I and II):

Eligible subjects will be randomized to one of two initial regimens using the DMC SES system. A prescription with the SID number must be written for the pharmacist to dispense Step 1 study drugs.
STEP 1: Initial regimens (Table 1)

Stage I – Weeks 1-2
Stage II - Weeks 1-4

Arm A:

GPO-VIR® Pediatric tablet(s) [d4T 7 mg/3TC 30 mg/NVP 50 mg], orally, q 12 hours

Dose per weight is calculated on Day 0 according to the dosage for each individual study drug and given according to the group weight range-dose recommendation (Table 1); administered orally q 12 hours, approximately 8 AM and 8 PM. Doses will not be modified if the weight changes during the study.

Arm B:

3TC + d4T + NVP liquid formulations administered orally q 12 hours (Table 1):

- Lamivudine (3TC); dose by weight as in Table 1
- Stavudine (d4T); dose by weight as in Table 1
- Nevirapine (NVP); dose by weight as in Table 1
Table 1. GPO-VIR® Pediatric Dose per Body Weight and the Corresponding Liquid Formulation Doses to be used for Step 1 and 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Wt (kg)</th>
<th>Number of Subjects per Group</th>
<th>GPO-VIR® Pediatric Tablet</th>
<th>Liquid Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of Tablet(s) per dose</td>
<td>3TC dose 10 mg/mL</td>
<td>d4T dose 1 mg/mL</td>
</tr>
<tr>
<td>1</td>
<td>≥6-8</td>
<td>(6-8)</td>
<td>1</td>
<td>30 mg (3 mL)</td>
</tr>
<tr>
<td>2*</td>
<td>&gt;8-13</td>
<td>(8-12)</td>
<td>1.5</td>
<td>45 mg (4.5 mL)</td>
</tr>
<tr>
<td></td>
<td>&gt;13-16</td>
<td></td>
<td>2</td>
<td>60 mg (6 mL)</td>
</tr>
<tr>
<td>3*</td>
<td>&gt;16-19</td>
<td>(8-12)</td>
<td>2.5</td>
<td>75 mg (7.5 mL)</td>
</tr>
<tr>
<td></td>
<td>&gt;19-23</td>
<td></td>
<td>3</td>
<td>90 mg (9 mL)</td>
</tr>
<tr>
<td>4*</td>
<td>&gt;23-27</td>
<td>(8-12)</td>
<td>3.5</td>
<td>105 mg (10.5 mL)</td>
</tr>
<tr>
<td></td>
<td>&gt;27-30</td>
<td></td>
<td>4</td>
<td>120 mg (12 mL)</td>
</tr>
</tbody>
</table>

*Note: For Stage I, all 8 evaluable children will be ≥12 to ≤30 kg, study drug dosages will be based on weight at Day 0, according to this table (shaded areas).

The PK study day fasting schedule and allowed liquids and foods will be standardized as much as possible given the age group and hospital meals to be provided (see Section 9.2). Immediately after the satisfactory completion of the PK study in Step 1 (i.e. the predose and at least 5 of 6 postdose samples were collected, and all information recorded on the appropriate CRF, see Section 9.21) subjects will switch treatment regimens. Subjects must be registered to Step 2 through the DMC SES system. A new prescription with the new SID number must be written for the pharmacist to dispense Step 2 study drugs. (Ineligible subjects, i.e. those that need to reschedule the PK study, or those that discontinue study drugs for toxicity or other reasons, will remain in Step 1, until either eligible for Step 2 or off-study drugs. Follow-up for safety will continue until the defined end of the study, for both Stage I and Stage II.

STEP 2: Cross-over regimen

Stage I – Weeks 3-4
Stage II – Weeks 5-8
Arm A:

3TC + d4T + NVP liquid formulations, administered orally q 12 hours:

- Lamivudine (3TC); dose by weight as in Table 1.
- Stavudine (d4T); dose by weight as in Table 1
- Nevirapine (NVP); dose by weight as in Table 1.

Arm B:

GPO-VIR® Pediatric tablet(s), [d4T 7 mg/3TC 30 mg/NVP 50 mg] administered orally q 12 hours per Table 1.

5.12 Drug Administration

GPO-VIR® Pediatric tablet(s) are specifically formulated to be chewable, and will be chewed whenever possible. The tablets are scored, to facilitate division into halves. Subjects unable to chew the tablet or who refuse to chew the tablet will be allowed to either crush or swallow the tablet(s) with water. The tablet(s), should be crushed in a mortar (glass), see Appendix III for supply information).

Tablets will be crushed using the mortar and pestle (split the tablet, if necessary, and place the required half in the glass mortar). Crush the tablet(s) to a powder with the pestle. Add water (3-5 mL) directly to the powder in the mortar, and have the subject drink the resulting suspension immediately, using the mortar as a cup. Add water (3-5 mL) to rinse any remaining residue, and have the subject drink the remainder.

Subjects prescribed the liquid formulations will receive equivalent doses of 3TC, d4T and NVP, by weight, as in the GPO-VIR® Pediatric tablet. Oral syringes and instructions will be provided.

3TC, d4T and NVP oral suspension/solution

- Each liquid formulation will be administered every 12 hours, with or without food

GPO-VIR® Pediatric tablet
[d4T 7 mg/3TC 30 mg/NVP 50 mg]
• Chewable tablet(s) will be administered every 12 hours, with or without food.

5.13 Duration

For Stage I, the study treatment is a minimum of 4 weeks, which may extend to a maximum of 6 weeks, dependent on adherence, toxicity/tolerability and/or the need to repeat PK studies. A 6 week follow-up period for safety (on study, off study drug treatment, but on a resumed ARV treatment regimen) will bring the maximum study duration to 12 weeks.

For Stage II, study treatment is a minimum of 8 weeks, which may be extended to a maximum of 18 weeks, dependent on adherence, toxicity/tolerability, and/or the need to repeat PK studies. A 6 week follow-up period for safety [on study, off study drug treatment, but on a resumed ARV treatment regimen] will bring the maximum study duration to 24 weeks.

5.2 Drug Formulation

5.21 Nevirapine (NVP, Viramune®): 10 mg/mL oral suspension:

NVP oral suspension is a white to off-white preserved suspension containing 50 mg NVP (as nevirapine hemihydrate) in each 5 mL. The oral suspension should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Store in a safe place out of the reach of children.

5.22 Lamivudine (3TC, Epivir®): 10 mg/mL oral solution.

3TC oral solution is a clear, colorless to pale yellow, strawberry-banana flavored liquid, containing 10 mg of lamivudine in each mL. This product does not require reconstitution. Store in tightly closed bottles at 25°C (77°F).

5.23 Stavudine (d4T, Zerit®):

A dye free, fruit flavored powder yielding a 1 mg/mL strength following reconstitution. Prior to reconstitution, stavudine powder should be stored at room temperature, 15-30°C (59-86°F). Reconstitute the powder with 202 mL of Purified Water, USP to obtain a concentration of 1 mg/mL of stavudine for a deliverable volume of 200 mL. Dispense solution in the original container. After reconstitution, the oral solution should be stored
in a refrigerator at 2-8°C (36-46°F). The reconstituted solution is stable for 30 days. Shake the container vigorously prior to measuring each dose. Discard any unused portion after 30 days.

5.24 GPO-VIR® Pediatric tablet:

Each pale yellow, citrus-flavored, scored tablet contains 7 mg d4T + 30 mg 3TC + 50 mg NVP. Store in tightly closed bottles below 25°C (77°F). [This is a new product, based on the active ingredients in the GPO-VIR® S30 tablet, but formulated specifically for children. A package insert is not currently available, as the product is being tested IAW GMP and ISO standards].

Available information is based on the GPO-VIR® S30 and S40 formulation, www.gpo.or.th. GPO is working with the US FDA on a New Drug Application (NDA) submission for GPO-VIR® S30. NDA 21-886, was assigned in May, 2005. GPO-VIR® is also under consideration by the World Health Organization (WHO) for their ARV program. GPO has submitted a packet to the WHO for their pre-qualification program. See http://mednet2.who.int/sourcesprices/sources.pdf for a list of ARVs. GPO products conform to Good Manufacturing Practice (GMP) and International Standard Operation (ISO) Standards.

5.3 Drug Supply, Distribution and Pharmacy

5.31 Supply

- GPO-VIR® Pediatric tablets will be provided by the Government Pharmaceutical Organization (GPO), Thailand.

- Lamivudine (3TC); Epivir® liquid (GlaxoSmithKline; 10 mg/mL; (240 mL bottles) will be provided by GlaxoSmithKline (GSK). Specific gravity of the solution is 1.08 mg/mL (typically).

- Nevirapine (NVP); Viramune® liquid (Boehringer Ingelheim; 50 mg/mL suspension) will be provided through GPO. Specific gravity is 1.1 g/mL.

- Stavudine (d4T); Zerit® liquid (Bristol Myers-Squibb; 1 mg/mL/200 mL) will be provided through GPO. Specific gravity is 1.020 mg/mL.
5.32 Study Supply Acquisition

Study materials will be available through the NIAID Clinical Research Products Management Center. The PACTU pharmacist can obtain the study agents for this protocol by following the instructions in the manual “Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks” in the section Study Product Control. Oral syringes, glass mortar and pestle (if needed) will be supplied by the study site staff (see Appendix III).

GPO-VIR® Pediatric tablets and the brand name liquid study drugs used in P1056 will not be provided to subjects prematurely discontinuing the study or after study termination. The study staff will discuss other options based on the best benefit to the subject, the results of the study to date and availability, in accordance with regulatory agencies. An alternative ARV will be prescribed by the subject’s physician if the FDC pediatric formulation has not been approved by the Thai FDA for treatment of HIV in pediatric subjects by that time.

5.33 Study Agent Accountability

The PACTU pharmacist is required to maintain complete records of all study medication received from the NIAID Clinical Research Products Management Center and subsequently dispensed. All unused study medication must be returned to the NIAID Clinical Research Products Management Center after the study is completed or terminated. The accountability procedures to be followed are provided in the manual, Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, in the section on Study Product Control. Non-US site pharmacists should contact the Pharmaceutical Affairs Branch (PAB) protocol pharmacist for further instructions before returning any study products.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 [December 2004]) http://rcc.tech-res-intl.com will be used for screening eligibility and for grading toxicities. Alternate explanations for clinical or laboratory abnormalities that may at first appear to be related to the
study drug(s) must be explored. The use of reduced doses of the study drugs is not allowed.

General toxicity management guidelines are provided below. The management of specific adverse events is detailed in Section 6.2 and supercedes the general guidelines for the following: Skin Rash/Cutaneous Dermatitis (6.21), Clinical Pancreatitis (6.22), Hyperlipasemia (6.23), Hyperamylasemia (6.24), ALT/AST Increases, Lactic Acidosis and Clinical Hepatitis or Hepatitis Steatosis (6.25), Peripheral Neuropathy (6.26), and Neutropenia and Anemia (6.27).

All ARVs prescribed for the entry regimens (Step 1, Day 0) and cross-over regimens (Step 2) in Stage I (and subsequently, Stage II if stopping criteria are met) will be considered study drugs (see Section 7.0).

Note: Whenever a toxicity grade includes the use of the “ULN”, as part of the calculation of the toxicity grade itself, sites must follow:
• "ULN" values reported by the laboratory report for the test, or
• "ULN" values routinely used/established by the site

For abnormal clinical or laboratory observations of:

<table>
<thead>
<tr>
<th>Grade 1:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continue study treatment</td>
</tr>
<tr>
<td>• Routine monitoring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>For cutaneous toxicity (Refer to Section 6.21).</td>
</tr>
</tbody>
</table>

For non-cutaneous Grade 2 toxicities:
• Continue study treatment.
• Monitor closely with more frequent visits.
• Work-up to exclude other causes.

<table>
<thead>
<tr>
<th>Grade 3 and non-life threatening Grade 4*:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Repeat observation within 72 hours for confirmation.</td>
</tr>
</tbody>
</table>

For cutaneous toxicities (Refer to Section 6.21).

For non-cutaneous toxicities:
• Subjects may continue taking study drugs, pending receipt of the confirmatory laboratory tests. The clinician has the option of immediately interrupting the study drugs if a repeat confirmatory laboratory test cannot be performed within 72 hours, or if the clinician determines that the continuation of study drugs is unsafe while awaiting test results.

• If the clinician and the P1056 protocol team decide that a Grade 3 non-cutaneous toxicity is definitely, probably or possibly study drug-related (that is, it is a serious toxicity of one or more of the study drugs, e.g. hepatitis, pancreatitis, peripheral neuropathy, lactic acidosis without other identified etiology), then study drugs will be permanently discontinued, the subject will come off study drugs, but follow-up will continue, i.e. off study treatment but on study. Such subjects should be followed and remain on study with appropriate clinical and/or laboratory monitoring until toxicity has resolved to Grade 2 or less. (See Section 8.51 and SADR reporting requirements).

• If the clinician and the P1056 protocol team decide that the confirmed Grade 3 non-cutaneous toxicity is not related to one or more of the study drugs (that is, the toxicity is not one of the serious toxicities of lamivudine, stavudine, or nevirapine and/or their combinations; e.g. headache, loss of appetite anemia) then the subject may remain on treatment with close follow-up, if that is determined to be the best treatment option. Study drugs may also be discontinued, with close clinical and laboratory follow-up until the toxicity resolves to Grade 2 or less.

This waiting period may be up to 7 days. If the toxicity resolves, treatment with study drugs should be resumed in full doses. The interval between restarting study drugs and the PK studies should be at least 14 days, and the study calendar (Step 2) should be altered to reflect this change, if necessary.

• If, after discontinuation of study drugs, toxicity persists at Grade 3 for more than 7 days or recurs on re-challenge, all study drugs must be permanently discontinued, and the subject will come off treatment, but follow-up on study will continue. Such subjects should be followed with appropriate clinical and/or laboratory monitoring until toxicity has resolved to Grade 2 or less. Clinicians and the protocol team will consult on treatment options on a case-by-case basis.
Grade 4*:
For cutaneous toxicity (Refer to section 6.21).

For non-cutaneous toxicity:

- Hold study treatment and notify the P1056 protocol team to determine course of action, actg.teamp1056@fstrf.org. Obtain confirmatory laboratory results within 72 hours and notify the P1056 protocol team of those results.

- For all confirmed (via laboratory results or verification by the site clinician by exam or detailed consistent history) non-cutaneous Grade 4 toxicities, all study drugs must be stopped, and the protocol team must be notified within 48 hours through an e-mail message to actg.teamp1056@fstrf.org. Clinicians must contact the Protocol Chair and Co-Chairs in Thailand by telephone or FAX* (see next page and Section 8.51).

- If the clinician and the protocol team decide that a confirmed non-cutaneous Grade 4 toxicity is study drug-related, then study drugs will be permanently discontinued. The subject will come off treatment, but follow-up will continue on study. Such subjects should be followed with appropriate clinical and/or laboratory monitoring until toxicity has resolved to Grade 2 or less. (See Section 8.51).

- If the clinician and the protocol team decide that there is reasonable doubt that a confirmed non-cutaneous Grade 4 toxicity is due to one or more of the study drugs, then the subject may remain on study but off treatment with close clinical and laboratory follow-up until the toxicity resolves to Grade 2 or less.

  This waiting period may be up to 7 days. If the toxicity resolves, treatment with study drugs should be resumed in full doses. The interval between restarting study drugs and the PK studies should be at least 14 days, and the study calendar (Step 2) should be altered to reflect this change, if necessary.

- If, after discontinuation of study drugs, toxicity persists at Grade 4 for more than 7 days or recurs on re-challenge, all study drugs must be permanently discontinued, and the subject will come off treatment, but on study follow-up will continue with appropriate clinical and/or laboratory monitoring until toxicity has resolved to Grade 2 or less. Clinicians and the protocol team will consult on treatment options on a case-by-case basis.
*NOTIFICATION REQUIRED*

Send an e-mail to the protocol team at actg.teamp1056@fstrf.org *(immediately or within 48 hours of the event.)* Please provide the team with all confirmatory laboratory results for the following toxicities:

- Skin rash/cutaneous dermatitis ≥Grade 2-*immediately*
- Confirmed* cutaneous toxicity ≥Grade 2-*within 48 hours*
- Hyperlipasemia ≥Grade 2-*immediately*
- Signs/symptoms of pancreatitis-*immediately*
- Signs/symptoms of hepatitis-*immediately*
- Confirmed lactate level ≥Grade 2-*immediately*
- All other confirmed Grade 3 and 4 toxicities-*within 48 hours*

*defined as verified by the clinician at the site either by exam or detailed consistent history*

Thailand is 11 hours ahead of US EDT and 12 hours ahead of US EST.

**Site 8251:** Dr. Nirun Vanprapar, Dr. Kulkanya Chokephaibulkit or Dr. Wasana Prasitsuebsai: 662-418-0545, Nongluck Seetapun: 622-418-0545; FAX: 662-418-0544

**Site 8252:** Dr. Tawee Chotpitayasunondh, Dr. Naris Waranawat, Dr. Piyarat Suntarattiwong and Sirinya Somsaen 662-246-0054 ext. 3913 and FAX: 662-246-0382.

The P1056 protocol team roster lists contact information for all team members.

6.2 Management of Specific Adverse Events

All toxicities that are ≥Grade 1 will be collected on PACTG P1056 study forms. (Follow EAE reporting guidelines)

The following specific adverse events will be managed as indicated:

6.21 Skin Rash/Cutaneous Dermatitis

Rashes which meet the criteria for ≥Grade 2 using the DAIDS Table (Version 1.0) must be reported immediately to the P1056 Team by e-mail at actg.teamp1056@fstrf.org.

For subjects who develop cutaneous reactions ≥Grade 2 with any of the following signs/symptoms, study drugs should be immediately discontinued. Sites should contact the protocol Chair and Co-Chairs for
PACTG Thailand Sites to receive instructions on course of action:

- Systemic symptoms (such as fever, nausea, or vomiting) if clinically relevant
- Allergic symptoms (such as pruritus, angioedema, wheezing, bronchospasm, laryngeal edema, anaphylaxis, or hypotension).
- Generalized rash or
- Exfoliation
- Target lesions
- Mucosal involvement

Subjects who report a rash, but cannot be seen immediately, will be told by the investigators to discontinue study drugs if the description of the rash matches the Grade 2 or higher criteria. Subjects will be instructed to come to the clinic as soon as possible.

For confirmed*Grade 2 or greater cutaneous toxicities, discontinue all study drugs and notify the protocol team within 48 hours at actg.teamp1056@fstrf.org.

*Confirmed is defined as a repeat observation by the site investigators, to be done as soon as possible within 48 hours, based on the appearance of the rash and matching the descriptions listed for Cutaneous reaction-rash in the DAIDS Table (Version 1.0).

If the clinician and protocol team determine the toxicity is definitely, probably or possibly related to one of the study drugs, the subject will come off study treatment. (SADR reporting, Section 7.0, also see Section 8.51).

If subjects present with a suspected study drug-related rash, liver function tests must be performed. Subjects with rash-associated AST or ALT elevations (i.e. Grade 2: [>2.5 x ULN], Grade 3: [>5.0-10.0 x ULN]) or greater should permanently discontinue Viramune®. Subjects must be monitored closely if isolated rash of any severity occurs. Subjects will remain on study for follow-up until the toxicity resolves to Grade 2 or less.

All study drugs must be permanently discontinued for any study drug-related Grade 3 or 4 rash as defined in the DAIDS Table for Grading the Severity of Adults and Pediatric Adverse Events, Version 1.0 (December 2004). Notify the protocol team at actg.teamp1056@fstrf.org.
6.22 Clinical Pancreatitis

If a subject develops nausea, vomiting, or abdominal pain of any grade associated with any elevation of serum fractionated pancreatic amylase or lipase, or develops a clinical syndrome that in the opinion of the subject's clinician is classified as pancreatitis, study drugs should be permanently discontinued. Future consideration should be given to avoiding drugs potentially affecting the pancreas. Notify the protocol team at actg.teamp1056@fstrf.org. (See EAE reporting).

6.23 Hyperlipasemia

For elevations of lipase in blood, follow this algorithm:

- For Grade 2 hyperlipasemia (>1.5 x ULN), consider holding all study drugs, notify the protocol team at actg.teamp1056@fstrf.org immediately, schedule follow-up visits every two weeks if necessary until toxicity resolves to Grade 1 or less.
- For any Grade 3 hyperlipasemia (>3.0 x ULN), hold all study drugs until both lipase and pancreatic amylase are Grade 1 or less. Notify the protocol team at actg.teamp1056@fstrf.org immediately.
- For Grade 4 hyperlipasemia (>5.0 x ULN), all study drugs should be held and may be permanently discontinued, do not restart until both lipase and pancreatic amylase are Grade 1 or less. Notify the protocol team at actg.teamp1056@fstrf.org immediately to determine course of action. If hyperlipasemia recurs, discontinue all study drugs.

6.24 Hyperamylasemia

Management of this toxicity will be prompted for a Grade 3 or 4 hyperamylasemia.

Upon presentation of Grade 3 or 4, the amylase should be fractionated and the pancreatic fraction should then be used to determine the toxicity management. (See Laboratory section, pancreatic amylase parameter, pg. 19 of 20 of the DAIDS Toxicity Table, Version 1.0).

Additionally, a lipase should also be obtained and the following algorithm applies: (Remember that this is done as secondary assay to a Grade 3 or 4 hyperamylasemia. Hyperlipasemia alone must be managed as described in the previous section).
• If there is an elevation in lipase, hold all study drugs until both pancreatic amylase and lipase are Grade 1 or less. Notify the protocol team at actg.teamp1056@fstrf.org immediately.

• Pending the results of the fractionated amylase evaluation if the lipase is normal, study medications may be continued. Notify the protocol team at actg.teamp1056@fstrf.org.

• Once available, fractionated pancreatic amylase elevations should be managed per the toxicity grade as described in Section 6.1.

6.25 Increases in Values for ALT and/or AST:

The following algorithm for management of this toxicity should be observed:

• For all Grade 2 ALT and/or AST values, monitor the subject every two weeks or more often until values return to Grade 1. Notify the protocol team at actg.teamp1056@fstrf.org.

• In general, all Grade 2 ALT and/or AST values or higher, should be reported to the P1056 protocol team every other week.

• Elevations in ALT and/or AST values should be managed based on the toxicity grade.

6.251 Lactic Acidosis

Development of lactic acidosis is considered a toxicity endpoint. Lactic acidosis and liver dysfunction syndrome have been associated with NRTIs (mono-and combination therapies).

• Lactate level will be obtained for subjects with ALT and AST values above 2.5 x ULN with no easily discernable etiology (e.g. acute hepatitis A, B, C, or chronic hepatitis B or C), or for subjects who have a new and persistent, otherwise unexplained findings of nausea, vomiting, abdominal pain, abdominal distension, unexplained fatigue and dyspnea.

• If the lactate level is ≥2.0 x ULN without acidosis (Grade 2), confirmed by a repeat level within 72 hours, and obtained by standard techniques for the specimen, stop all study drugs immediately and contact the protocol Chair and Co-chairs (PACTG P1056 Thailand Sites). Also, send an e-mail to the protocol team actg.teamp1056@fstrf.org. The protocol team
will work with the subject's clinician to determine the best course of action.

6.252 Clinical Hepatitis or Hepatic Steatosis

Subjects should be monitored for the development of non-specific prodromal signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels per the DAIDS Grading Table, Laboratory values (Version 1.0).

- Subjects with signs and symptoms of hepatitis must have LFTs performed.
- All study drugs must be permanently discontinued immediately if ALT or AST is even one grade higher than baseline.
- Subjects with normal AST and/or ALT levels who have symptomatic clinical hepatitis must also permanently stop all study drugs immediately.
- The above three situations require notification to the protocol team at actg.teamp1056@fstrf.org. Subjects who develop hepatic steatosis must immediately and permanently discontinue study treatment. Notify the protocol team at actg.teamp1056@fstrf.org.

6.26 Symptoms of Peripheral Neuropathy

For grading symptoms of peripheral neuropathy, follow the DAIDS Table, (Clinical/Neurologic/parameter: neuromuscular weakness, pg. 10 of 20, Version 1.0).

- Grade 2: Subjects should be watched closely with visits or telephone calls every week or more frequently in order to ensure that symptoms are indeed transient.
- Grade 3 and Grade 4: Symptoms should be managed in the general way Grade 3 and Grade 4 toxicities are managed, as indicated in Section 6.1.
- It should be noted that infectious agents other than HIV can precipitate a neuropathy and should be considered, especially Cytomegalovirus (CMV). Neuropathies which do not resolve after discontinuation
should be pursued for alternative infectious or non-infectious etiologies, since drug-related neuropathies will usually resolve after drug discontinuation.

- It should be borne in mind that many subjects will worsen for up to one month after drug discontinuation prior to improvement ("coasting"). Suspected neuropathies should be confirmed by neurological examination, and if warranted, nerve conduction studies (NCS) +/- electromyographic studies (EMG).

Contact the protocol team via e-mail at actg.teamp1056@fstrf.org if you have any doubts on how to proceed after observing specific symptoms of peripheral neuropathy.

6.27 Neutropenia and Anemia:

Erythropoietin and/or G-CSF/GM-CSF may be administered. Neutropenia and anemia are managed as illustrated in Figure 1.

FIGURE 1: Management of Neutropenia and Anemia

Neutropenia or anemia ≥Grade 3, thought to be study drug related: Repeat laboratory measurement within 72 hours to confirm, then monitor weekly

Recovery to ≤Grade 2 (w/in 7 days): Restart study drugs at full dose

Return to ≥Grade 3

Recovery maintained ≤Grade 2 (for ≥7 days)

Continue study drugs at full dose

No recovery

Stop study drugs and contact the Protocol Chair and Co-chairs to determine course of action.

Stop study drugs and contact the Protocol Chair and Co-chairs to determine course of action.
6.3 Study Management Plan

6.3.1 Stopping Rules for Stage I

The study will be stopped if two or more subjects experience one or more of the following conditions definitely, probably or possibly related to treatment with the GPO-VIR® Pediatric tablet (Stage I, Step 1/Arm A or Step 2/Arm B):

- Confirmed ≥Grade 3 cutaneous toxicity or
- Confirmed ≥ Grade 3 non-cutaneous toxicity or
- Confirmed ≥ Grade 2 lactate

Enrollment to Stage I will be suspended temporarily if two or more subjects experience persistent or recurring confirmed ≥Grade 2 cutaneous toxicities that are definitely, probably or possibly related to any of the components in the GPO-VIR® Pediatric tablet. The team will evaluate these cases in accordance with Section 6.1 - Toxicity Management and 6.21 - Skin Rash/Cutaneous Dermatitis and SADR requirements for nevirapine.

The study can also be stopped, after Stage I is completed, if it is determined that the GPO-VIR® Pediatric tablet is therapeutically inadequate as defined in Section 8.51.

Any additional events considered study treatment related identified during subsequent clinical visits or via telephone contact should be reported to the protocol team within 48 hours. (Follow EAE reporting requirements, if applicable). The safety follow-up period for Stage I is six weeks.

Stage II

Based on the outcomes of Stage I, subject management will be similar in Stage II, and stopping rules should be unnecessary. Subjects will be followed on study and/or off treatment until the final scheduled visit (Day 56, or later, if an extension is necessary) or until the toxicity has resolved. An additional 6 week period for safety follow-up, will be included in Stage II. The maximum study duration for Stage II is 24 weeks.
6.32 PK Study Management

6.321 Eligibility

Eligibility for the PK study will be dependent upon:

- 100% adherence to the ARV regimen in the 72 hours prior to the PK study. Subjects will be admitted to the hospital prior to the PK study days. See Section 9.0-Pharmacology Plan for PK study details.

6.322 PK Study

- If either the predose sample or more than one of the six postdose samples are not obtainable, the subject will be requested to continue treatment for at least 3 days, and then repeat the entire PK study per the Clinical Pharmacology Plan (Section 9.0).

- If emesis occurs within 2 hours of study drug administration during an intensive PK Day, the rest of the PK study will be postponed, and the PK study will be rescheduled. See Section 9.22 for repeat PK guidelines.

- Replacement of subjects will be allowed, to cover unforeseen circumstances, (e.g. PK samples unevaluable due to improper storage or damage during shipping, or subjects unable to complete the study).

If no adverse events have occurred after the last PK time point (12 hours post dose) of the second PK Study (Day 28 of Stage I and Day 56 of Stage II, respectively) or a repeated PK study, if necessary, the subject can be considered off study treatment. Follow-up for safety will continue.

6.4 Criteria for Study Discontinuation

- The subject or legal guardian refuses further participation and/or follow-up evaluations.
- The clinician determines that further participation would be detrimental to the subject's health or well-being.
7.0 EXPEDITED ADVERSE EVENT REPORTING

Expedited Adverse Event Reporting to DAIDS

The expedited adverse event (EAE) reporting requirements and definitions for this study and the methods for expedited reporting of adverse events (AEs) to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual) dated May 6, 2004. The DAIDS EAE Manual is available on the RCC website: [http://rcc.tech-res-intl.com/](http://rcc.tech-res-intl.com/).

AEs reported on an expedited basis must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: [http://rcc.tech-res-intl.com](http://rcc.tech-res-intl.com).

EAE Reporting Requirements for this Study

EAE Reporting Level

This study uses the Intensive Level of expedited AE reporting as defined in the DAIDS EAE Manual.

Intensive Level: “In addition to all adverse events reported for the Standard Level, also report all Grade 3 suspected adverse drug reactions (SADRs), i.e. definitely, probably, possibly, and probably not related to a study agent” (the Intensive Level includes reporting Grades 3 and 4 SADRs). Additional grades or types of AEs to be reported to DAIDS on an expedited basis are:

- The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
- The subject requires treatment with medications that are disallowed while on this study (see Section 4.4).
- The subject experiences toxicity of Grade 3 or Grade 4 that does not resolve after discontinuation of study drugs, or persistent or recurring ≥Grade 2 cutaneous toxicity, or meets other toxicity endpoints (i.e. lactic acidosis, clinical hepatitis).
- Stopping criteria are met in Stage I.
- The study may be discontinued at any time by the NIAID, Office of Human Research Protection (OHRP), the FDA, IRB or local (Thai) governmental regulatory agencies, as part of their duties to ensure that research subjects are protected.
• Grade 2 or higher cutaneous toxicities that are clearly NVP-related
• Confirmed pancreatitis
• Confirmed lactic acidosis
• Hepatitis related symptoms, AST/ALT elevations one grade higher than baseline, or confirmed hepatic steatosis

Study Agents for Expedited Reporting to DAIDS

The study agents that must be considered in determining relationships of AEs requiring expedited reporting to DAIDS are:

• Lamivudine (3TC)
• Nevirapine (NVP)
• Stavudine (d4T)
• GPO-VIR® Pediatric tablet [d4T 7 mg/3TC 30 mg/NVP 50 mg]

Grading Severity of Events

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December, 2004 must be used for grading toxicities. It is available on the RCC website at http://rcc.tech-res-intl.com/ and a copy must be available at each site.

EAE Reporting Periods

AEs must be reported on an expedited basis at the Intensive Level during the Protocol-defined EAE Reporting Period, which is:

• The entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason) and for as long as is necessary for any toxicity to resolve, if applicable; after the subject’s last study visit has been completed. For Stage I and II, safety follow up for 6 weeks, after study drug dosing, for a maximum study duration of 12 and 24 weeks, respectively.

• After the end of the Protocol-defined EAE Reporting Period stated above, sites must report serious, unexpected, clinical suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.
DAIDS EAE forms should be submitted to DAIDS through the Regulatory Compliance Center (RCC) Safety Office (RCCSafetyOffice@tech-res.com) or call 1-800-537-9979 (US) or 1-301-897-1730 or FAX 1-800-275-7619 (US) or 1-301-897-1710. In addition, the site investigator is required to submit AE information as required by local regulatory or other local authority.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This study addresses the use of GPO-VIR® in pediatric populations. The first primary objective is to describe the comparative bioavailability of NVP in the GPO-VIR® Pediatric tablet formulation relative to that achieved with a standard oral solution (administered as standard oral solutions of d4T, 3TC and NVP). The second primary objective is to estimate the population average exposure to NVP delivered in the GPO-VIR® Pediatric formulation, and to compare this exposure to an adult exposure of therapeutically adequate NVP concentration. Secondary objectives address the PK parameters of d4T, 3TC and NVP and intra and inter-subject variability in the study population taking the liquid formulations compared to the GPO-VIR® Pediatric tablet.

The design consists of two stages. In Stage I, 8 evaluable Thai children (≥12 to ≤30 kg) will be evaluated for toxicity and therapeutic adequacy using standard (i.e. recommended doses of liquid d4T, 3TC and NVP) and the GPO-VIR® Pediatric tablet(s) in a cross-over design. Formal criteria for terminating the protocol are given, based on the number of Stage I subjects experiencing certain toxicities that are definitely, probably or possibly study drug-related (see 8.51 below) or manifestations of therapeutic inadequacy (see 8.42 below) of the regimen. Should Stage I be completed satisfactorily, Stage II will be conducted. In Stage II, 30-44 Thai children, stratified by weight, will be randomized to a cross-over design for a longer term evaluation of 1) the comparative bioavailability of the standard and generic formulations and 2) a better estimation of the population average exposure to NVP delivered in the GPO-VIR® Pediatric formulation.

The two stage design is motivated by the current lack of information on tolerability and adequacy of GPO-VIR® in Thai children. Stage I involves a two-week treatment period for each formulation being evaluated. This allows very rapid assessment of bioavailability and the lower bound on Stage I participant weight ensures that very young children are not exposed to experimental risk in the absence of any clinical trial data. Stage II involves a four-week treatment period for each formulation being evaluated. The rationale for the four-week
period in Stage II is based primarily on the blood draw limitations of the PK study for very young children, which necessitate spacing of blood draws over a longer period. Additionally, a four-week observation interval affords greater opportunity to assess toxicity risks.

Although Stage I and Stage II employ different durations of treatment, it is strongly believed that the pharmacokinetic phenomena of interest are invariant to the treatment duration. If this belief is correct, it is appropriate and efficient to analyze Stage I and Stage II data together for purposes of final inference from this protocol. The P1056 Protocol team will check the soundness of this belief using sensitivity analyses and if there is no clear reason to separate Stage I and Stage II observations, will analyze the amalgamated dataset for final study reporting purposes.

The GPO-VIR® Pediatric tablet dosing is based on a child’s body weight. This leads to dose- or weight-based groupings. In Stage II, there will be a minimum of eight children allocated to each of the groupings of children weighing greater than 8 kg, and six to eight children weighing from ≥6-8 kg. These constraints are introduced to ensure broad representation of children of different weights. No dose/weight group-specific data analyses will be performed.

8.2 Outcome Measures

8.2.1 Primary

8.2.1.1 Comparative bioavailability

For each drug component in each formulation, concentrations will be computed for each subject for each exposure. Standard tests for equality of carryover effects based on subject-specific sums will be conducted and reported. The concentration difference between the GPO-VIR® Pediatric formulation and the standard liquid will be calculated for each subject and the standard t test of zero mean concentration difference will be reported.

8.2.1.2 Therapeutic adequacy

Stage I subjects will be analyzed but not included in the primary determination of adequacy of formulation exposure.

Therapeutic levels are not analyzed at an individual level. The average exposure over the entire cohort will be computed along with a confidence interval (CI) and this CI must lie in a pre-
specified interval, such that therapeutic levels are exceeded or not achieved by the cohort as a whole. Treatment-specific concentration distributions will be assessed for approximate normality. Log transformation will be used if required. The CI for mean concentration will be computed and compared to a priori boundaries (or their transformation).

8.22 Secondary

As described in Section 8.4 below, standard PK analyses generate numerous parameters regarding details of drug absorption. Full analyses using standard pharmacokinetic models and software will be prepared to facilitate an understanding of drug exposure using both GPO-VIR® Pediatric tablets and standard liquid formulations.

8.3 Stratification

For Stage I, all 8 evaluable subjects will weigh 12 kg or greater. For Stage II, subjects will be stratified according to weight as described in Section 3.2. Dosage based on weight at entry (Day 0) will be determined according to Table 1 in Section 5.11.

8.4 Sample Size

8.41 Comparative bioavailability of NVP in the GPO-VIR® Pediatric tablet and the standard oral solutions of NVP, d4T, and 3TC

P1056 proposes to establish 80% power to detect a 15% departure from target mean AUC, under the assumption that the standard formulation achieves the target mean, with a Type I error rate of 0.05. If the intra-individual standard deviation (s.d.) is 80% of the inter-individual s.d., N=30 children are sufficient for these operating characteristics (30).

8.42 Therapeutic adequacy of NVP plasma concentrations with GPO-VIR® Pediatric tablets

This component of the study does not require the cross-over component. The data analysis proposed here will employ observations collected only on the GPO-VIR® Pediatric tablet exposures.

The therapeutic adequacy of GPO-VIR® Pediatric tablets will be defined in terms of the area under the curve (AUC). For NVP, this quantity was estimated by Boehringer Ingelheim at 63.6 mcg*hr/mL (average plasma
concentration of 5.3 mcg/mL), with s.d. approximately 1.33, (based on coefficient of variation (CV) \(\approx\) approximately 25%; (17), (31). The PACTG P1056 team will require that the estimated 90% CI for mean concentration lie completely within +/- 15% of the target mean. These limits are approximately 54 and 73.2 mcg*hr/mL. Assuming that the average plasma concentration results are approximately normally distributed, the CI-based rule has the following characteristics, shown in Table 2.

Table 2. Probabilities of Affirming the GPO-VIR® Pediatric Formulation using the CI Inclusion Rule

<table>
<thead>
<tr>
<th>True Mean AUC (mcg*hr/mL)</th>
<th>78.0</th>
<th>72.0</th>
<th>67.2</th>
<th>63.6</th>
<th>60.0</th>
<th>54.0</th>
<th>48.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 20</td>
<td>0%</td>
<td>7%</td>
<td>47%</td>
<td>62%</td>
<td>42%</td>
<td>4%</td>
<td>0%</td>
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<tr>
<td>N= 30</td>
<td>0%</td>
<td>10%</td>
<td>61%</td>
<td>85%</td>
<td>62%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>N= 40</td>
<td>0%</td>
<td>13%</td>
<td>71%</td>
<td>92%</td>
<td>69%</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table margins are sample size and true mean AUC of NVP using GPO-VIR® Pediatric tablets. Table cells give the probability of affirming the adequacy of the GPO-VIR® Pediatric formulation using the CI inclusion rule. Cells of the table are computed using 10000 simulations for each configuration of sample size and true mean. These numbers assume that Stage I and Stage II data are determined to be homogeneous and are combined.

Accrual of 30 children will provide an 85% probability of affirming this formulation if the true NVP AUC is 63.6 mcg*hr/mL (average plasma concentration is 5.3 mcg/mL). If the true NVP AUC exceeds 72 or is less than 54 mcg*hr/mL, the probability of affirming the GPO-VIR® Pediatric formulation is no greater than 13%. These probability calculations include the probability that the study is terminated in Stage I owing to observation of two events of study-terminating toxicity or therapeutic inadequacy. Therapeutic inadequacy is declared if the GPO-VIR® Pediatric tablet regimen-based 90% CI for AUC lies either entirely below <70% of the target mean AUC or entirely above >143% of the target mean AUC. These values are 44.5 mcg*hr/mL and 90.9 mcg*hr/mL, respectively.

8.5 Monitoring

PACTG P1056 is a two stage Phase I/II comparative PK study. It will be monitored as a Phase I study, with an additional external person unaffiliated with the study participating in the protocol monitoring calls. [This person may be from
the Thai FDA or MOPH]. Since Phase I studies are not routinely reviewed by a Data and Safety Monitoring Board (DSMB), it is the responsibility of the Protocol Team to interpret the toxicity data, and make any decisions regarding SADRs that are needed to protect subjects from undue risk.

The safety and tolerability of the study drugs will be monitored by means of adverse events reports and toxicity reports presenting all ≥Grade 1 laboratory and clinical events. It is required that these data be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available. Reports compiled by the DMC will be discussed by the P1056 Protocol Team on monthly calls; however, conference calls will be scheduled as needed in response to any adverse event that requires the immediate attention of the Protocol Team. Notification of core team members will be by e-mail, phone or FAX, depending on time differences. Data on accrual, toxicity, adherence, and the evaluability of the PK samples for the primary outcome variables will be reviewed.

8.51 Early Stopping Rules

The study will be stopped if two or more subjects experience one or more of the following conditions during treatment using GPO-VIR® Pediatric tablets (Stage I, Step 1/Arm A or Step 2/Arm B).

- Confirmed ≥Grade 3 cutaneous toxicity or
- Confirmed ≥Grade 3 non-cutaneous toxicity or
- Confirmed ≥Grade 2 lactate

Confirmation for cutaneous toxicities is defined as “a verification by the clinician at the site” either by exam or detailed consistent history.

The toxicities will be evaluated in accordance with SADR definitions (see Section 7.0, i.e. definitely, probably, possibly, and probably not related to a study agent). Enrollment to Stage I will be suspended temporarily if two or more subjects experience persistent or recurring confirmed ≥Grade 2 cutaneous toxicities that are definitely, probably or possibly study drug-related. The team will evaluate these cases in accordance with Section 6.1 - Toxicity Management and 6.21 - Skin Rash/Cutaneous Dermatitis and SADR requirements for nevirapine.

The study can also be stopped, after Stage I is completed, if it is determined that the GPO-VIR® Pediatric formulation is therapeutically inadequate. This determination will be based on the initial noncompartmental pharmacokinetic analysis for NVP in Stage I that will
be completed within one week of data assembly. Target thresholds for 3TC and d4T will also be examined as additional safeguards, to prevent the possibility of continuing the study, if d4T and 3TC in the pediatric tablet have substandard bioavailability.

To address this possibility, a general target for the Stage I d4T and 3TC AUC, similar to the threshold for NVP, is required. The target values for the expected AUC are:

1.28 mcg*hr/mL for d4T (32) and 4.43 mcg*hr/mL for 3TC (33).

The GPO-VIR® Stage I NRTI AUC would be too high if the 90% CI for d4T or 3TC AUC lies entirely above twice the target mean AUC value or too low if the upper bound of the 90% CI lies entirely beneath the ½ target mean AUC value.

Provided the study is not stopped in Stage I, Stage II will be initiated as soon as the analysis of Stage I is completed and the data are reviewed. An external review of the Stage I results may be required by a Study Monitoring Committee (SMC) or similar panel.

Stage I subjects will be analyzed but not included in the primary determination of adequacy of formulation exposure.

For Stage II, the determination of therapeutic inadequacy is based on the location of the 90% CI for the mean NVP AUC based on all subjects in the given weight ranges, receiving the GPO-VIR® Pediatric tablet. Therapeutic inadequacy is declared if the GPO-VIR® Pediatric tablet regimen-based 90% CI for AUC lies entirely below either <70% of the target mean AUC or entirely above >143% of the target mean AUC. These values are 44.5 mcg/hr/mL and 90.9 mcg/hr/mL, respectively.

The Protocol Chair(s) will prepare a brief summary of the status of the protocol every six months (starting from the date of the first enrollment) or as required by the Thai MOPH. These summaries and/or interim safety reports will be provided to the participating study sites for submission to their Institutional Review Boards (IRBs) and/or Ethics Committees (ECs).

If accrual has not been completed in 12 months from the date of first enrollment, after the site is protocol registered, study feasibility will be assessed by the Protocol Team in conjunction with the Primary Therapy RAC and International Steering Committee. Any discussion regarding study continuation or
modification will include DAIDS and the Clinical Science Review Committee (CSRC).

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Study Design

This is a two stage, Phase I/II, two arm, randomized, open-label, multiple dose pharmacokinetic cross-over study of 8 evaluable (Stage I) and minimum of 30, maximum of 44 (Stage II) evaluable HIV-1 infected Thai children currently receiving NVP + 2 NRTIs every 12 hours for at least four weeks prior to entry as detailed in Section 3.0.

Stage I

Children weighing ≥12 to ≤ 30 kg will be enrolled and randomized into treatment groups (Step 1). 12 hour PK studies will be performed after a two week treatment period on either Arm A (GPO-VIR Pediatric tablets) or Arm B (d4T, 3TC and NVP oral solutions) on Day 14, if adherence and toxicity parameters are acceptable. Cross-over to the alternate regimen (Step 2) will then occur. A second PK study will follow after two weeks (Day 28) if adherence and toxicity parameters are acceptable. The minimum study treatment duration of Stage I is 4 weeks. Additional time for repeat PK studies will be allowed, (Section 9.21, below). For toxicities, the interval between restarting study drugs and the PK studies should be at least 14 days, and the study calendar (Step 2) should be altered to reflect this change, if necessary. A safety follow-up period of 6 weeks after the specified study drugs are stopped will bring the maximum study duration to 12 weeks. The PK results of Stage I will be analyzed (as close to real-time as logistically feasible, within 1 week of data assembly) and a final analysis completed before Stage II can be initiated.

Stage II

Children will be stratified into one of four groups based on body weight and randomized to either treatment Arm A or B (Step 1), as in Stage I, but for a longer period (four weeks). The first 12 hour PK study will be done on Day 28 of the study, if adherence and toxicity parameters are acceptable. Upon satisfactory completion of the PK study, cross-over to the alternate regimen (Step 2), as in Stage I, but for a longer period (4 weeks) will occur immediately afterwards. The second 12 hour PK study will be done on Day 56 if adherence and toxicity parameters are acceptable, and conclude the treatment portion of the study. The minimum study duration for Stage II is 8 weeks. A maximum of 18 weeks will be
allowed for repeat PK studies and study calendar adjustments for toxicity, if needed. Six weeks of safety follow up (as in Stage I) will bring the maximum study duration to 24 weeks.

9.2 Pharmacokinetic (PK) Evaluation

9.21 d4T, 3TC and NVP plasma levels

Eligibility for the PK studies:

- Hospitalization 72 hours prior to the PK study to ensure 100% adherence to the study treatment regimen.

1st Intensive PK study

On Day 11 (Stage I) and Day 25 (Stage II) of the study, subjects will be admitted to the hospital for Direct Observation of Therapy (DOT) for the 72 hours prior to the first PK study. The times of all study drug doses will be recorded (note also if the subject chews, swallows or crushes the GPO-VIR® Pediatric tablet).

During the PK studies, subjects will be required to fast for at least two hours before and one hour after study drug administration, if feasible. For logistical reasons, during the hospitalization period for the intensive PK blood sampling, study drug administration will be around 6 AM and 6 PM. The solid and liquid diet, including milk and/or formula, will be restricted between 4-7 AM and 4-7 PM (this schedule may be modified, if needed, especially for the youngest children). Only a clear liquid such as water or an artificially flavored syrup water (Hale’s Blue Boy™) will be allowed during these times.

On the morning of Day 14 (Stage I) and 28 (Stage II), a predose blood sample (2 mL) will be obtained prior to the directly observed morning dose. The recommended dose of the specified study drugs in each treatment arm will be administered and the time and method recorded. Blood samples (2 mL each) will be obtained at 0.5, 1, 2, 4, 8, and 12 hours postdose. The total blood volume will be 14 mL for each PK study (2 mL; n=7). A short intravenous catheter (heparin lock) will be used to reduce repeated skin puncture and ease the discomfort of blood sampling.

If either the predose or more than one of the six postdose blood samples are not obtainable, the subject will be requested to continue treatment for at least 3 days, and then repeat the entire PK study. The maximum blood
volume drawn cannot exceed the amount allowed in Table 3 (Section 9.22).

Replacement of subjects will be allowed if blood samples are unevaluable due to damage during shipment or for unforeseen circumstances (see section 9.4).

9.22 Rescheduling PK studies

The PK study will be delayed if:

- Adherence parameters are not acceptable. This should be a rare event (given the hospitalization and DOT), however, if unexpected problems unrelated to toxicity do occur, continue on current study drugs for at least 72 hours, re-evaluate and then continue with the PK study.

- Toxicity occurs and resolves within the allowed waiting period (per Section 6.1). If the toxicity resolves, treatment with study drugs should be resumed in full doses. The interval between restarting study drugs and the PK studies should be at least 14 days, and the study calendar (Step 2) should be altered to reflect this change, if necessary.

A repeat PK study will be scheduled if:

- The predose sample is missed (continue treatment for at least 3 days, and then repeat the entire PK study, including hospitalization 3 days prior). The maximum blood volume drawn cannot exceed the amount allowed in Table 3.

- Two or more postdose samples are missed (reschedule as above).

Table 3. Pediatric Blood Volume Limits over a 28-Day Period (Thailand)

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>WT (kg)</th>
<th>Upper limit of allowed blood draw volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥12 to ≤30 kg</td>
<td>Group 1</td>
<td>≥6-8</td>
<td>24-31.6</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>&gt;8-13</td>
<td>32-51.6</td>
</tr>
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<td></td>
<td>Group 3</td>
<td>&gt;13-16</td>
<td>32-51.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;16-19</td>
<td>64-75.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;19-23</td>
<td>76-91.6</td>
</tr>
<tr>
<td></td>
<td>Group 4</td>
<td>&gt;23-27</td>
<td>92-107.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;27-30</td>
<td>108-120</td>
</tr>
</tbody>
</table>
• Emesis within 2 hours of study drug administration (reschedule based on medical management). If more than one subsequent dose of study drugs must be missed, the PK study should be postponed until the subject is stable on study drugs (a minimum of 3 days, maximum of 14 days). Reschedule the PK study as described previously. (If additional time is required, the subject may be replaced.)

2nd Intensive PK Study

On Day 25 (Stage I) and 53 (Stage II) of the study, subjects will again be admitted to the hospital for DOT and documentation of the doses prior to the second PK study. On Day 28 (Stage I) and 56 (Stage II) of the study, a predose blood sample will be obtained, the recommended morning dose of the specified study regimen will be administered (DOT), and method and time recorded. Samples will be obtained in the same manner as the first 12 hour PK study. A repeat PK study will be scheduled for missed samples, as described above. Evaluability is defined in Section 9.4.

9.23 Analytical methodology

Measurement of NVP, 3TC and d4T drug concentrations in plasma will be performed by validated High Performance Liquid Chromatography (HPLC) methods as subjects are accrued (Pharmacology Laboratory, Chiang Mai University, Chiang Mai; Laboratory Data Management System (LDMS) Lab Code 251).

A combined HPLC assay that reduces sample volume will be used to measure d4T and 3TC (Simultaneous Determination of 3TC, ddI, d4T, ZDV, and ABC in Human Plasma by Reversed-Phase UV HPLC: supplied by Dr. Courtney Fletcher, University of Colorado). This assay has been validated in the PK laboratory in Chiang Mai and its sensitivity is 25 ng/mL for d4T and 3TC. These limits are sufficient to accurately characterize the AUC for all GPO-VIR® components. For both 3TC and NVP, the average steady-state trough concentrations are expected to exceed the limits of detection by ~5 and 100 fold, respectively. For d4T, the peak will be more than 10 times the limit of detection of the assay which has the same sensitivity as those used in the pediatric Phase I studies of Zerit®. Stavudine concentrations may fall below the limit of detection at the very last time point (C_{12}) due to the very rapid elimination rate of d4T. However, it is expected that all of the AUC data will be captured before concentrations reach the limit of detection and only ~ 6% of the total AUC will need to be extrapolated.
9.3 Data Analysis

PK Parameters (Stage I and II)

Following the blood sample collection during the intensive PK sampling visits, samples will be shipped from Bangkok to the PHPT-IRD Pharmacology laboratory in Chiang Mai via authorized courier within one week. Analysis of plasma drug levels (d4T, 3TC and NVP) will be completed and results reported via the LDMS within two weeks of receiving the samples at the laboratory. The initial noncompartmental pharmacokinetic analysis for NVP in Stage I will be completed within one week of data assembly.

The plasma concentrations of d4T, 3TC and NVP following administration of the GPO-VIR® Pediatric tablet(s) and the oral liquid formulations, will be characterized using non-compartmental methods. Standard pharmacokinetic software (WinNonLin™) will be used in this analysis. The PK parameters determined will include:

- Area under the plasma concentration-time curve (AUC), estimated by the trapezoidal method.
- Maximum observed concentration of drug in plasma ($C_{\text{max}}$) and time of the maximum observed concentration in plasma ($T_{\text{max}}$)
- Minimum concentration of drug in plasma ($C_{\text{min}}$)
- Average concentration of drug in plasma at steady state ($C_{\text{av}}$), which can be calculated by the following equation:
  \[
  C_{\text{av}} = \frac{\text{AUC}}{\tau} \quad \text{Where } \tau \text{ is the dosing interval}
  \]
- Half-life ($T_{\frac{1}{2}}$) will also be estimated for 3TC and d4T.
- Pharmacokinetic parameters will be presented by weight group and by mode of administration (chewed, crushed, with in water, etc.) with additional exploratory analysis performed as warranted by the data.
- Additional compartmental methods may be utilized to describe the PK data if warranted by the data.
9.4 **Evaluable Subjects**

For a subject to be included in the estimation of AUC, a predose plasma concentration and at least 5 of the 6 postdose plasma concentrations for 3TC, d4T and NVP must be available. Subjects that experience emesis within 2 hours after study dose administration will be rescheduled, according to the repeat PK guidelines, if possible.

If it is known that the PK samples will be insufficient to estimate AUC (as detailed above), at the time of the scheduled PK study, the subject will be requested to remain in the hospital or return for a repeat PK study per Section 9.22 and Table 3. Scheduling of the repeat PK blood draw is dependent on the weight of the child and the volume of blood previously drawn in accordance with Thai guidelines.

The planned analysis is designed to minimize the impact of “outliers”. However, “outlier” observations may be encountered at two levels:

- Individual samples that appear to be physiologically implausible (e.g. pre-dose concentration higher than all post dose concentrations) and

- Unexpected individual subject parameter estimates.

If outlier observations are suspected, the samples will be re-assayed (if there is residual sample volume) and the site will be contacted to determine if there were difficulties in drug administration or sample processing that may have contributed. Summary statistics of pharmacokinetic parameters will be presented that both include and exclude outliers with a report on full details for any subject with an outlier observation.

10.0 **HUMAN SUBJECTS**

The Division of AIDS has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local Institutional Review Boards (IRBs) or equivalent Ethics Committees (ECs) for the recruitment of prisoners.

10.1 **Institutional Review Board/Ethics Committee Review and Informed Consent**

This protocol, the informed consent document (Appendix VII) and any subsequent modifications must be reviewed and approved by the IRB and/or EC
responsible for oversight of the study (Thai MOPH). Written informed consent must be obtained from the subject (or parent or legal guardian of subjects who cannot consent for themselves, such as those below the legal age). The subject’s assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

Each site which receives United States Department of Health and Human Services (HHS) funding and follows the US Code of Federal Regulations Title 45 – Public Welfare, Part 46 – Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR resigns the consent. The plan should follow all IRB/EC, local, state and [host country] guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

The P1056 protocol registration materials will reference the applicable Thai laws if similar to the above.

10.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject/parent or legal guardian, except as necessary for monitoring by the US Food and Drug Administration (FDA), by the Thai FDA, by the pharmaceutical sponsors (GPO and GSK) by the NIAID, IRB/EC, the U.S. Office for Human Research Protection (OHRP), by the MOPH in Thailand or sponsor’s designee.

10.3 Study Discontinuation

The study may be discontinued at any time by the MOPH, Thai FDA, US FDA, NIAID, GPO and other pharmaceutical sponsors, IRB/EC or other government agencies as part of their duties to ensure that research subjects are protected.
10.4 Regulatory Authorities

At the designated clinical sites in Thailand, the protocol will be carried out under the provisions of Good Clinical Practice Guidelines (GCP) and regulated by the Thai FDA and U.S. FDA IND # assigned to the study (71,844).

In addition to the GCP Guidelines and the U.S. FDA IND #, the trial will be regulated and conducted as per the 1993 Revision of the Ethical Review Committee of the MOPH (on file) in Thailand.

PACTG P1056 will be conducted in full concordance with the principles of the Declaration of Helsinki, October 2000 and the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, May 1997.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by PACTG policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsor(s) prior to submission.

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other bloodborne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Thai MOPH, Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to the instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations or Thai equivalent for Ground Transportation. Refer to individual local couriers for specific instructions.
13.0 REFERENCES

Reference Manager® is the database program used to manage bibliographic references and prepares formatted in-text citations and bibliographies for protocols. All references must be entered in the Reference Manager PACTG.DATABASE.rmd.


(2) Center for Disease Control and Prevention MoPHT. Medical service development project for HIV-infected individuals and AIDS patients. 1st edition. 2001. Bangkok, Thailand, JS Publisher.


APPENDIX I

SCHEDULE OF EVALUATIONS-STAGE I

<table>
<thead>
<tr>
<th>EVALUATIONS</th>
<th>Screening</th>
<th>Entry Enroll &amp; Randomize Day 0</th>
<th>Week 2*</th>
<th>Week 11*</th>
<th>Week 14 PK</th>
<th>Week 14-15</th>
<th>Week 25*</th>
<th>Day 28 PK</th>
<th>End of Stage I</th>
<th>Early Discont OR Off-Tx Safety F/U (q 3-4 wks)</th>
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<td>History &amp; Physical exam2</td>
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<td>Assessment of HIV-related symptoms</td>
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<td>1 mL</td>
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<td>(X)</td>
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<td></td>
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<td>Intensive PK (spray dried K2 EDTA, lavender top)</td>
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<td>Urinalysis</td>
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<tr>
<td>TOTAL BLOOD VOLUME</td>
<td>6 mL</td>
<td>6 mL</td>
<td>17 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

1* Home visits and * admission to the hospital to facilitate eligibility for the PK study.

1. Evaluations should be completed within 14 days prior to study entry, except HIV-RNA PCR and CD4+ counts which must be obtained within 30 days prior to study entry. Document current regimen (NVP +2 NRTIs), method of administration and adherence assessment at screening.

2. History: current regimen; concomitant medications; significant non-HIV diagnoses, signs and symptoms ≥ Grade 1.
   Physical exam: height, body weight, and vital signs (pulse rate, blood pressure, respiratory rate and body temperature). Weight at entry (Day 0) will be used for dosing calculations for Step 1 AND Step 2 (Day 14-15) study drug regimens.
3. Adherence for eligibility for the PK study must be 100% in the 72 hours immediately prior to the PK Study. *Subjects will be admitted to the hospital for 3-4 days prior to the PK study. Hospital dosing records will be used to document eligibility for entry into the PK study in Step 1 (Day 14), entry into Step 2 and PK study (Day 28). See Section 9.0 Pharmacology Plan for rescheduling. + Home visits and weekly phone calls during the first week on each study treatment regimen will be attempted, see Appendix III.

4. Hematology (CBC, cell differential, platelet count), 1 mL Vacutainer® EDTA (lavender top) tube. CBC on Day 14 and 28 will be drawn after the last PK blood sample. Draw the minimum amount of blood required by the local lab.

5. Chemistries (Blood urea nitrogen (BUN), AST (SGOT), ALT (SGPT), ALP, serum creatinine, amylase, lipase and electrolytes), 2 mL Vacutainer® (no additive, red top tube). Draw the minimum amount of blood required by the local lab.

6. For females of childbearing potential only. If the pregnancy test (urine) result is negative, participation in the study (Step 1 and 2) will be permitted.

7. The Roche Amplicor® 1.5 HIV-1 RNA PCR assay will be used. Process according to the P1056 Lab Processing Chart (LPC) and Appendix IV.

8. CD4/8+ counts and percentage-process according to the P1056 LPC and Appendix V.

9. PK: Day 14, 28: For repeat PKs, see Section 9.22 and Table 3. Process according to the P1056 LPC and Appendix VI.

10. Early discontinuation (toxicity only): Subjects will remain on study and be followed and data collected until the toxicity resolves; or until 4 weeks after entry, whichever occurs latest. Evaluations as indicated, plus any specified assay per Section 6.2. Urinalysis (include sediment, blood, protein, and glucose); to be done if an abnormality is suspected. Pregnancy test, if indicated. For early discontinuation for subject refusal, family moving, etc., final study visit evaluations will be as indicated.

Follow up: For subjects that are off-study treatment, F/U will continue until the completion of Stage I or if stopping criteria have been met. Safety follow-up, once off study drugs, will continue for 6 weeks, in conjunction with clinical visits (standard of care schedule, Access to Care program treatment regimen, minimum every 4 weeks). Study Visits for safety follow-up are ± 1 day.

11. Thai Laboratory designations are as follows:
   S=Siriraj Hospital, Bangkok; LDMS Lab Code 258
   Q=Queen Sirikit National Institute of Child Health, Bangkok, LDMS Lab Code 259
   C= Pharmacology Lab, Chiang Mai University, Chiang Mai; LDMS Lab Code 251.
   For insufficient blood draws priorities are as follows:
   1) Safety (hematology, chemistries); 2) Pharmacokinetics*; 3) Virology, 4) Immunology.
APPENDIX II

SCHEDULE OF EVALUATIONS-STAGE II

<table>
<thead>
<tr>
<th>STUDY VISITS</th>
<th>Study-Drug Treatment</th>
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</thead>
<tbody>
<tr>
<td><strong>EVALUATIONS</strong></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
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</tr>
<tr>
<td>History &amp; Physical exam</td>
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<tr>
<td>Assessment of HIV-related symptoms</td>
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<td>Adherence Assessment</td>
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<tr>
<td>Pregnancy Test (urine)</td>
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<tr>
<td>HIV RNA PCR (lavender top)</td>
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<td>Lymphocyte subsets (lavender top)</td>
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<tr>
<td>TOTAL BLOOD VOLUME</td>
<td>6 mL</td>
</tr>
</tbody>
</table>

*Home visits and admission to the hospital to facilitate eligibility for the PK study.*

1. Evaluations should be completed within 14 days prior to study entry except HIV-RNA PCR and CD4+ counts, which must be obtained within 30 days prior to study entry. Document current regimen (NVP + 2 NRTIs), method of administration and adherence assessment at screening.

2. **History:** current regimen, concomitant medications, significant non-HIV diagnoses, signs and symptoms ≥Grade 1.

**Physical exam:** height, body weight, and vital signs (pulse rate, sitting blood pressure, respiratory rate and oral body temperature). Weight at entry (Day 0) will be used for dosing calculations for Step 1 AND Step 2 (Day 28-29) study drug regimens.
APPENDIX II (Cont.)

3. Adherence for eligibility for the PK study must be 100% in the 72 hours immediately prior to the PK Study. *Subjects will be admitted to the hospital for 3-4 days prior to the PK study.* Hospital dosing records will be used to document eligibility for the PK study Step 1 (Day 28), entry into Step 2 and the PK study (Day 56). See Section 9.0 Pharmacology Plan for rescheduling. + Home visits and weekly phone calls during the first week on each study treatment regimen will be attempted, see Appendix III.

4. Hematology (CBC, cell differential, platelet count). 1 mL Vacutainer® EDTA (lavender top) tube. CBC on Day 28 and 56 will be drawn after the last PK blood sample. Draw the minimum amount of blood required by the local lab.

5. Chemistries (Blood urea nitrogen (BUN), AST (SGOT), ALT (SGPT), ALP, serum creatinine, amylase, lipase and electrolytes), 2 mL Vacutainer® (no additive, red top tube). Draw the minimum amount of blood required by the local lab.

6. For females of childbearing potential only. If the pregnancy test (urine) result is negative, participation in the study (Step 1 and 2) will be permitted.

7. The Roche Amplicor® 1.5 HIV-1 RNA PCR assay will be used. Process according to the P1056 Lab Processing Chart (LPC) and Appendix IV.

8. CD4/8+ counts and percentage-process according to the P1056 LPC and Appendix V.

9. PK: Day 28, 56: For repeat PK, see Section 9.22 and Table 3. Process according to the P1056 LPC and Appendix VI.

10. Early discontinuation (toxicity only): Subjects will remain on study and be followed and data collected until the toxicity resolves or until 8 weeks after entry, whichever occurs latest. Evaluations as indicated, plus any specified assay per Section 6.2. Urinalysis (include sediment, blood, protein, and glucose); to be done if an abnormality is suspected. Pregnancy test, if indicated. For early discontinuation for patient refusal, family moving, etc., final study visit evaluations will be as indicated.

Follow up: For subjects that are off-study treatment, F/U will continue until Stage II of the study has ended. After completion of Stage II study treatment (maximum of 18 weeks) subjects will remain on-study for safety follow-up for an additional 6 weeks. Safety follow-up, once off study drugs, will continue in conjunction with clinical visits (standard of care schedule, Access to Care Program treatment regimen, minimum every 4 weeks). Study Visits for safety follow-up are ± 1 day.

11. Thai Laboratory designations are as follows:
   S=Siriraj Hospital, Bangkok; LDMS Lab Code 258.
   Q=Queen Sirikit National Institute of Child Health, Bangkok, LDMS Lab Code 259
   C= Pharmacology Lab, Chiang Mai University, Chiang Mai; LDMS Lab Code 251.
For insufficient blood draws priorities are as follows:
1) Safety (hematology, chemistries); 2) Pharmacokinetics*, 3) Virology, 4) Immunology.
APPENDIX III

STUDY DRUG ADMINISTRATION PROCEDURES

GPO-VIR® Pediatric Tablets

The GPO-VIR® Pediatric tablet is specifically formulated to be chewable. It should be chewed whenever possible. If children are unable or refuse to chew the tablet(s), they will be allowed to crush or swallow them with water. The tablet is scored, to facilitate division into halves. Children and their caregivers will be instructed on how to use the pill crusher and take the study drugs as directed (Table 1). The weight of the child, recorded on Day 0 (Step 1), will be used to calculate the dosage.

A glass mortar and pestle to crush the tablets, if needed, will be provided by the site and study staff will instruct caregivers on how to use them to accurately crush the tablet(s).

CRUSHING PROCEDURE:

Tablets will be crushed using a glass mortar and pestle (cut/split the tablet, if necessary, and place the required tablet fraction in the glass mortar). Crush the tablet(s) to a powder with the pestle. Add water (3-5 mL) directly to the powder in the mortar, and have the child drink the resulting suspension immediately, using the mortar as a cup. Add water (3-5 mL) to rinse any remaining residue, and have the child drink the remainder.

NVP, 3TC and d4T Oral Solutions

Pre-labeled oral syringes with the appropriate dose per child’s weight (Day 0, per Table 1), and instructions on how to take these study drugs as directed, will be provided by the study staff.

ADHERENCE:

Tablet or liquid counts will be evaluated during each study visit that the subject is on study drugs. The number of total tablets or quantity of liquid study drugs dispensed (bottles will be weighed) will be compared to the remaining study drugs returned; and calculated as an adherence percentage.

For pill count:  Adherence % = \( \frac{\text{number of pills taken}}{\text{number of pills expected to be taken}} \times 100 \)
APPENDIX III (Cont.)

Table 1. GPO-VIR® Pediatric Dose per Body Weight and the Corresponding Liquid Formulation Doses to be used for Step 1 and 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Wt (kg)</th>
<th>Number of Subjects per Group</th>
<th>GPO-VIR® Pediatric Tablet</th>
<th>Liquid Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3TC dose 10 mg/mL</td>
</tr>
<tr>
<td>1</td>
<td>≥6-8</td>
<td>(6-8)</td>
<td>1</td>
<td>30 mg (3 mL)</td>
</tr>
<tr>
<td>2*</td>
<td>&gt;8-13</td>
<td>(8-12)</td>
<td>1.5</td>
<td>45 mg (4.5 mL)</td>
</tr>
<tr>
<td></td>
<td>&gt;13-16</td>
<td></td>
<td>2</td>
<td>60 mg (6 mL)</td>
</tr>
<tr>
<td>3*</td>
<td>&gt;16-19</td>
<td>(8-12)</td>
<td>2.5</td>
<td>75 mg (7.5 mL)</td>
</tr>
<tr>
<td></td>
<td>&gt;19-23</td>
<td></td>
<td>3</td>
<td>90 mg (9 mL)</td>
</tr>
<tr>
<td>4*</td>
<td>&gt;23-27</td>
<td>(8-12)</td>
<td>3.5</td>
<td>105 mg (10.5 mL)</td>
</tr>
<tr>
<td></td>
<td>&gt;27-30</td>
<td></td>
<td>4</td>
<td>120 mg (12 mL)</td>
</tr>
</tbody>
</table>

*Note: For Stage I, all 8 evaluable children will be ≥12 to ≤30 kg, study drug dosages will be based on weight at entry (Day 0), according to this table (shaded areas).

For liquid count: The research pharmacist will develop a conversion table for each liquid study drug based on the density or specific gravity* (g/mL) of the particular study drug. The research pharmacist will weigh each bottle (empty and full) separately, before it is dispensed. These weights (g) are recorded in the pharmacy log. The difference in the weight of each dispensed bottle that is returned (as weighed by the site pharmacist and recorded to the nearest decimal point, using the same gram scale), will be calculated and recorded in the pharmacy log. The volume expected to be taken can be calculated from dosage and doses directly. The weight of the returned bottle containing the study drug will be converted to volume (mL). The adherence percentage will be calculated as follows:

\[
\text{Adherence} \% = \frac{\text{liquid study drug taken}}{\text{liquid study drug expected to be taken}} \times 100
\]

*lamivudine (3TC) oral solution 10 g/mL, specific gravity = 1.08 mg/mL, empty bottle 26 g ± 1 g
*nevirapine (NVP) suspension, specific gravity = 1.1 g/mL
*stavudine (d4T) oral solution, specific gravity =1.020 g/mL
Home visits:

During the first week of the study and first week after the cross-over period (i.e. during the initial regimen of Step 1 or alternate regimen, Step 2), home visits (to assure that study drugs are taken correctly) will be attempted. After the initial home visit, follow-up by either a home visit or telephone call will be done, as determined appropriate by the initial assessment by the home visit team.

Hospital Admissions:

Children will be admitted to the hospital on study Day 11 and 25 (Stage I) and Day 25 and 53 (Stage II) to implement Direct Observation of Therapy (DOT) for the critical time period prior to the start of the PK study and facilitate the administration of the study drug doses and subsequent blood draws. Hospital dosing records will be used for adherence assessment on the day of each PK study (14 and 28 of Stage I) and 28 and 56 of Stage II). To be included in the PK study, children must be 100% adherent in the past 72 hours. Admission to the hospital/clinic earlier than indicated in the Schedule of Evaluations for each Stage may be an option to address non-adherence, or problems with taking study drugs as directed, so that DOT may be implemented.
APPENDIX IV

VIROLOGY COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Quantitative HIV-1 RNA PCR (Roche Amplicor® 1.5) | 2 mL blood collected by venipuncture | Tripotassium EDTA Vacutainer® tubes (lavender top) | • Gently invert tubes 10-15 times to mix. Do not shake.  
• Specimen should be identified as to patient ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.  
• Ship samples ambient to Lab 258, Siriraj Hospital. |
| Residual plasma storage for future virology studies. | | | |

Test Code: RNAHIVRS

Test Code: VIRSTOR

PROCESSING INSTRUCTIONS:
1. Blood samples should ideally be processed within 4 hours but can remain at room temperature for up to 30 hours prior to separation of plasma.
2. Separate plasma from blood by centrifugation at 800 x g for 10 minutes at room temperature (18-24°C). Transfer plasma to another tube and repeat centrifugation of plasma as above. Aliquot double-spun plasma ~0.5 mL plasma in each of 2 properly labeled, leak-proof, O-ring containing plastic screw top cryovials.
3. Freeze the cryovials in the upright position immediately and maintain frozen at -70°C. One aliquot is to be used for RNA testing. Store the second aliquot on site if possible (if not needed for repeat testing)
4. Log all samples in the LDMS system on the day the sample is drawn.

DESIGNATED LABORATORY/CONTACT PERSON:
Pilaipan Puthavathana, Ph.D., Chief, Division of Virology, Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Prannok Road, Bangkoknoi, Bangkok 10700, Phone: (662) 419-7463, 419-7067-8, FAX: (662) 418-4148, E-mail: siput@mahidol.ac.th LDMS Lab Code 258

SHIPPING: None. Transfer between sites in Thailand using the required forms per local courier guidelines.

OTHER INSTRUCTIONS: All specimens must be logged into the LDMS by the processing laboratory and computer generated labels should be used. The ACTG LDMS standard label includes: LDMS specimen number, patient identification number (PID), visit identification number (VID), specimen draw date specimen draw time, protocol number, LDMS specimen code (primary, additive, derivative, sub-additive/derivative). LDMS specimen code: BLD/EDT/PL2.
## APPENDIX V

### IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Lymphocyte Subsets</td>
<td>1 mL blood collected by venipuncture</td>
<td>Tripotassium EDTA Vacutainer® tubes (lavender top)</td>
<td>• Gently invert tubes several times to mix. Do not shake.</td>
</tr>
<tr>
<td>(CD4+/CD8+ cell counts and percentages)</td>
<td></td>
<td></td>
<td>• Specimen should be identified as to patient ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.</td>
</tr>
<tr>
<td>Test Code: CD4/CD8</td>
<td></td>
<td></td>
<td>• Specimen should be kept at room temperature (18-24°C) and transported to the local CLIA compliant (or equivalent) and DAIDS IQA (UKNEQAS) certified Flow Laboratory as soon as possible. Analysis must be performed within 30 hours of specimen draw.</td>
</tr>
</tbody>
</table>

**PROCESSING INSTRUCTIONS:** None

**LDMS SPECIMEN CODE:** Samples are not required to be logged into the LDMS for this test.

**SHIPPING:** None.

**OTHER INSTRUCTIONS:** None
### APPENDIX VI

PHARMACOLOGY COLLECTION, STORAGE AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Intensive Pharmacokinetic Studies for NVP, 3TC and d4T | 2 mL blood per time point collected by venipuncture at Predose, 0.5, 1, 2, 4, 8 and 12 hours postdose (7 samples for each subject per PK study) | Vacutainer® (lavender top) spray-dry K$_2$EDTA | • Invert the tubes several times to mix the blood and EDTA, process the samples as described below.  
• Freeze the samples upright and store at -70 ºC or lower until shipment.  
• Specimen should be identified as to patient ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.  
• Specimen should be processed within 1 hour of collection. |

**SPECIMEN PROCESSING:**

1. Obtain a minimum of 2.0 mL of blood at each time point and gently invert sample tube several times to mix blood. Blood samples can remain at room temperature for up to 1 hour prior to separation of plasma.
2. Separate plasma from blood by centrifugation at 800 x g for 10 minutes at room temperature (18-24°C), remove plasma and place ~0.5mL plasma in each of 2 properly labeled, leak-proof, O-ring containing plastic screw top cryovials.
3. Freeze the cryovials in the upright position immediately and maintain frozen at -70°C until shipment.
4. Log all samples in the LDMS system on the day the sample is drawn.

**DESIGNATED LABORATORY/CONTACT PERSON:** Dr. Tim Cressey, IRD 054-PACTG Laboratory, Faculty of Associated Medical Sciences, Dept. of Clinical Microbiology, 6th Floor, Chiang Mai University, Chiang Mai, 50200, Phone: +66 53 894431, FAX: +66 53 894220, tim@phpt.org, LDMS Lab Code 251

**SHIPPING:** Ship according to LDMS Lab 251, IRD 054-PACTG guidelines:

1. Pack samples with sufficient dry ice (3-4 kg) to ensure frozen condition upon receipt.
2. Label and pack samples in accordance with current IATA guidelines for diagnostic specimens (*Packing Instructions 650.*)
3. Include an inventory of the contents of the shipment, an LDMS shipping disk, and copies of the appropriate case report forms (CRFs) with shipment.
4. All samples will be shipped via ground transportation from the subunits to the IRD 054-PACTG Laboratory by local courier. Ship at least two days in advance of a major holiday. All samples will be shipped on enough dry ice to keep samples frozen for at least 72 hours (i.e. 3 to 4 kg per shipment container). Include a copy of the tracking form with the shipment. Each shipment MUST include an LDMS shipping diskette and manifest report.
5. Note: Residual samples received by IRD 054-PACTG Laboratory should be stored on site.

**OTHER INSTRUCTIONS:** All specimens must be logged into the LDMS and computer generated labels should be used. The ACTG LDMS standard label includes: LDMS specimen number, patient identification number (PID), visit identification number (VID), specimen draw date, specimen draw time, protocol number, LDMS specimen code (primary, additive, derivative, sub-additive/derivative). LDMS specimen code: BLD/DPE/PL1.
APPENDIX VII

DIVISION OF AIDS
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)
SAMPLE INFORMED CONSENT
For Protocol:

PACTG P1056: 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.
Version 1.0, dated February 3, 2006

Short Title for the Study: GPO-VIR® Pediatric Tablet PK Study

INTRODUCTION

Your child is being asked to take part in this research study because your child is infected with HIV, the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

This study is sponsored by the National Institutes of Health (NIH) of the United States.

The doctor in charge of this study at this site is: (insert name of Principal Investigator).

Before you decide if you want your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you and your child about this information. You are free to ask questions about this study at any time. If you agree to allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

This study is being done to learn more about the anti-HIV drugs produced by the Government Pharmaceutical Organization (GPO) in Thailand. This study will look at the new fixed dose combination (or FDC) tablet, GPO-VIR® for children, a “chewable tablet”.
This study will compare this chewable tablet to the liquid anti-HIV drugs available to treat your child, such as nevirapine (NVP or Viramune®), stavudine (d4T or Zerit®) and lamivudine (3TC or Epivir®). Your child may be taking these liquid anti-HIV drugs already.

This study will measure how much of each of the anti-HIV drugs NVP, 3TC and d4T, are in your child’s blood and how long they stay in your child’s blood. The new GPO-VIR® chewable tablet for children has been made so that NVP, 3TC and d4T can be taken together, all at once. This study will see if there is any difference between the chewable tablets and the liquids, and see if the chewable tablet works just as well.

The new chewable tablet has not been tested in HIV-infected children before and this is the first time it will be tested in people. That is why this study is being done in two parts, called Stage I and Stage II. The study staff will tell you which one your child will be in. Stage I, for a small group of children, will be done first. Stage II, for a larger group of children, will be done after Stage I is over.

This informed consent explains both parts. The number of study visits and tests are the same for both Stage I and II.

WHAT DOES MY CHILD HAVE TO DO IF HE/SHE IS IN THIS STUDY?

Stage I is 4 weeks long and will be done first. Stage II is 8 weeks, and will be done next. A short outline of the study is below:

**STEP 1:** You will be in a treatment Group
You will take the study drugs
Arm A: GPO-VIR® chewable tablets
Arm B: liquid d4T + 3TC + NVP
In Stage I-for 2 weeks, in Stage II-4 weeks

**STEP 2:** You will switch study drugs and take them for (2 weeks in Stage I, 4 weeks in Stage II)
You will then have another PK study.

At Screening (Stage I and II):

If you allow your child to be in this study your child will be asked about his/her medical history and have a physical examination. You and your child will be asked questions about his/her anti-HIV drugs, and if there are any problems taking his/her anti-HIV drugs. Your child must be taking certain types of anti-HIV drugs, for at least 4 weeks, without any problems, to be eligible for this study. The study staff will ask you how your child normally takes his/her doses, and may show you a different way, so that all children
in the study take them in the same way. Your child will also have about 1 ½ teaspoons (6 mL) of blood drawn for routine tests to make sure it is safe for your child to be in this study. The amount of HIV in your child’s blood (HIV viral load) and the number of CD4+ cells (special cells that fight HIV) will be measured. Girls, who have had their first menses, will have a pregnancy test done. Less than 1 teaspoon of urine will be needed. If your adolescent girl is pregnant, she will not be able to be in the study. Your adolescent girl must agree to use a birth control method during the study period. The results of all these tests will be made available to you and your child before you can start the study. This visit should take the same amount of time as your routine clinic visit, but may be longer (2-4 hours). Your study doctor will let you know if your child is eligible for entry in the study.

At Entry (Stage I and II)

The study entry visit will be done within 14 days after screening. Your child will have another physical exam and a review of medical history and HIV symptoms. The same amount of blood will be needed, as at screening for the same types of evaluations (routine tests and measurement of viral load and CD4+ cells). Your child will be randomly assigned, a process like flipping a coin, into one of two treatment groups. This is Step 1 of the study. One group will take the new GPO-VIR® chewable tablet(s) twice a day (every 12 hours). The second group will take an equal dose of each of the liquid study drugs (NVP, 3TC and d4T), as those that are in the GPO-VIR® chewable tablet(s), every 12 hours.

On Study Drugs (Step 1, Stage I and II)

The study staff will make sure that you and your child know how to take these study drugs the right way. A tablet cutter and crusher and syringes with labels for your child when taking the liquid study drugs and instructions will be given to you by the study staff, if needed. Your child will take the same doses, based on weight, as the other children in this part of the study.

For Stage I, your child will take these study drugs for the next 2 weeks. For Stage II, your child will take these study drugs for the next 4 weeks.

There will be a home visit during the first week of the study and a weekly phone call to see how your child is taking the study drugs and to help if you have or your child has any problems. You and your child will be asked to come to the clinic for two visits during the study, while on the study drugs.

If your child is in Stage I, the visits will be during the 2nd and 4th week of the study.
If your child is in Stage II, the visits will be during the 4\textsuperscript{th} and 8\textsuperscript{th} week of the study.

At each visit you will be asked to bring all of your child’s remaining anti-HIV drugs to the clinic so the study doctor can see how well your child is taking them. At the clinic, your child will be seen by a study doctor, who will check your child’s HIV symptoms, ask about his/her health history and do another physical examination.

Your child will have about \( \frac{1}{2} \) a teaspoon (3 mL) of blood drawn for routine tests to make sure it is still safe for your child to continue the study. Your child will have the same routine tests done as before. If your child has had her first menses, a pregnancy test will also be done.

If your child has not taken his/her study drugs the right way, the study doctor may want to continue your child’s study drugs for at least 7 more days, and then check again.

If your child has taken all the study drugs the right way, your child will be admitted to the hospital for special blood tests (called a pharmacokinetic study, or PK study for short). Your child will be in the hospital for 3-4 days.

The study staff will make sure your child takes the study drugs the right way during the hospital stay. On his/her 4\textsuperscript{th} day in the hospital, your child will have the PK study done to measure the study drugs in his/her blood.

**PK study**

Your child will have a total of about 1 tablespoon (17 mL) of blood drawn over 12 hours. A small tube called a heparin lock (a small needle connected to a plastic tube that allows blood to be drawn more than once, without re-sticking the vein) may be placed in your child’s arm during the first blood draw. The first blood sample will be taken before your child takes his/her morning dose of his/her study drugs. Your child will then take his/her morning dose with food. Your child’s blood will be taken at 0.5, 1, 2, 4, 8 and 12 hours after the study drugs were taken. For each timepoint, less than \( \frac{1}{2} \) a teaspoon of blood (2 mL) will be taken. About \( \frac{1}{2} \) a teaspoon or more of blood will be drawn for the routine tests. If there are no problems, your child can go home. The study staff will give you and your child instructions for the next step in the study, before you leave the hospital.

If there are any problems taking your child’s blood for the PK study, you and your child will be asked to either remain in the hospital, or come back to repeat this test. Your study doctor and study staff will let you know what your child needs to do and when this can happen.
Changing Study Drugs (Step 2, Stage I and II)

In Step 2 of this study, your child will switch study treatments. If your child took the GPO-VIR® chewable tablet(s), he/she will switch to the liquid study drugs. If your child took the liquid study drugs, he/she will now take the GPO-VIR® chewable tablet(s), as instructed by the study staff.

If your child is in Stage I, he/she will take these study drugs for 2 weeks. If your child is in Stage II, he/she will take these study drugs for 4 weeks.

For Stage I, you and your child will be come back to the clinic near the end of the 4th week of the study.

For Stage II, you and your child will come back to the clinic near the end of the 8th week of the study.

You will be asked to bring your child’s remaining study drugs. This visit will be the same as the other clinic visit. Your child will be admitted to the hospital for the 2nd PK study in the same way as the first one. The PK study will be done exactly the same way, except the very last blood sample will be 1½ teaspoons (6 mL). This last sample will be for the routine tests and the HIV-viral load and CD4+ cell count to make sure your child does not have any problems at the end of the study.

If your child did not take his/her study drugs the right way, the study doctor will let you know. Your child may have to continue on the study drugs, and be rechecked. If eligible, your child will be admitted to the hospital for the 2nd PK study.

If there are any problems taking your child’s blood for the 2nd PK study, you and your child will be asked to come back to repeat this test. Your study doctor and study staff will let you know what your child needs to do and when this can happen.

After the 2nd PK study is done successfully, there are no more study visits on study drugs. Your child will take the anti-HIV drugs he/she was taking at the very beginning of the study unless your child’s doctor changes them. There will be a safety follow-up visit in about four to six weeks. This visit will include a physical exam and history, and about one teaspoon (6 mL) of blood drawn for routine tests and to measure your child’s viral load and CD4+ count again. The total follow-up time, once your child stops taking the study drugs, is about 6 weeks.
Early Discontinuation/Off Treatment Follow-up (Stage I and II):

If you or your child decide to stop participating in the study at any time, you will be asked to bring the remaining study drugs to the clinic and your child will be asked to have about one teaspoon of blood collected for routine tests, viral load and CD4+ measurements. Another physical exam, history and check on HIV-related symptoms, will also be done.

You should tell your child’s nurse or doctor before your child takes any non-study drugs or medications or enrolls in other clinical trials. No PK study will be done if your child is not on study drugs.

Your child will continue to be followed on study if his/her study drugs are stopped for any reason. These safety follow-up visits will be scheduled about every four weeks, or until it has been 6 weeks after your child stopped taking the study drugs.

Other Information (Stage I and II):

Storage of blood samples:

Some of your child’s blood (if there is any leftover from tests required in this study) may be stored. If it is stored, your child’s identity will be protected. The sample(s) may be used for future PACTG and Thai Ministry of Public Health (MOPH)-approved HIV-related research. Your child’s sample(s) may be stored in Thailand, at either a special laboratory facility or at the study site. Some of these samples may be sent outside of Thailand, for laboratory evaluation, if there is a need to do so. Only approved researchers will have access to them. People who work at the facility will also have access to your child’s samples to keep track of them, but these people will not have information that directly identifies your child. Your child’s samples will not be sold or directly used to produce commercial products. All research studies that ask to use your child’s samples will be reviewed by the Thai MOPH Ethical Committee.

There is no time limit on how long your child’s samples will be stored. The researchers do not plan to contact you or your child’s regular doctor with the results of studies done using your child’s stored samples. Because research studies are often done with experimental procedures, results of such studies should not be used to make decisions about your child’s medical care. If the researchers decide that the result of a certain study provides important information for your child’s medical care, then your child’s study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your child’s address or phone number.
APPENDIX VII (Cont.)

You may decide that you do not want to have your child’s samples stored for future research studies. Your child can still be in this study even if you make this decision.

You may withdraw your consent for the storage and use of your child’s samples at any time. Your request must be in writing.

If you withdraw your consent, all efforts possible will be made to destroy the stored samples. Please read the following statement carefully and then mark your initials in the space provided.

STAGE I or STAGE II:

I agree to allow my child’s blood samples to be stored for use in future PACTG/DAIDS and MOPH-approved, HIV-related research studies.

_____________ Yes                        ____________ No              ___________ Date

I understand I may contact the Principle Investigator (insert name of site) or IRB/EC [insert contact information] to withdraw my consent, if I so choose.

_____________ Yes                        ____________ No              ___________ Date

Data Sharing:

The information collected in this study may be used for other PACTG/DAIDS-approved, HIV-related research.

HOW MANY CHILDREN WILL TAKE PART IN THIS STUDY?

STAGE I: About 8 Thai children will take part in the first part of this study.
STAGE II: About 44 Thai children will take part in the second part of this study.

HOW LONG WILL MY CHILD BE IN THIS STUDY?

STAGE I: Your child will be in this study a maximum of 12 weeks.
STAGE II: Your child will be in this study a maximum of 24 weeks.
WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take your child off the study early without your permission if:

- The Thai MOPH, Thai FDA, US FDA, National Institutes of Health (NIH), the drug company(s) supporting this study [Government Pharmaceutical Organization (GPO) and GlaxoSmithKline (GSK)] or the site’s Institutional Review Board (IRB) or Ethics Committee (EC) decides to discontinue the study. (An IRB/EC is a committee that watches over the safety and rights of research subjects.)
- Your child is not able to attend the study visits as required by the study.
- You or your child refuses to participate further or refuse follow-up evaluations.

The study doctor may also need to take your child off the study drug(s) without your permission if:

- continuing the study may be harmful to your child
- your child needs a treatment that he/she may not take while on the study
- your child is not able to take the study drug(s) as required by the study
- your child becomes pregnant

During the study:
If your child must permanently stop taking study provided GPO-VIR® pediatric tablets and/or the Zerit®, Epivir® or Viramune® liquids before your child’s study participation is over, the study staff will discuss other options that may be of benefit to your child.

After the study:
After your child has completed the study treatment, the study will not be able to continue to provide your child with the GPO-VIR® pediatric tablets and/or the Zerit®, Epivir® or Viramune® liquids that were received on study. If continuing to take these or similar anti-HIV drugs would be of benefit to your child, the study staff will discuss how your child may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

Your child may feel some discomfort when blood is drawn for this study. Other risks may include bleeding, bruising, and swelling or a small blood clot may form where the
needle enters the body. There is a small risk of a minor infection where the needle enters the body. A heparin lock may cause discomfort, bleeding and/or bruising where the needle enters the skin. In rare cases lightheadedness or fainting can occur.

**Risk List for Informed Consent**

**General Disclaimer**

The anti-HIV drugs used in this study may have side effects, some of which are listed below. Please note that these lists may not include all the possible side effects related to these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site.

**Use of Combination Antiretroviral Drugs**

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs and arms
- Breast enlargement

**Nucleoside Analogues, NRTIs [lamivudine (3TC) and stavudine (d4T)]**

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications and death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death has been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

**Lamivudine (3TC, EPIVIR®)**

*GlaxoSmithKline*

The following side effects have been associated with use of lamivudine:

- Headache
- Feeling of vague overall discomfort
- Feeling tired
- Dizziness
- Depression
Lamivudine (3TC, EPIVIR®) Continued

- Upset stomach
- Vomiting
- Loose or watery stools
- Decrease in appetite
- Abdominal cramps
- Sleeplessness
- Rash
- Numbness, tingling, and pain in the hands or feet
- Decrease in the number of white blood cells that help fight infection
- An increase in a substance in the blood (a type of a pancreatic enzyme) which could mean a problem with the pancreas
- Increased liver function tests, which could mean liver damage

The following side effect has been seen in children:
- Inflammation of the pancreas with abdominal pain

Children who are infected with both Hepatitis B and HIV should be warned that their liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen after lamivudine has been stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

Stavudine (d4T, ZERIT®)
*Bristol-Myers Squibb (revised July 2004)*

The following side effects have been associated with the use of stavudine:

- Deaths from liver failure have been reported in pregnant women receiving the combination of stavudine and didanosine with other anti-HIV drugs. Please note: Pregnant females are not eligible for PACTG P1056.
- People who take stavudine together with didanosine, with or without hydroxyurea, may be at greater risk for pancreatitis or liver problems or both. These conditions may result in death. Please note: This combination will not be used in PACTG P1056.
- Numbness, tingling, and pain in your hands or feet
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Rash
- Upset stomach, vomiting and loose or watery stools
- Abdominal pain
APPENDIX VII (Cont.)

Stavudine (d4T, ZERIT®) Continued

- Abnormal liver function blood tests or abnormal pancreatic function blood tests
- Rare cases of muscle weakness, which may progress to paralysis and inability to breathe (This may be associated with elevation of lactic acid in the blood).

When stavudine is used with other medicines with similar side effects, these side effects may be seen more often, and may be more severe, than when stavudine is used alone.

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) [nevirapine (NVP)]

Nevirapine (NVP, VIRAMUNE®)
Boehringer Ingelheim Pharmaceuticals, Inc. (updated March 2005)

The following serious side effects have been associated with use of nevirapine:

Severe liver damage that can result in death may occur and is often associated with rash. Being female or having a higher CD4 cell count, regardless of gender, increase the risk of developing liver damage.

Women with CD4 cell counts greater than 250, including pregnant women receiving chronic nevirapine therapy, are at greatest risk for developing liver damage. Men with CD4 cell counts greater than 400 are also at increased risk. However, these reactions can happen at any CD4 count in both men and women. People who have abnormal liver function tests before starting nevirapine and people with active Hepatitis B or C infection are also at higher risk for liver damage.

If you are developing liver damage, you may have one or more of the following:

- Tiredness
- General feeling of illness or flu-like feeling
- Loss of appetite
- Nausea
- Pale stools
- Dark urine
- Yellowing of the skin or whites of your eyes
- Liver tenderness or abnormal liver function tests
Nevirapine (NVP, VIRAMUNE®) Continued

Hypersensitivity reactions ("allergic reaction") may occur. These reactions are rarely fatal. The symptoms that you notice are: rash, fever, tiredness, muscle or joint aches, flu-like feeling, blisters, mouth sores, facial swelling, red eyes and irritation of the eyes, general feeling of discomfort, and/or liver damage described above, kidney problems, and/or changes in white blood cell levels.

Rash is the most common side effect associated with nevirapine. Rash occurs more often in women. Most rashes occur early during treatment. The rash may be severe and rarely may cause death. One of the risk factors for developing serious skin reactions includes failure to take nevirapine properly during the first 14 days of treatment.

The risk of people developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If you develop any of the side effects listed above, no matter how long you have been receiving nevirapine, you must contact your health care provider right away and before you take your next dose. Your health care provider will instruct you on what to do next. If you and your doctor then decide to stop your treatment because of liver damage, hypersensitivity or severe skin reactions, you should never take nevirapine again.

Other than the serious side effects listed above, additional side effects include:

- Tiredness
- Fever
- Headache
- Upset stomach (nausea, vomiting)
- Muscle pain

Fixed Dose Combinations (FDCs) of the above drugs

The GPO-VIR® chewable tablet for children is a new formulation that has not been tested in children before. If you have questions concerning possible GPO-VIR® side effects, please ask the study staff at your child’s site.

(NOTE: The GPO-VIR® chewable tablet is produced only in Thailand. No Risk list is available from DAIDS/RCC. The available information is from the GPO package insert for S30, which is approved by the Thai FDA.)
GPO-VIR® S30, tablets

*Government Pharmaceutical Organization (Thailand), updated February 2005*

The major side effects include:
- Tingling, burning, numbness or pain in the hands or feet
- Nausea, vomiting, severe abdominal or stomach pain
- Skin rash, mild to moderate
- Severe and life-threatening skin reactions (e.g. Stevens-Johnson syndrome).

Other side effects include:
- Diarrhea
- Inability to sleep
- Headache
- Fever
- Anemia and below normal production of red blood cells
- Joint pain
- Muscle pain
- Abnormal liver function test results
- Hepatitis.

GPO-VIR® Pediatric Chewable Tablets

*Governmental Pharmaceutical Organization (Thailand)*

The side effects are expected to be the same as the side effects reported for the GPO-VIR® S30 tablet, but are not known at this time.

There is the risk of serious and/or life-threatening side effects when non-study medications are taken with study drugs. For your child’s safety, you/your child must tell your child’s doctor or nurse about all the medications your child is taking before your child starts the study and before taking any non-study medications while your child is on the study.

In addition, you/your child must tell the study doctor or nurse before enrolling in any other clinical trials while your child is on the study.
ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the drug or drug combinations in this study harm unborn babies. If your child is having sex that could lead to pregnancy, your child must agree not to become pregnant or make a woman pregnant.

If your child can become pregnant, a pregnancy test must be done, and the result must be negative before she can enter this study. Your child will be advised on methods of birth control, and instructed to use at least one reliable method. The study staff will discuss these options with you and your child. Your child must continue to use birth control until 1 month after stopping study drug(s). If your child becomes pregnant while on this study, she will be taken off the study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

This study may have no direct benefit to your child. Your child may benefit from being closely watched on study and taught how to take his/her anti-HIV drugs the right way. This study may make it easier for your child and other HIV-infected children to take their anti-HIV drugs, if the new GPO-VIR® chewable tablets work as well as the liquid study drugs.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study your child has the choice of:

- Treatment with prescription drugs available to your child
- Treatment with experimental drugs, if your child qualifies
- No treatment

Please talk to your doctor about these and other choices available to your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

For International Sites in Thailand:

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if
required by law. Any publication of this study will not use your child’s name or identify him/her personally.

Your child’s records may be reviewed by the (Siriraj Hospital, Mahidol University, PACTG Site 8251 or Queen Sirikit National Institute of Child Health, Site 8252) 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(s) supporting this study (GPO and GSK) and their designees.

**WHAT ARE THE COSTS TO MY CHILD?**

**Thailand Sites:**

Taking part in this study should not lead to added costs to you and or your child. The cost for treatment related to the study or the study drugs will be covered by the study doctors and study sites in Thailand.

**WILL I/MY CHILD RECEIVE ANY PAYMENT?**

You and or your child will receive a **100 Baht** food allowance for each clinic visit and additional payment to cover travel expenses.

**WHAT HAPPENS IF MY CHILD IS INJURED?**

If your child is injured as a result of being in this study, your child will be given immediate treatment for his/her injuries. There will be no compensation provided through NIH for study-related injuries. You will not be giving up any of your legal rights by signing this consent form.

**WHAT ARE MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?**

Taking part in this study is completely voluntary. You may choose not to allow your child to take part in this study or to have your child leave the study at any time. Your child will be treated the same no matter what you/your child decide(s).

We will tell you about new information from this or other studies that may affect your child’s health, welfare or willingness to stay in this study. If you would like the results of the study, let the study staff at your child’s site know.
WHAT DOES MY CHILD DO IF HE/SHE HAS QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your child’s rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or Ethics Committee (EC)
- telephone number of above

STAGE I - SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to have your child take part in this study, please sign your name below.

___________________________                 ___________________________________
Participant’s Name (print)   Participant’s Signature and Date

____________________________               ___________________________________
Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

____________________________              ____________________________________
Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date

____________________________               ___________________________________
Witness’s Name (print)   Witness’s Signature and Date
(As appropriate)
STAGE II - SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to have your child take part in this study, please sign your name below.

___________________________                 ___________________________________
Participant’s Name (print)   Participant’s Signature and Date

____________________________               ___________________________________
Participant’s Legal Guardian (print)   (As appropriate)  Legal Guardian’s Signature and Date

____________________________              ___________________________________
Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date

____________________________
Witness’s Name (print)   (As appropriate)  Witness’s Signature and Date
APPENDIX VIII

Protocol P1056 Patient Information Handout (PIH)

Purpose: The PIH is an educational tool to help explain the protocol to parents, guardians, families, site staff and IRB/Ethics Committees. It does not replace the Sample Informed Consent.

Title: 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 tablet vs. the Individual Liquid Formulations in HIV-Infected Children ≥6 months to <13 years of age in Thailand.

<table>
<thead>
<tr>
<th>Eligible Children: (This study will be done in two Stages, I and II). Your child can only be in either Stage I or in Stage II, but not both.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV infected Thai infants and children, ages greater than 6 months to less than 13 yrs of age</td>
</tr>
<tr>
<td>• Taking a HAART regimen (NVP + 2 NRTIs) and receiving the maintenance dose of NVP for at least 4 weeks prior to entry (cannot take didanosine (ddI) within 30 days of study entry)</td>
</tr>
<tr>
<td>• For Stage I: children must weigh between 12 and 30 kg (only 8 children will be in Stage I)</td>
</tr>
<tr>
<td>• For Stage II: children must weigh between 6 and 30 kg (between 30 and 44 children will be in Stage II)</td>
</tr>
<tr>
<td>• Both Stages involve a pharmacokinetic or PK study. Children must be able to come and stay in the hospital for the PK study days.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purpose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To look at how the GPO-VIR® pediatric chewable table (based on the same ARV drugs that are in the GPO-VIR® S30 tablet, a fixed dose of d4T, 3TC, NVP) is absorbed in the body compared to the liquid doses of d4T, 3TC and NVP.</td>
</tr>
<tr>
<td>• To compare the chewable tablet and liquid medication and see how safe and tolerable they are. This type of study is known as a cross-over study, because children will take both kinds of anti-HIV medications (tablets and liquids), at different times in the study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Stage I:</strong> Maximum of 12 weeks (maximum 6 weeks of treatment + 6 weeks of safety follow-up)</td>
</tr>
<tr>
<td>Stage I will be done first to make sure the new GPO-VIR® anti-HIV medications are safe and effective for children. If Stage I was successful, Stage II can begin, and involve more children, in different weight groups, to complete the study requirements</td>
</tr>
<tr>
<td>• <strong>Stage II:</strong> Maximum of 24 weeks (maximum 18 weeks of treatment + 6 weeks safety follow up)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications Involved:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The new GPO-VIR® pediatric chewable tablets (a combination tablet of d4T, 3TC &amp; Nevirapine) that can also be crushed or swallowed</td>
</tr>
<tr>
<td>• Stavudine (d4T), Lamivudine (3TC) and Nevirapine (NVP) liquid medications</td>
</tr>
<tr>
<td>• All medications are taken twice a day (every 12 hours) by mouth, with or without food</td>
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</tbody>
</table>
APPENDIX VIII (Cont.)
P1056 PIH

Visit/Study Requirements:

- **Screening visit:** Exam, lab tests, urine specimen (screen for pregnancy) & medication. Must be 14 days within screening to enroll in study. Lab and urine tests and questions about taking the medications on schedule will be done. This is the same in Stage I and II.

- **Step 1:** Children will be randomized to a treatment group. Group “A” taking the GPO-VIR® pediatric tablet or group “B” taking d4T, 3TC, NVP liquid. This step is 2 weeks long in Stage I and 4 weeks long in Stage II.

- Home visits/phone calls may be needed to make sure that the study medication is taken on schedule. If it is, children will be admitted to the hospital several days before the actual PK study. (If there are problems, the hospital scheduling may be adjusted).

- PK study days will be scheduled at the end of the first 2 week or 4 week treatment periods (Stage I, Stage II). Blood is drawn 7 times for each PK study to see if the treatment is working.

- **Step 2:** This is the crossover to the different form of medications (tablets to liquids OR liquids to tablets).

- For Step 2-home visits, phone calls may be used to help with the new study drugs. At the end of this second treatment period (Week 4 in Stage I and Week 8 in Stage II), the PK study will be scheduled, with a stay in the hospital, the same as before. After the last PK study, the study treatment will be over, but a safety follow up period of 6 weeks (both Stage I and Stage II) will monitor the children.

- Extra visits, including home visits or another clinic or hospital stay may be needed if the medications are not being taken as scheduled, or if there were problems during the PK study, or children reacted badly to any of the study drugs that may delay the PK study.

Risks/Benefits:

As with all research, there are certain risks and benefits that come with participation in a study like this. Please refer to the informed consent for a complete description. Parents/guardians have the option to stop their child’s participation in the study at any time, if they so choose.

*This Patient Information Handout must be approved by the site’s IRB/EC prior to distribution.*

**This is an informational tool only and not a substitute for the informed consent – refer to the informed consent for specific study information.

Version Date: 02/03/06