IMPAACT P1069

A PHASE I/II COMPARATIVE PHARMACOKINETIC STUDY OF THE FIXED-DOSE COMBINATION (FDC) OF ZIDOVUDINE (ZDV), LAMIVUDINE (3TC) AND NEVIRAPINE (NVP) AS GPO-VIR® Z30 PEDIATRIC TABLETS VERSUS THE INDIVIDUAL LIQUID FORMULATIONS IN HIV-INFECTED CHILDREN ≥ 5 MONTHS TO < 13 YEARS OF AGE IN THAILAND

An International Limited Center (Thailand) Trial of the International, Maternal, Pediatric, Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID)

and

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Pharmaceutical Support Provided by:

The Government Pharmaceutical Organization (GPO), Thailand

IND# _______ Held by NIAID

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IMPAACT P1069 is a collaborative study restricted to IMPAACT eligible sites in Thailand. It is designed to compare the pharmacokinetics and bioavailability of the new GPO-VIR® pediatric fixed-dose combination (FDC) tablet, GPO-VIR® Z30 produced by the Thai Government Pharmaceutical Organization (GPO) with the standard, brand name liquid formulations of zidovudine (ZDV), lamivudine (3TC) and nevirapine (NVP) in HIV-infected children in Thailand. This generic FDC pediatric formulation, hereafter referred to as “GPO-VIR® Z30” is expected to become the first line of therapy for children in the (Thailand) National Access to ARV Program for People Living with HIV/AIDS (NAPHA). IMPAACT P1069 is modeled after IMPAACT/PACTG P1056, Stage I which is using GPO-VIR® S7 pediatric tablets. P1069 is the second international treatment protocol that will use generic anti-HIV drugs.

All subjects will be enrolled at IMPAACT eligible sites in 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 will hold the IND for this study. Pharmaceutical company support and consultation are being provided by GPO. Subjects in Thailand will be consented and treated as per their country guidelines.

In Thailand, the trial will follow the June 2006 Revision of the Ethical Review Committee of the Ministry of Public Health, the Ethical Principles for Medical Research Involving Human Subjects (http://www.jrecthai.org/html/th/index.php; English and Thai versions on file). It will also follow current World Medical Association Declaration of Helsinki, and ICH Tripartite Harmonised Guidelines for Good Clinical Practice (GCP now E6 (R1), see http://www.ich.org).
GLOSSARY

3TC  Lamivudine
AE   Adverse event, also adverse experience
ALT  Alanine aminotransferase
ART  Antiretroviral Therapy
ARV  Antiretroviral
ATC  (Thailand) Access to Care Program (replaced by NAPHA)
BSA  Body Surface Area
CBC  Complete Blood Count
CRF  Case Report Form
d4T  stavudine
DAIDS (United States) Division of AIDS
DMC (United States) Data Management Center
DOT Direct Observation of Therapy
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® S7 (d4T + 3TC + NVP) FDC pediatric tablet
GPO-VIR® Z250 (ZDV + 3TC + NVP) FDC adult tablet
GPO-VIR® Z30 (ZDV + 3TC + NVP) FDC pediatric tablet
HAART Highly active antiretroviral therapy
ICH International Conference of Harmonization
IMPAACT International, Maternal, Pediatric, Adolescent AIDS Clinical Trials Group
IND Investigational new drug
IRB Institutional Review Board
LAR Legally Authorized Representative
LDMS Laboratory Data Management System
LFT Liver function test
LPC Laboratory Processing Chart
GLOSSARY (Cont.)

MOPH   (Thailand) Ministry of Public Health

NAPHA  (Thailand) National Access to ARV Program for People Living with HIV/AIDS

NEC    (IMPAACT) Network Executive Committee

NIAID  (United States) National Institute of Allergy and Infectious Diseases

NICHD  (United States) National Institute of Child Health and Human Development

NIH    (United States) National Institutes of Health

NNRTI  Non-Nucleoside Reverse Transcriptase Inhibitor

NRTI   Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitor

NVP    Nevirapine

OHRP   (United States) Office for Human Research Protections

PCR    Polymerase Chain Reaction

PI     Protease Inhibitor

PID    Patient Identification Number

PK     Pharmacokinetic (parameters include Area Under the Curve (AUC), Clearance (CI/F), Concentration (maximum and minimum) [Cmax; Cmin], Rate constant (absorption and elimination) [Ka; Kel], Half-life (T1/2 or t1/2), and Volume (distribution) [Vd])

q      Every

RCC    (United States, DAIDS) Regulatory Compliance Center

RIHES  (Thailand) Research Institute for Health Sciences

SADR   Suspected Adverse Drug Reaction

SAE    Serious Adverse Event

SES    Subject Enrollment System

SID    Study Identification Number

SIP    (IMPAACT) Site Implementation Plan

SNP    Single Nucleotide Polymorphisms

SOC    (IMPAACT) Scientific Oversight Committee

ULN    Upper Limit of Normal

U.S.A.  United States of America

VQA    Virology Quality Assurance

WHO    World Health Organization

ZDV    Zidovudine—also called AZT
IMPAACT P1069 PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to actg.teamp1069@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.teamp1069@fstrf.org. All decisions requiring immediate attention, i.e. 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 team members directly via FAX or telephone, (see below) from the USA: 011 + Country and City Codes + phone number [Codes: Chiang Mai, Thailand 66-53; Bangkok, Thailand 66-2. Note-mobile phones: [code 66-8]. From other countries: [USA-IDD=011 and USA Code=1] + Area Code (US) + Number]. Thailand is 12/11 hours ahead of US Eastern Standard Time (EST)/Daylight Time (EDT) respectively. For protocol registration questions, e-mail protocol@tech-res.com or call 1-301-897-1709 and FAX 1-301-897-1710. For Expedited Adverse Events (EAE) questions, e-mail RCCSafetyOffice@tech-res.com or call 1-301-897-1730 or FAX 1-301-897-1710 (International). To order study drugs, contact GPO. For randomization or enrollment questions, contact the Data Management Center (DMC) randomization desk at sdac.random.desk@fstrf.org or (716) 834-0900 x7301. Also refer to the “IMPAACT Protocol Contact List”, on the network website (http://impaact.s-3.com [username = impaact; password = cure]).

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II: STUDY DRUG ADMINISTRATION PROCEDURES
III: SAMPLE INFORMED CONSENT
IV: P1069 PATIENT INFORMATION HANDOUT
SCHEMA

A PHASE I/II COMPARATIVE PHARMACOKINETIC STUDY OF THE FIXED-DOSE COMBINATION (FDC) OF ZIDOVUDINE (ZDV), LAMIVUDINE (3TC) AND NEVIRAPINE (NVP) AS GPO-VIR® Z30 PEDIATRIC TABLETS VERSUS THE INDIVIDUAL LIQUID FORMULATIONS IN HIV-INFECTED CHILDREN ≥ 5 MONTHS TO < 13 YEARS OF AGE IN THAILAND

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

POPULATION: HIV-infected Thai children ≥ 5 months (20 weeks) 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. Subjects must be ≥ 22 weeks of age to be scheduled for the first PK study visit.

SAMPLE SIZE: Minimum 31, maximum 48 evaluable children

STRATIFICATION: Children are stratified by weight, ≥6 to ≤30 kg (n=31-48):

Group 1: ≥6-8 kg (n=5-12)
Group 2: >8-16 kg (n=9-12)
Group 3: >16-23 kg (n=9-12)
Group 4: >23-30 kg (n=8-12)

STEP 1: Randomization into two treatment arms:

REGIMEN: Arm A: Starting regimen: GPO-VIR® Z30 tablet(s) [ZDV 30 mg/3TC 15 mg/NVP 28 mg] orally q 12 hours for two weeks: (Weeks 1-2) Dosing per body weight (See Table 1, Section 5.1 and Appendix II).

Arm B: Starting regimen: Liquid formulations (ZDV + 3TC + NVP), orally q 12 hours for two weeks: Dosing per body weight (See Table 1, Section 5.1 and Appendix II for Viramune®, Epivir® and Retrovir®)

STEP 2: Register into the cross-over regimens, after the PK (end of week 2):

(Weeks 3-4) Arm A: Liquid formulations (ZDV + 3TC + NVP), orally q 12 hours for two weeks (dosing per Table 1)

Arm B: GPO-VIR® Z30 tablet(s) orally q 12 hours for two weeks (dosing per Table 1).
Study Flow Chart:

**STEP I**

<table>
<thead>
<tr>
<th>Day 0</th>
<th>ARM A</th>
<th>Day 14</th>
<th>PK at pre-dose, 0.5, 1, 2, 4, 8 and 12 hrs post-dose</th>
<th>ARM B</th>
<th>PK at pre-dose, 0.5, 1, 2, 4, 8 and 12 hrs post-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GPO-VIRZ30 FDC Q12 hr 2 weeks</td>
<td></td>
<td></td>
<td>Liquid ZDV, 3TC, and NVP Q12 hr 2 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**STEP II**

<table>
<thead>
<tr>
<th>Day 15</th>
<th>ARM B</th>
<th>Day 28</th>
<th>PK at pre-dose, 0.5, 1, 2, 4, 8 and 12 hrs post-dose</th>
<th>ARM A</th>
<th>PK at pre-dose, 0.5, 1, 2, 4, 8 and 12 hrs post-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GPO-VIRZ30 FDC Q12 hr 2 weeks</td>
<td></td>
<td></td>
<td>Liquid ZDV, 3TC, and NVP Q12 hr 2 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacogenomic study for single nucleotide polymorphisms will be tested on buccal swab specimen during the study.

NOTE: PK studies will be conducted at the end of Week 2 and Week 4, respectively. During the 24 hours immediately prior to the PK studies, study drug administration, observation and documentation of ARV ingestion by the subject, will be performed by a health care worker, defined in this study as directly observed therapy (DOT).

**STUDY DURATION:**

8 weeks (On treatment + safety follow-up)

Treatment: Minimum of 4 weeks: (2 weeks on GPO-VIR® Z30 tablet(s) and 2 weeks on the ZDV, 3TC and NVP liquid formulations).

Safety follow-up: 4 weeks
OBJECTIVES:

Primary

1. To evaluate the safety and compare the bioavailability of ZDV, 3TC and NVP in the GPO-VIR® Z30 pediatric tablet formulation with the liquid formulations of ZDV, 3TC and NVP in HIV-infected children in Thailand.

2. To estimate the population average exposure to NVP delivered in the GPO-VIR® Z30 pediatric formulation, and to compare this exposure to an adult exposure of therapeutically adequate NVP concentration.

Secondary

1. To describe the pharmacokinetic parameters of ZDV, 3TC and NVP in HIV-infected Thai children ≥ 22 weeks to <13 years of age in the weight range of ≥6 to ≤30 kg.

2. To evaluate the intra- and inter-subject (e.g. age, pharmacogenomic) variability of the pharmacokinetics of ZDV, 3TC and NVP when administered as the GPO-VIR® Z30 pediatric tablet(s) and as the individual liquid drug formulations.

3. To describe any adverse drug reactions due to the GPO-VIR® Z30 pediatric tablet and the individual ZDV, 3TC and NVP liquid formulations.

4. To evaluate the influence of single nucleotide polymorphisms (SNPs) on nevirapine pharmacokinetic parameters in Thai children.
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 2005 there were 50,620 HIV-infected children. Approximately 0.8 million pregnancies occur each year with a current seropositivity rate in pregnant women of 1.04%. Given a perinatal transmission rate with the current Thai Ministry of Public Health (MOPH)-Mother to child transmission (MTCT) program of 3-8%, 250-665 HIV-infected infants are born annually.

The MOPH 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. 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 MOPH.

In December 2001, GPO-VIR® was registered by the Thai Food and Drug Administration for treatment of HIV infection in adults. 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. The two formulations were listed as the first-line ARV drugs in the national treatment guidelines for HIV-infected adults as part of the Access to Care program. 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 MOPH launched the National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPHA) replacing the Access to Care program, 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 publication on the efficacy of HAART at 72 weeks 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 \(^4\). The long term follow up of this group of children also confirmed the effectiveness of the NVP and EFV-based HAART \(^5\).

GPO-VIR\(^®\) S30 has been used widely in Thai HIV-infected patients. However, the main long-term side effect of GPO-VIR\(^®\) S30 is lipodystrophy due to d4T with 16.8% of adult patients using GPO-VIR\(^®\) S30 reporting lipodystrophy (LD) within two years of treatment initiation \(^6\). In a longitudinal study of lipodystrophy and other metabolic changes in HIV-infected children receiving NNRTI-based HAART, 90 children who began HAART (either nevirapine or efavirenz, together with lamivudine and stavudine) were prospectively followed. Children received nevirapine (53) and efavirenz (37)-based HAART, respectively. The prevalence of LD was 9%, 47%, and 65% at 48, 96, and 144 weeks after HAART initiation respectively \(^7\). Lipodystrophy may therefore be a higher risk in children than in adults on stavudine-containing regimens. Stavudine–free FDCs are especially needed as alternative treatments for children with HIV in order to preserve quality of life for them.

1.11 Why Pursue Pediatric Formulations?

Pharmacokinetics in children is different from that in adults. Various factors specific to the pediatric population dictate the need for additional specific pediatric 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.

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 \(^9\). 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.

GPO has therefore proceeded with its development of pediatric formulations despite having success with giving its adult FDC product to children in limited studies \(^\text{10}\). In 2004, GPO developed a FDC formulation of GPO-VIR\(^\text{®}\) containing d4T (7 mg)/3TC (30 mg)/NVP (50 mg) for pediatric use. It is now called GPO-VIR\(^\text{®}\) S7. It is a chewable, citrus flavored, scored tablet that is taken twice a day (every 12 hours). GPO provided support for the IMPAACT/PACTG P1056 pharmacokinetic study in children. P1056 opened to enrollment in December 2006. Stage I accrual (n=9 evaluable, target was 8) was completed very quickly, on January 29, 2007. Stage I closed to accrual and follow-up on May 3, 2007. The Stage I safety analysis was completed May 2, 2007, and the requirements to continue with Stage II were met. Stage II opened to accrual on May 11, 2007. As of March 2008, 33 subjects have accrued to Stage II.

Initial PK results from Stage I were presented at the IMPAACT Meeting (Primary Therapy session, March 30, 2007 in Washington, DC.-available through the IMPAACT website http://impaact.s-3.com). An abstract was presented (11/18/07) to the 5th World Congress of the World Society for Pediatric Infectious Diseases, November 15-18, 2007 in Bangkok Thailand \(^\text{11}\). An abstract by Chokephaibulkit, K. et al, “Nevirapine Pharmacokinetics in Thai Children Receiving either an Adult or Pediatric Fixed-Dose Combination of Stavudine (d4T), Lamivudine (3TC) and Nevirapine (NVP)” was presented for the 15th Conference on Retroviruses and Opportunistic Infections (CROI 2008), February 3-6, 2008, Boston, MA \(^\text{12}\).
In 2005 the Thai GPO developed a new FDC tablet called GPO-VIR® Z250, in which zidovudine (ZDV) has replaced stavudine (d4T). GPO-VIR® Z250 consists of ZDV 250 mg, 3TC 150 mg and NVP 200 mg. GPO-VIR® Z250 has been used in Thai HIV-infected adult patients since 2005 (package insert for Z250 (English translation dated 7/23/07 from GPO)\textsuperscript{13}.

In 2006 GPO developed a new FDC pediatric tablet. It will be referred to as “GPO-VIR® Z30”, in this study. It consists of ZDV (30 mg)/3TC (15 mg)/NVP (28 mg). This ratio was in accordance with the proposed first line FDC regimen containing AZT/3TC/NVP of 60/30/55 mg by WHO following the expert working group in Geneva in October 2006 (available at http://www.who.int/hiv/events/paediatricmeetingreport.pdf). It was developed to account for the unique metabolic and adherence issues in children. In addition, the substitution of ZDV for d4T may minimize the long-term risks of lipodystrophy in this population where both lifespan and quality of life should be emphasized. If the GPO-VIR® Z30 pediatric tablet is proven to be safe with acceptable PK parameters and becomes available, it is expected to be the preferred first line drug for children, replacing adult GPO-VIR® S30. Moreover, GPO has been distributing their ARVs to Cambodia, Vietnam, Myanmar, Nigeria and Somalia. The GPO plans to expand their market in the future. The availability of pediatric FDCs will make the treatment of HIV in children in many developing countries more feasible.

GPO-VIR® Z30 is a white, round, scored, film-coated tablet that is taken twice a day (every 12 hours). A package insert will be developed, similar to the one for GPO-VIR® Z250. For additional information on GPO-VIR® Z30 refer to the Investigator’s Brochure.

1.12 Previous Pharmacokinetic studies of Lamivudine (3TC), Zidovudine (ZDV) and Nevirapine (NVP)

The nucleoside reverse transcriptase inhibitors (NRTIs), 3TC and ZDV, are 2’ and 3’ modified dideoxynucleosides 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). The pharmacokinetics study of lamivudine in 11 pediatric patients (age 4 months to 14 years of age) receiving oral administration of lamivudine 4 mg/kg twice daily, reported $C_{\text{max}}$ was $1.1 \pm 0.6 \text{ mcg/mL}$ and half-life was $2.0 \pm 0.6$ hours.

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. The median $\text{CL/F}$ 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 ($IC_{50}$) 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 $AUC_{12}$ of 5.2 mg*hr/L and $t_{1/2\beta}$ 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. 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. The mean clearance of 3TC ($\pm$ standard deviation) in the children was $0.53 \pm 0.19$ L/kg/hr and the mean half-life at the distribution and elimination phases were $0.23 \pm 0.18$ and $2.2 \pm 2.1$ hours, respectively. The absolute bioavailability reported from study A2002 was $66 \pm 25\%$ (mean $\pm$ SD) which was less than that observed in adults. The mechanism for the diminished absolute bioavailability in infants and children is unknown. There is limited pharmacokinetic and safety data in infants < 3 months of age.

Elimination of 3TC occurs through renal excretion. Adult patients with severe renal impairment experience >90% reduction in 3TC clearance. In pediatric patients, systemic clearance decreased with increasing age in pediatric patients. The intracellular 3TC triphosphate (TP) concentrations correlate more closely with efficacy than serum 3TC concentrations. Significant relationships were observed between intracellular concentrations of lamivudine triphosphate and baseline CD4 levels. However, intracellular 3TC-TP concentrations demonstrate tremendous inter-patient variability and are not strongly correlated with plasma concentrations.
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.

Zidovudine (ZDV, Retrovir®)

Zidovudine is a synthetic nucleoside analogue. ZDV was the first antiretroviral approved for use in children for the treatment of HIV infection and it remains a component of combination antiretroviral therapy in pediatric patients who are more than 3 months of age 20.

ZDV is phosphorylated to its active 5′-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is DNA chain termination after incorporation of the nucleotide analogue via HIV reverse transcriptase. Following oral administration, ZDV is rapidly absorbed and extensively distributed, binding to plasma protein is low. ZDV is extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hrs in adults. ZDV has its greatest activity in replicating cells. It has good CNS penetration, CSF-to-plasma concentration ratio is 0.68 and ZDV is the NRTI of choice when treating children with HIV-related CNS disease 21.

ZDV is primarily eliminated by hepatic metabolism. The major metabolite of ZDV is 3′-azido-3′-deoxy-5′-O-β-D glucopyranuronosylthymidine (GZDV). GZDV AUC is about 3-fold greater than the ZDV AUC. Urinary recovery of ZDV and GZDV accounts for 14% and 74% respectively, of the dose following oral administration in adults. A second metabolite 3′-amino-3′-deoxythymidine (AMT) has been identified in the plasma following single-dose intravenous (IV) administration of ZDV. The AMT AUC was one fifth of the ZDV AUC. Pharmacokinetics of ZDV were dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours 22. In children, the major route of elimination was metabolism to GZDV. After IV dosing about 29% of the dose was excreted in the urine unchanged, about 45% was excreted as GZDV 22.

Overall, the pharmacokinetics of ZDV in pediatric patients greater than 3 months of age are similar to that of ZDV in adult patients. Oral bioavailability, terminal half-life, and systemic clearance were 65 ± 24%, 1.5 ± 0.7 hr., and 1.85 ± 0.47 L/hr/kg respectively. [Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV

The recommended dose in pediatric patients 6 weeks to 12 years is 160 mg/m² every 8 hours in combination with other antiretroviral agents (480 mg/m²/day up to maximum of 200 mg every 8 hours). Due to the clinical benefit of improved medication adherence expected with twice daily regimens, an oral dose of 180 to 240 mg/m² is suggested in children and adolescents. However, there are few studies of twice daily dosing in children.

The pharmacokinetics of ZDV were evaluated in 6 HIV-infected children who received ZDV 120 mg/m² every 8 hours compared to ZDV 180 mg/m² every 12 hours. ZDV every 12 hours did not result in a higher Cmax than every 8 hours. The pharmacokinetic parameters of both groups did not reveal significant differences, suggesting equivalence of both regimens in terms of plasma pharmacokinetics.

According to the November 2006 Retrovir® package insert, Ribavirin has been found to inhibit the phosphorylation of ZDV in cell culture. In children with HIV and HCV co-infection, concurrent use of ribavirin and ZDV may result in decreased zidovudine efficacy; fatal and nonfatal lactic acidosis; hepatic decompensation; neutropenia; and anemia. Thus, ribavirin use will be disallowed in P1069.

**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 most current Package Insert dated June, 2007. 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. [http://www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov).

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).

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.

In the pediatric pharmacokinetic multiple dose study (BI 882; ACTG 180), nevirapine suspension or tablets (240 or 400 mg/m^2/day) were administered as monotherapy or in combination with ZDV or ZDV + ddI to 37 pediatric patients (2 months – 15 years old). The majority of these patients received 120 mg/m^2/day of nevirapine for approximately 4 weeks followed by 120 mg/m^2/BID (>9 years of age) or 200 mg/m^2/BID (≤9 years of age). Nevirapine apparent clearance adjusted for body weight reached maximum values by age 1 to 2 years and then decreased with increasing age. In the single-dose pharmacokinetics study of nevirapine, BI 858/ACTG 165, 9 children age between 9 months to 14 years were administered a single dose (7.5 mg, 30 mg, or 120 mg/m^2 ; n=3 per dose) of nevirapine suspension after an overnight fast. The mean nevirapine clearance adjusted for body weight was greater in children compared to adults.

Verweel et al. examined their retrospective results of nevirapine use in children and concluded that higher doses (at or over 300 mg/m^2/day)
appeared to achieve more satisfactory virologic results without additional toxicity\textsuperscript{32}. Please refer to the most current Viramune\textsuperscript{®} Package Insert for complete prescribing information.

1.13 Previous Studies of GPO-VIR\textsuperscript{®} FDC tablets

**GPO-VIR\textsuperscript{®}-S30 and S40 in Adults**

GPO-VIR\textsuperscript{®} is indicated for the treatment of patients with HIV infection. For adults and adolescents 60 kg of body weight or over, oral GPO-VIR\textsuperscript{®} S40 1 tablet two times a day; for adults and adolescents less than 60 kg of body weight, oral GPO-VIR\textsuperscript{®} S30 1 tablet two times a day; for children up to 12 years of age-use under physician prescription (English translation).\textsuperscript{2}

There have been several GPO-VIR\textsuperscript{®} S30 and S40 efficacy and safety studies done in Thailand\textsuperscript{33,34,35,36}. 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\textsuperscript{®}. 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\textsuperscript{34}.

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%)\textsuperscript{35}.
GPO-VIR®-S30 and S40 in Children

While there are few published studies of the use of GPO-VIR® S30 in children, a study of children ages 3-15 years was completed by investigators at Siriraj Hospital, Chiang Mai University, and the University of California San Diego. Thirty-five (35) HIV-infected children, who were stable on GPO-VIR® S30 [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; Cmin of 6.0 (2.6-24.4) mcg/mL; T½ of 25.5 (12.1-105.2) h; NVP clearance of 0.08 (0.02-0.16) L/ kg/hr and Vd of 2.95 (2.7-3.2) L/kg. 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.

An efficacy study of GPO-VIR® S30 FDC in 46 Thai children in Chiang Mai, aged 2-14 years, at 72 weeks of treatment found 71% successful viral suppression (<50 copies/mL) by intention-to-treat, and 64% by on-treatment analysis. This efficacy was a bit lower than EFV-based regimen.

GPO-VIR®-Z250 in Adults

Each GPO-VIR® Z250 FDC tablet contains NVP 200 mg, lamivudine 150 mg and zidovudine 250 mg. It is approved for adults, adolescents and children (12 years of age and up) (English translation). The normal dosage is 1 tablet, two times a day, orally.

The bioequivalence study of GPO-VIR® Z250 was conducted in 30 healthy Thai volunteers to compare the oral bioavailability with reference formulation of nevirapine, zidovudine, and lamivudine. The result shows that the 90% confidence intervals of the mean ratios for Cmax, AUC of lamivudine and nevirapine were all within 80.0-125.0%; therefore, lamivudine and nevirapine were bioequivalent. The 90% confidence intervals of the mean ratios for AUC of zidovudine were also within 80-
125%. However, the 90% confidence interval of the mean ratio for $C_{max}$ of zidovudine was 88.6-140.1%. This range is not expected to be clinically significant. (Project No:04002, synopsis report, version: 24 October 2006-on file).

**GPO-VIR® Z250 in Children**

Recently, GPO-VIR® Z250 containing ZDV (250 mg)/3TC (150 mg)/NVP (200 mg) became available for adults and children in the NAPHA program. Forty four (44) children who took GPO-VIR S30, containing d4T (30 mg)/3TC (150 mg)/NVP (200 mg) were switched to GPO-VIR® Z250. At the median of 43 weeks after switching, there was no significant change in CD4 percentage, CD4 lymphocyte count and HIV RNA level. There were statistically significant decrease in hemoglobin level (12.5 vs.12.0 g/dL, p<0.001), white blood cells (WBC) count (8088 vs. 6921/mm³, p<0.001), and absolute neutrophil count (4280 vs. 3462/mm³, p<0.001). No child had neutropenia either before or after the substitution. No child developed clinical symptoms as a result of the hematologic changes. The substitution of stavudine with zidovudine in HIV-infected children receiving HAART did not result in clinically significant hematologic changes.\textsuperscript{37}

**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. 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.

In November 2006, the WHO provided a draft summary statement of recommendations on ARV medicines for treating and preventing HIV infection in younger children. It stated that there is an urgent need for affordable, safe, quality ARV formulations appropriate for pediatric use, particularly solid fixed dose combination (FDC) formulations to facilitate programming planning, improve adherence and facilitate scale up of HIV care for children in line with the public health approach. WHO strongly encourages the development and use of affordable, safe quality ARV formulations appropriate for paediatric use, particularly solid fixed dose combination (FDC) formulations (e.g. crushable, dispersible, granular, scored tablets or capsules) in doses that can be safely used to treat HIV infected pediatric patients, particularly younger ones.
At the same time, the WHO and an international group of pediatric ARV experts (Pediatric ARV Working Group, or PAWG) met to examine existing FDC products, as well as future products to try to identify “ideal” and “acceptable” FDC formulations for children. Target dosing was based on the WHO 2006 Antiretroviral treatment (ART) guidelines for children (these are contained in Annex E of the 2006 guidelines http://www.who.int/hiv/pub/guidelines/WHOpaediatric.pdf).

FDCs that were examined by WHO were as follows 38:

<table>
<thead>
<tr>
<th>Fixed dose combination</th>
<th>Active Components</th>
<th>Strength in mg</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDC 5</td>
<td>D4T/3TC/NVP</td>
<td>5:20:35</td>
<td>Ranbaxy Laboratories Ltd</td>
</tr>
<tr>
<td>FDC 6</td>
<td>D4T/3TC/NVP</td>
<td>6:30:50</td>
<td>Cipla Ltd.</td>
</tr>
<tr>
<td><strong>FDC 7</strong></td>
<td><strong>D4T/3TC/NVP</strong></td>
<td><strong>7:30:50</strong></td>
<td><strong>Thai Government Pharmaceutical Organization (GPO)</strong></td>
</tr>
<tr>
<td>FDC 10</td>
<td>D4T/3TC/NVP</td>
<td>10:40:70</td>
<td>Emcure Pharmaceuticals &amp; Ranbaxy Laboratories Ltd</td>
</tr>
<tr>
<td>FDC 10 suspension (FD10S)</td>
<td>D4T/3TC/NVP</td>
<td>10:40:70 per 5 mls reconstituted</td>
<td>Emcure Pharmaceuticals</td>
</tr>
<tr>
<td>FDC 12</td>
<td>D4T/3TC/NVP</td>
<td>12:60:100</td>
<td>Cipla Ltd.</td>
</tr>
</tbody>
</table>

Subsequently, the WHO has released a technical summary identifying the “ideal” and most urgent FDC products: AZT/3TC/NVP, strength in mg [60:30:55]; AZT/3TC [60:30]; d4T/3TC [7:30]; d4T/3TC/NVP [7:30:55] and Lopinavir/ritonavir (Lop/r) [90:22.5] (http://www.who.int/hiv/paediatric/technicalsummary113006.pdf), as well as the FDC dosing for different weight bands.

The FDA expedites reviews under provisions developed for the President's Emergency Plan for AIDS Relief (PEPFAR). A list of all approvals and tentative approvals under these provisions can be found at http://www.fda.gov/oia/pepfar.htm.

In the previous WHO Table, the Cipla Ltd. (FDC 12) combination and strength in mg, respectively, which was recently approved is d4T/3TC/NVP, [6:30:50]. In IMPAACT P1056, the GPO-VIR® S7 FDC combination being studied is d4T/3TC/NVP [7:30:50].

Specific PK studies of the FDC combination and strength in the new GPO-VIR® Z30 pediatric tablet, ZDV/3TC/NVP [30/15/28] 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 ZDV/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 ZDV plasma levels and response, the dosing strategy for the GPO-VIR® Z30 pediatric tablet is designed to achieve plasma NVP concentrations, e.g. those historically associated with therapeutic success.

In addition to assuring that the GPO-VIR® Z30 pediatric formulation in this protocol results in therapeutic drug exposure, it will be important to know if the bioavailability differs from the brand name liquid formulations. While bioequivalence between the original single drug and the GPO-VIR® Z30 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 P1069 will be generating pharmacokinetic data on the GPO-VIR® Z30 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. P1069 will restrict the subject age for the PK study to at least 22 weeks of age, per conservative estimates of 6 months plus or minus 2 weeks for PK results to be valid.

**Rationale for P1069 Evaluations**

CD4/8+ T-cell count and percentage will be 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 source of drug inter-patient variability can be multi-factorial i.e. drug-drug interactions, drug-food interactions, sex, age, disease state (i.e. renal and hepatic function) and pregnancy. In addition to these known variables, genetic differences in HIV-infected patients have been reported to impact antiretroviral drug, pharmacokinetics, response and toxicity. To date, pharmacogenetics studies of antiretroviral drugs have identified several genetic polymorphisms in critical metabolizing (cytochrome P450) and drug-transporter (P-glycoprotein)
genes which can influence specific antiretroviral drug pharmacokinetics \(^{39}\). In 126 children from PACTG 366 and 377 cohorts the single nucleotide polymorphism G516T in the gene of cytochrome 2B6 (CYP2B6) impacted the pharmacokinetics of nevirapine and clinical responses \(^{40}\). Children with the homozygous variant (TT) had significantly lower NVP oral clearance compared to the other genotype. Within this trial we will assess the influence of common SNPs on the pharmacokinetics of nevirapine in this patient population.

P1069 will utilize buccal swabs for the pharmacogenomic assay; and use the CYP2B6 genotyping method according to procedures provided by Dr. Chanin Limwongse at Siriraj Hospital.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 To evaluate the safety and compare the bioavailability of ZDV, 3TC and NVP in the GPO-VIR® Z30 pediatric tablet formulation with the liquid formulations of ZDV, 3TC and NVP in HIV-infected children in Thailand.

2.12 To estimate the population average exposure to NVP delivered in the GPO-VIR® Z30 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 ZDV, 3TC and NVP in HIV-infected Thai children $\geq 22$ weeks 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 (e.g. age, pharmacogenomic) variability of the pharmacokinetics of ZDV, 3TC and NVP when administered as the GPO-VIR® Z30 pediatric tablet(s) and as the individual liquid drug formulations.

2.23 To describe any adverse drug reactions due to the GPO-VIR® Z30 pediatric tablet and the individual ZDV, 3TC and NVP liquid formulations.

2.24 To evaluate the influence of single nucleotide polymorphisms (SNPs) on nevirapine pharmacokinetic parameters in Thai children.
3.0 STUDY DESIGN

IMPAACT P1069 is a Phase I/II, two arm, randomized, open-label, and multiple-dose comparative pharmacokinetic cross-over study. P1069 is limited to eligible IMPAACT sites in Thailand. It will compare the levels of NVP, 3TC and ZDV in children receiving the new GPO-VIR® Z30 pediatric tablet to those in children receiving the individual liquid formulations as Viramune®, Epivir® and Retrovir®.

The study is divided into two steps per the Study Flow Chart (see SCHEMA). An initial regimen (Step 1) followed by cross–over into the alternate regimen. Advancement into the subsequent step (Step 2) will be dependent on a successful PK study in Step 1. The PK study will be performed after 2 weeks of study drug taken with the requirement of 100% adherence in the 72 hours prior to the PK study day (regimen taken 6 times). During the 24 hours immediately prior to the PK studies, study drug administration, observation and documentation of ARV ingestion by the subject (2 doses); will be performed by a health care worker, defined in this study as directly observed therapy (DOT).

Options for ensuring adherence during the prior 48 hours (4 doses) before the required 24 hour DOT are:

- All doses will be confirmed by DOT (as defined above) OR
- Telephone confirmation via study personnel, verified by a research staff member within 2 hours of the dosing time. (A dosage administration calendar or similar tool will be provided by the sites to caregivers for this purpose).

If either DOT or telephone confirmation reveals any problem or questionable adherence, the subject will have to be hospitalized for 72 hours prior to the PK visit to assure adherence or replaced at the site’s discretion.

On the scheduled PK study visits, the subject will be in the hospital and DOT is documented.

Case Report Forms (CRFs) specific to P1069 and tablet/liquid count will be used to assess subject adherence during this study (see Appendix I and II). The required lead-in period, on a NVP-containing regimen is designed to eliminate the associated skin rash, which usually occurs within the first six weeks of therapy. To be eligible, children must be considered stable on treatment i.e. without acute opportunistic infection and with stable CD4/8+ T-cell counts and percentages; and not considered an “immunological failure” as defined in Section 4.24; and safely beyond the lead-in period for NVP and on maintenance dosing. 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.

P1069 is weight stratified and designed with two-week periods on study drugs for the new GPO-VIR® Z30 formulation.

Children are stratified by weight, ≥6 to ≤30 kg (n=31-48):

Group 1: ≥6-8 kg (n=5-12)
Group 2: >8-16 kg (n=9-12)
Group 3: >16-23 kg (n=9-12)
Group 4: >23-30 kg (n=8-12)

The sample size is expected to result in a maximum of 48 evaluable children, if all Groups achieve maximum accrual. A minimum of 30 is required for adequate statistical evaluation (see Table 2, Section 8.42). The minimum target of evaluable children is designed to be 31. The targets in each stratum are based on potential children, in that weight range, per site projections. The lowest weight group minimum number is only 5, as that group is difficult to enroll due to the success of the prevention of mother-to-child transmission (PMTCT) effort in Thailand, and the fact that any children that may be eligible in that weight group quickly outgrow it. The age requirement for the PK study is ≥ 22 weeks, based on conservative estimates of acceptable PK values (6 months ± 2 weeks, assuming 4 weeks = 1 month).

3.1 Adherence Assessments

Adherence assessments will be done at screening in order to obtain baseline data and give reasonable assurance of subjects’ qualifications for the study. 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 I and II). Early intervention, such as a home visit or more frequent telephone follow-up, will be implemented, as necessary, to identify any potential adherence problems.

In order to ensure eligibility for each PK study (Day 14 in Step 1, Day 28 in Step 2), telephone verification of compliance to the study drug doses will be done, on Days 11, 12 and 25, 26, respectively, prior to the scheduled PK study. DOT by the clinical staff will be done on Day 13, 14 and 27, 28 respectively, as part of the admission for the PK study. The subject will be ineligible for the scheduled PK study visit if the 100% in 72 hours adherence percentage is not met.
The study PK visits are designed to occur on Day 14 and Day 28. However, allowances will be made to account for unexpected issues i.e. national holidays, or subject transport problems. PK studies should be scheduled no sooner than 14 days after initiation of study drug treatment in each Step. PK visits can be rescheduled as detailed in Section 9.22.

3.2 Adherence Assistance

The research staff will provide assistance, as needed, as follows:

- **Phone follow-up** with caregivers will be used to verify subject adherence, as well as to check on adverse events. In addition, a dosage administration calendar tool will be provided by the site (see Appendix I).

- **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, if a problem with taking the study drugs is reported from a phone call (see Appendix I and II).

- Caregivers will be provided with **cell-phones**, if phone contact by the study staff is a problem.

3.3 Cross-over Design

See the Study Flow chart in the SCHEMA. Study drug doses will be administered as detailed in Table 1, Section 5.1 and drug administered as detailed in Section 5.12. See Section 9.0-Pharmacology Plan for PK study details. STEP 1 is designed to be completed in the first two weeks and STEP 2 in the next two weeks.

Additional time on each Step may be granted by the protocol team according to Section 6.2, 6.32 or 9.22.

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® Z30 pediatric tablet(s) for the next two weeks.

Stopping rules and parameters for enrollment pauses for the study are defined in Section 6.3 - Study Management and Section 8.5 - Monitoring.

The P1069 protocol team will review toxicities as reported through clinical evaluation and laboratory monitoring for the duration of the study (designed as
four weeks on treatment with study supplied drugs and a four week safety follow-up period) or eight weeks per subject, 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 supplemental table for grading amylase will be used—see Section 6.24.

CD4/8+ T-cell counts and percentages are measured at screening and/or entry and the final study visit or for early discontinuation, and for safety follow-up. Blood samples for laboratory evaluations hematology/chemistry (3 mL) will be collected in conjunction with the PK studies (14 mL). Laboratory evaluations for early discontinuation, and for off-treatment follow-up, on study, will be collected. Blood volumes for Group 1 will be minimized to the extent possible. Scheduled visit 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). The pharmacogenomic analysis (SNPs) will be done on the collected samples after subjects are off-study. The sample, using a buccal swab for DNA, can be collected at entry, or any other visit.

The P1069 Laboratory Processing Chart (LPC) will contain all details regarding specimen collection, shipping, and storage. Any special procedures will be included in the LPC. The LPC will be available for download from the IMPAACT Protocol Specific Webpage for P1069, http://impaact.s-3.com.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

P1069 will be site restricted to IMPAACT eligible sites in Thailand.

4.1 Inclusion Criteria

4.11 Weight: ≥6 to ≤30 kg

4.12 Age: ≥20 weeks 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 Virology Quality Assurance (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.

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. 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] is necessary during the study. Condoms alone are considered adequate. Hormonal birth control alone (e.g. pills, shots, or slow release inserts placed under the skin) would not be considered adequate. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission. Birth control must continue for 1 month after stopping the study drugs.

4.16 Demonstrated ability and willingness to swallow study drugs, and maintain adherence.

4.17 Willingness to be hospitalized for the 12-hour intensive PK study (must also be ≥ 22 weeks of age, for the PK study).

4.18 Parent or legally accepted representative/guardian able and willing to provide written informed consent.

For subjects to be eligible for Step 2, 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 and be eligible for the second PK study (Day 28) the subject must meet the criteria, as detailed in Section 3.0 (i.e. 100% adherence in the 72 hours prior to the PK study.

If either DOT or telephone confirmation reveals any problem or questionable adherence, the subject will have to be hospitalized for 72 hours prior to the PK visit to assure adherence or replaced at the site’s discretion.

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

Previous CD4+ T-cell values (percent and/or count) will be available from the baseline values collected upon entry to the NAPHA program, as well as from the 6 month follow-up visits recommended in the NAPHA 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 experimental drugs for any indication within 30 days prior to study entry.

4.210 Acute hepatitis due to any cause.

4.211 Chemotherapy for active malignancy.

4.212 Pregnancy

4.213 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.

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

Step 2 Exclusion:

Subjects will be excluded from Step 2, 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.

Deferral of PK study:

- The eligibility for the PK study will be dependent on 100% adherence to the study drugs in the 72 hours prior to the PK study, as described in Section 3.0. The PK study will be deferred as needed until the 100% adherence requirement in the prior 72 hours is met.

- The PK study will be deferred as needed if there is an intercurrent acute illness that may be affected by the study or may affect the study outcome.
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 4.5 will be allowed while on study. Topical corticosteroids, for external application (cream, eye drops, ear drops, nasal spray) are allowed. Note: Prednisone (within the first 6 weeks of NVP therapy), is not recommended to prevent NVP-associated rash per the Viramune® package insert [June 2007].

4.4 Concomitant Medications

Please refer to the study medications most recent package inserts, Investigator's Brochures, or updated information from DAIDS (RCC) to obtain the most current information on drug interactions, contraindications, and precautions.

4.5 Disallowed Medications

A complete list of current medications, including over-the-counter medications will be taken at the screening/entry visit and prior to performing the intensive PK. Disallowed drugs are listed on the following page.

<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, Crixan, Fascar,</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Sporanox®</td>
<td>Candidiral, 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, Ketocrine, Ketomed, Ketonazole, Ketoisol, Ketojal, Manoketo, Masarol, Mizonar, Ninazol, Nizoral, Pasalen, Sporoxyl</td>
</tr>
<tr>
<td>Rifabutin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifadin®, Rimactane®, Rifamate®, Rifampicin®</td>
<td>Manorificin, Myrin, Myrin-P, Ramfin, Rampilicin, Ricin, Ridafour e-200, Rifamcin, Rifampyrid, Rininis, Rifagen, Rifano, Rifater, Rifinah, Rifam, Rifam-P, Rifamed, Rifadin, Rifodex, Rimactane, Rimguee 3-FDC, Rimactazid, Rimecin, Rimstar 4-FDC, RP-Pose, Tibirim,</td>
</tr>
</tbody>
</table>

Anticonvulsants such as those listed below or any medications that may interfere with cytochrome P450
4.6 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 Site Implementation Plan (SIP), for the IMPAACT-eligible Thai sites participating in P1069, must be on file with IMPAACT/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 using the SES. Screening evaluations must be completed within two weeks prior to the start of the study (Entry Day 0). Step 2 will require registration using the SES.

4.7 Co-enrollment

Co-enrollment into any other treatment protocols is discouraged. However, if co-enrollment into an IMPAACT Long Term Follow-up study (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 P1069 study Chair and Co-Chairs.

4.8 Replacement of Subjects
Subjects will be replaced if PK results cannot be evaluated (e.g. samples mistimed, missing, contaminated, mislabeled, insufficient quantity etc.), and if a repeat PK at the entry criteria dosage is not feasible, or has already been done and the results also cannot be evaluated. Subjects will also be replaced for pregnancy or noncompliance to the regimen as detailed in Section 3.1 -adherence assessment.
5.0  STUDY TREATMENT

5.1  Drug Regimens, Administration and Duration

5.11  Regimen:

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.

<table>
<thead>
<tr>
<th>STEP 1: Initial regimens (Table 1): Weeks 1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A: GPO-VIR® Z30 pediatric tablet(s) [ZDV 30 mg/3TC 15 mg/NVP 28 mg] orally q 12 hours</td>
</tr>
</tbody>
</table>

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.

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

- Zidovudine (ZDV); dose by weight as in Table 1
- Lamivudine (3TC); dose by weight as in Table 1
- Nevirapine (NVP); dose by weight as in Table 1

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).
Table 1. GPO-VIR® Z30 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® Z30 [ZDV/3TC/NVP] Pediatric Tablet</th>
<th>Number of Tablet(s) per dose</th>
<th>ZDV dose 10 mg/mL</th>
<th>3TC dose 10 mg/mL</th>
<th>NVP dose 10 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6-6.9</td>
<td>(5-12)</td>
<td>2</td>
<td>ZDV dose 60 mg (6 mL)</td>
<td>30 mg (3 mL)</td>
<td>56 mg (5.6 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7-8</td>
<td></td>
<td>3</td>
<td>90 mg (9 mL)</td>
<td>45 mg (4.5 mL)</td>
<td>84 mg (8.4 mL)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&gt;8-11.9</td>
<td>(9-12)</td>
<td>3</td>
<td>90 mg (9 mL)</td>
<td>45 mg (4.5 mL)</td>
<td>84 mg (8.4 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12-16</td>
<td></td>
<td>4</td>
<td>120 mg (12 mL)</td>
<td>60 mg (6 mL)</td>
<td>112 mg (11.2 mL)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;16-16.9</td>
<td>(9-12)</td>
<td>4</td>
<td>120 mg (12 mL)</td>
<td>60 mg (6 mL)</td>
<td>112 mg (11.2 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17-19.9</td>
<td></td>
<td>5</td>
<td>150 mg (15 mL)</td>
<td>75 mg (7.5 mL)</td>
<td>140 mg (14 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-23</td>
<td></td>
<td>6</td>
<td>180 mg (18 mL)</td>
<td>90 mg (9 mL)</td>
<td>168 mg (16.8 mL)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;23-24.9</td>
<td>(8-12)</td>
<td>6</td>
<td>180 mg (18 mL)</td>
<td>90 mg (9 mL)</td>
<td>168 mg (16.8 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25-30</td>
<td></td>
<td>7</td>
<td>210 mg (21 mL)</td>
<td>105 mg (10.5 mL)</td>
<td>196 mg (19.6 mL)</td>
<td></td>
</tr>
</tbody>
</table>

Note: For Step 1 study drug dosages will be based on weight at Day 0, according to this table. For Step 2, the weight for Groups 2-4 is not expected to change in 2 weeks, therefore, they will not be re-weighed, and the Day 0 weight value will be used to determine the Step 2 study drug doses. For Group 1 see below.

Step 1 Completion

The satisfactory completion of the PK study in Step 1 is defined as: the predose and at least 5 of 6 postdose samples were collected, and all information recorded on the appropriate CRF, see Section 9.21). Immediately after this, 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/off study. Follow-up for safety will continue until the defined end of the study.

For Group 1 only: Doses will be adjusted per Table 1, if the subject’s weight changes during the study, i.e. between Step 1 and 2 (Day 14-15).
- If the weight change is greater than 10% of the Day 0 weight, (increase or decrease) the doses in Step 2 will be those corresponding to the new weight, per Table 1.
- If the weight change is less than or equal to 10% of the Day 0 weight (increase or decrease) study dosages will be based on the subject’s initial weight on Day 0.

<table>
<thead>
<tr>
<th>STEP 2: Cross-over regimen (Weeks –3-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm A:</strong> 3TC + ZDV + NVP liquid formulations, administered orally q 12 hours:</td>
</tr>
<tr>
<td>• Zidovudine (ZDV); dose by weight as in Table 1</td>
</tr>
<tr>
<td>• Lamivudine (3TC); dose by weight as in Table 1.</td>
</tr>
<tr>
<td>• Nevirapine (NVP); dose by weight as in Table 1.</td>
</tr>
<tr>
<td><strong>Arm B:</strong> GPO-VIR® Z30 pediatric tablet(s), [ZDV 30 mg/3TC 15 mg/NVP 28 mg] administered orally q 12 hours per Table 1.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.12 Drug Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>For P1069, the tablet(s) will be administered with water. If younger children cannot swallow them, the tablet(s), should be crushed in a mortar, see Appendix II for supply information.</td>
</tr>
</tbody>
</table>

Tablets will be crushed using the mortar and pestle. 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.

The GPO-VIR® Z30 tablet(s) and the individual liquid formulations will be administered without food.

<table>
<thead>
<tr>
<th>GPO-VIR® Z30 Pediatric tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ZDV 30 mg/3TC 15 mg/NVP 28 mg]</td>
</tr>
<tr>
<td>• Tablet(s) will be administered every 12 hours, without food.</td>
</tr>
</tbody>
</table>
Subjects prescribed the liquid formulations will receive equivalent doses of 3TC, ZDV and NVP, by weight, as in the GPO-VIR® Z30 pediatric tablet.

3TC, ZDV and NVP oral suspension/solution

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

5.13 Study Treatment Duration

The study treatment is a minimum of 4 weeks, for all Groups. However, Group 1 may be extended to a maximum of 8 weeks, dependent on blood volume limitations, toxicity/tolerability, and/or the need to repeat PK studies. [The maximum allowance for cumulative blood drawn in 8 weeks is 8 mL/kg].

For Groups 2-4 the minimum study treatment is 2 weeks per Arm (4 Weeks total), a maximum of 6 weeks, if needed for repeat PKs etc.

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).

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. Store in tightly closed bottles at 25°C (77°F).

5.23 Zidovudine (ZDV, Retrovir®):

ZDV syrup is a colorless to pale yellow liquid that is strawberry flavored. Each teaspoon (5 mL) contains 50 mg ZDV and these inactive ingredients: sodium benzoate 0.2% as a preservative, citric acid, flavor, glycerin and liquid sucrose. Sodium hydroxide may be added to adjust pH. Store at 15-25°C (59-77°F). 240 mL bottles have child-resistant caps.
5.24  GPO-VIR® Z30 Pediatric tablet:

GPO-VIR® Z30 pediatric tablet(s) are white, round-shaped and film-coated. One side is bisected (scored). Each tablet contains 30 mg ZDV + 15 mg 3TC + 28 mg NVP. Store in tightly closed bottles at below 30°C (86°F).

The package insert from GPO for the Z30 tablet, is available for review. GPO products conform to Good Manufacturing Practice (GMP) and International Standard Operation (ISO) Standards. Available information is based on the GPO-VIR® Z250 formulation, www.gpo.or.th. (See www.unicef.org/supply for a list of World Health Organization ARVs.)

5.3  Drug Supply, Distribution and Pharmacy

5.31  Supply

- GPO-VIR® Z30 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 through GPO. Specific gravity of the solution is 1.08 g/mL (typically).

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

- Zidovudine (ZDV); Retrovir® liquid (GlaxoSmithKline; 50 mg/5 mL or 10 mg/mL, 240 mL bottles) will be provided through GPO. Specific gravity is 1.17-1.23 g/mL (avg 1.2 g/mL).

5.32  Study Supply Acquisition

Study materials will be available through GPO. Oral syringes, glass mortar and pestle (if needed) will be supplied by the study site staff (see Appendix II).

GPO-VIR® Z30 tablets and the brand name liquid study drugs used in P1069 will not be provided to subjects prematurely discontinuing the study or after study termination, through IMPAACT.
GPO will continue to provide the fixed-dose combination (FDC) product until full approval by the MOPH if it is considered in the child’s best interest. 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 GPO-VIR® Z30 formulation has not been approved by the Thai FDA for treatment of HIV in pediatric subjects by the time P1069 closes to follow-up.

5.33 Study Agent Accountability

The site pharmacist is required to maintain complete records of all study medication received. 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; and referred to as the “DAIDS AE Grading Table”.

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator.

Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normals will be the institutional values. However, if a site does not have an age-specific normal range/value for a particular lab, the site should use the latest (17th) edition of the Harriet Lane Handbook 42 or Nelson’s Textbook of Pediatrics (18th ed.) 43 for normal ranges/values and document this for monitoring purposes. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2.
The toxicity management guidelines are for events for which a relationship to study drugs cannot be excluded. Clinical or laboratory adverse events (AEs) that are definitely unrelated to study drug(s) may not result in study drug interruption.

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. Study drugs will either be continued at protocol-specified doses or discontinued. See Section 6.3-Subject Management. See Section 9.32 for the PK parameters established for the study drug exposures. If results are inadequate, enrollment may be stopped as soon as the decision is made by the study team and Medical Officer.

If the protocol team determines that a study drug dose modification is necessary, the protocol will be amended accordingly.

General toxicity management guidelines are provided below. The management of specific adverse events is detailed in Section 6.2 and supersedes 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 the study, (provided stopping criteria are not 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.
Grade 3 and non-life threatening Grade 4*:

- The observation must be confirmed within 72 hours.

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 P1069 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 P1069 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, zidovudine, or nevirapine and/or their combinations; e.g. headache, loss of appetite, 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.

The maximum treatment interruption period is 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 monitoring...
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 P1069 protocol team to determine course of action, actg.teamp1069@fstrf.org. Obtain confirmatory laboratory results within 72 hours and notify the P1069 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.teamp1069@fstrf.org. Thai clinicians must contact the Protocol Chair and Co-Chairs 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 maximum treatment interruption period is 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.teamp1069@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.
Chair: Dr. Kulkanya Chokephaibulkit +66 2 4180545, FAX: +66 2 180544
The P1069 protocol team roster lists contact information for all team members, site investigators, pharmacists and coordinators.

6.2 Management of Specific Adverse Events

All toxicities that are ≥Grade 1 will be collected on IMPAACT P1069 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 AE Grading Table (Version 1.0) must be reported immediately to the P1069 Team by e-mail at actg.teamp1069@fstrf.org.

For subjects who develop cutaneous reactions ≥Grade 2 with any of the following signs/symptoms, study drugs should be immediately discontinued. Thai sites should contact the protocol Chair and Co-Chairs for 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.teamp1069@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\text{ x ULN}\]), Grade 3: [\(>5.0-10.0\text{ x ULN}\]) or greater should permanently discontinue nevirapine. 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.teamp1069@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.teamp1069@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 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 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 immediately to determine course of action. If hyperlipasemia recurs, discontinue all study drugs. All notifications should use the mailgroup: actg.teamp1069@fstrf.org.

6.24 Hyperamylasemia

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

Upon presentation of Grade 3 or 4 total amylase; the blood sample should be fractionated and the pancreatic fraction should then be used to determine the toxicity management. The toxicity grades for total amylase will be calculated using the local laboratory ULN and will be graded according to the table below:

<table>
<thead>
<tr>
<th>CHEMISTRIES (Standard International Units as per Local Laboratory)</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total amylase</td>
<td>&gt;1.0-1.5 x ULN</td>
<td>&gt;1.5-2 x ULN</td>
<td>&gt;2.0-5.0 x ULN</td>
<td>&gt; 5.0 x ULN</td>
</tr>
</tbody>
</table>
For purposes of this protocol the upper limit of normal (ULN) for pancreatic amylase is defined as 37% of the ULN for total amylase.

Pancreatic amylase will be graded according to the relationship to ULN (as determined above) and graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 [December 2004], [http://rcc.tech-res-intl.com](http://rcc.tech-res-intl.com) (see Laboratory section, pancreatic amylase parameter, pg. 19 of 20 of 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 (≥ Grade 2), hold all study drugs until both pancreatic amylase and lipase are Grade 1 or less. Notify the protocol team at actg.teamp1069@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.teamp1069@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.teamp1069@fstrf.org if values are ≥ 2.5 x ULN or higher.
- 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 Thai protocol Chair and Co-chairs. Also, send an e-mail to the protocol team actg.teamp1069@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 at least one grade higher than baseline. However, for the subject who had AST/ALT elevated to the upper limit of Grade 1 at enrollment (e.g. at 2-2.5 x ULN), the drug will be discontinued if AST/ALT becomes elevated to > 3.5 x ULN.

• 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.teamp1069@fstrf.org. Subjects who develop hepatic steatosis must immediately and permanently
6.26 Symptoms of Peripheral Neuropathy

For grading symptoms of peripheral neuropathy, follow the DAIDS AE Grading Table, (Clinical/Neurologic/parameter: neuromuscular weakness, pg. 10 of 20, Version 1.0, Dec. 2004).

- 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 occasionally 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.teamp1069@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 described below:

Neutropenia or anemia ≥Grade 3, thought to be study drug related:
- Stop study drugs and repeat laboratory measurement within 72 hours.
- If no recovery, contact the Protocol Chair and Co-chairs to determine course of action.
• If recovery to ≤Grade 2 (w/in 7 days): Restart study drugs at full dose and monitor weekly
• If recovery is maintained ≤Grade 2 (for ≥7 days), continue study drugs at full dose
• If there is a return to ≥Grade 3, 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 and Temporary Suspension of Enrollment

The study will be stopped if two or more of the first 10 subjects enrolled experience a confirmed ≥Grade 3 toxicity (cutaneous or non-cutaneous) or ≥ Grade 2 lactate thought by the protocol team to be definitely, probably, or possibly related to the GPO-VIR® Z30 pediatric tablets, while on treatment using the tablets (Step 1/Arm A or Step 2/Arm B), in accordance with Section 8.51. An initial noncompartmental PK analysis (for pediatric tablet bioavailability) for ZDV, 3TC and NVP will be performed after the first 10 subjects have completed both PK sampling visits, in accordance with Section 8.512 and 9.32.

Enrollment will be suspended temporarily if two or more of the first 10 subjects enrolled 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.

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). Subjects will be followed on study and/or off treatment until the final scheduled visit (see Appendix I and footnotes) or until the event is resolved if determined appropriate by the protocol team and DAIDS Medical Officer.

6.3.2 PK Study Management

6.3.2.1 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 and age. See Section 3.0. See Appendix II for adherence plan details, and 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.

• The PK study will be deferred as needed if there is an intercurrent acute illness that may be affected by the study or may affect the study outcome.

• 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, as stated in Section 4.8).

If no adverse events have occurred after the last PK time point (12 hours post dose) of the second PK Study (Day 28) for Groups 1-4 or a repeated PK study, if necessary, the subject can be considered off study treatment. The safety follow-up phone call (one week after the last PK visit) and final study visit for safety follow-up (about 4 weeks after the last PK visit) will be done to document any adverse events/problems.

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.

• 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.
7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 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).

7.2 EAE Reporting Requirements for this Study

7.21 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:

- 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

7.22 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:

• GPO-VIR® Z30 tablet [ZDV 30 mg/3TC 15 mg/NVP 28 mg]
• Lamivudine (3TC)
• Nevirapine (NVP)
• Zidovudine (ZDV)

7.23 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.

7.24 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 P1069, the safety follow up period is for 4 weeks, after the last PK visit, for an expected study duration of 8 weeks, if no additional time for repeat evaluations, PK, resolution of toxicity or blood volume limitations (Group 1) are necessary.

• 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@techres.com) or call 1-301-897-1709 or FAX 1-301-897-1710 (International). 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® Z30 in Thai pediatric populations. The first primary objective is to evaluate the safety and describe the comparative bioavailability of NVP ZDV and 3TC in the GPO-VIR® Z30 pediatric tablet formulation relative to that achieved with a standard oral solution (administered as standard oral solutions of ZDV, 3TC and NVP).

The second primary objective is to estimate the population average exposure to NVP delivered in the GPO-VIR® Z30 pediatric formulation, and to compare this exposure to an adult exposure of therapeutically adequate NVP concentration.

Secondary objectives address the PK parameters of ZDV, 3TC and NVP and intra and inter-subject variability (pharmacogenomics) in the study population taking the liquid formulations compared to the GPO-VIR® Z30 tablet.

The design consists of two steps. 31-48 Thai children (≥6 to ≤30 kg), stratified by weight, will be randomized to a cross-over design for evaluation of 1) the comparative bioavailability of the standard and generic formulations and 2) an estimation of the population average exposure to NVP delivered in the GPO-VIR® Z30 pediatric formulation. P1069 will be evaluated for toxicity and therapeutic adequacy using individual protocol specified liquid formulations and the GPO-VIR® Z30 pediatric tablet(s) in a cross-over design. Formal criteria for terminating the protocol are given, based on the number of subjects experiencing certain toxicities that are definitely, probably or possibly study drug-related (see 8.51 below).

This design is motivated by information from P1056 on the tolerability and adequacy of the GPO-VIR® S7 pediatric tablet studied in a similar population of Thai children. Stage I results met the safety and therapeutic adequacy criteria and no stopping rules were employed. The design of P1069 is based on Stage I of P1056. It involves a two-week treatment period for each formulation being evaluated in Groups 1-4. For Group 1, the time period is also expected to be 4 weeks, as the study visit requirements are reduced, when possible, to minimize
the blood draws, and to conform to the blood volume limitations for very young children. Toxicity risks are expected to be minimal; however, stopping rules will still be applied. The pharmacokinetic phenomena of interest are invariant to the treatment duration.

The GPO-VIR® Z30 tablet dosing is based on a child’s body weight. This leads to dose- or weight-based groupings. In P1069, there will be a five to twelve children allocated to the lowest weight group—Group 1. In Groups 2 and 3, a minimum of nine, maximum of 12 children weighing greater than 8 kg, but less than 23 kg and a minimum of eight, maximum of 12 children in Group 4 (those weighing >23 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® Z30 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

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 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 9.3, 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® Z30 pediatric tablets and standard liquid formulations. Subjects will be divided into two groups: wild type CYP2B6 versus those exhibiting single nucleotide polymorphisms (SNPs). The groups will be compared with respect to NVP AUC, using a t test if the data is normally distributed or a nonparametric test otherwise.

8.3 Stratification

Subjects will be stratified according to weight as described in Section 3.0. Dosage based on weight at entry (Day 0) will be determined according to Table 1 in Section 5.11 for Step 1. Dose adjustments, per weight gain or loss for Step 2 will be as described in Section 5.11.

8.4 Sample Size

8.41 Comparative bioavailability of NVP in the GPO-VIR® Z30 pediatric tablet and the standard oral solutions of NVP, ZDV, and 3TC

P1069 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.

8.42 Therapeutic adequacy of NVP plasma concentrations with GPO-VIR® Z30 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® Z30 tablet exposures.

The therapeutic adequacy of GPO-VIR® Z30 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) = approximately 25%, \textsuperscript{41,45}.}
The P1069 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® Z30 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=30</td>
<td>0%</td>
<td>9%</td>
<td>58%</td>
<td>81%</td>
<td>58%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>N= 31</td>
<td>0%</td>
<td>9%</td>
<td>60%</td>
<td>82%</td>
<td>58%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>N= 35</td>
<td>0%</td>
<td>9%</td>
<td>64%</td>
<td>86%</td>
<td>64%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>N= 40</td>
<td>0%</td>
<td>10%</td>
<td>68%</td>
<td>88%</td>
<td>68%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>N= 48</td>
<td>0%</td>
<td>11%</td>
<td>75%</td>
<td>90%</td>
<td>74%</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table margins are sample size and true mean AUC of NVP using GPO-VIR® Z30 pediatric tablets. Table cells give the probability of affirming the adequacy of the GPO-VIR® Z30 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 data from all weight strata are determined to be homogeneous and are combined.

Accrual of 35 children will provide an 86% 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® Z30 formulation is no greater than 11%. These probability calculations include the probability that the study is terminated early owing to observation of two events of study-terminating toxicity in the first 10 subjects enrolled or due to substandard bioavailability for NVP in the first 10 subjects enrolled.

Therapeutic inadequacy is declared if the GPO-VIR® Z30 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

IMPAACT P1069 is a Phase I/II two step comparative PK study. It will be monitored as a Phase I study. 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 P1069 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 evaluable of the PK samples for the primary outcome variables will be reviewed.

At any time during the study if ≥ 25% of the subjects have experienced a Grade 3 or higher toxicity thought by the protocol team to be definitely, probably, or possibly related to study drugs, the study will be placed on a safety pause and further evaluations by the core team and Medical Officer will be made with a report of the team’s determination made to the IMPAACT leadership, FDA, GPO, MOPH, NIAID and CSRC.

If no stopping rules are met, the Protocol Chair(s) will prepare a brief summary of the status of the ongoing safety reviews of the protocol every six months (starting from the date of the first enrollment) as required by DAIDS and/or as required by the Thai MOPH. These summaries and/or interim safety reports (and host language translations, if needed) will be provided to the participating study sites for submission to their Institutional Review Boards (IRBs) and/or Ethics Committees (ECs).
8.51 Early Stopping Rules

8.511 Toxicity

*The study will be stopped if two or more of the first 10 subjects enrolled experience:
  • Confirmed ≥ Grade 2 lactate
  • Confirmed ≥ Grade 3 toxicity (cutaneous or non-cutaneous) thought by the protocol team to be definitely, probably or possibly related to the GPO-VIR® Z30 pediatric tablets while on treatment using these tablets (Step 1/Arm A or Step 2/Arm B).

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

*The study enrollment will be suspended temporarily if two or more of the first 10 subjects enrolled experience:
  • Persistent confirmed ≥ Grade 2 cutaneous toxicities that are definitely, probably or possibly study drug-related.
  • 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.

8.512 Substandard Bioavailability

An initial noncompartmental pharmacokinetic analysis for ZDV, 3TC and NVP will be performed after the first 10 subjects have completed both PK sampling visits. This analysis is to prevent the possibility of continuing to enroll subjects in the study when the pediatric tablet has appreciably substandard bioavailability. See Section 9.32. Based on these results, enrollment may be stopped as soon as the decision is made by the study team and Medical Officer.
8.52 Therapeutic Inadequacy

For P1069, the determination of therapeutic inadequacy is based on the location of the 90% CI for the mean NVP AUC based on all subjects receiving the GPO-VIR® Z30 tablet.

- Therapeutic inadequacy is declared if the GPO-VIR® Z30 pediatric tablet regimen-based 90% CI for AUC lies entirely below <70% of the target mean AUC (i.e. 44.5 mcg*hr/mL)

OR

- Therapeutic inadequacy is declared if the GPO-VIR® Z30 pediatric tablet regimen-based 90% CI for AUC lies entirely above >143% of the target mean AUC (i.e. 90.9 mcg*hr/mL).

8.53 Accrual Rate Monitoring

The team will use site-generated accrual benchmark projections to assess accrual, based on the date of first enrollment, after a site is protocol registered. If accrual has not been steady (6 month review), study feasibility will be assessed by the Protocol Team in conjunction with the IMPAACT Primary Therapy Scientific Committee and IMPAACT International Resource Committee and/or IMPAACT Performance Evaluation Resource Committee (PERC) or Scientific Oversight Committee (SOC) and/or Network Executive Committee (NEC). Group sample sizes, in relation to accrual, will be evaluated. Any discussion regarding study continuation or modification will include DAIDS and the Clinical Science Review Committee (CSRC). If the study has not been completed in 12 months DAIDS/CSRC will require a formal decision on whether the study should remain open, or close to accrual.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Study Design

This is a two step, Phase I/II, two arm, randomized, open-label, multiple dose pharmacokinetic cross-over study of a minimum of 31, maximum of 48 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. Children will be stratified into one of four groups based on body weight and randomized to either treatment Arm A or B (Step 1), for two weeks. The first 12 hour PK study will be
scheduled to be done on Day 14 of the study, if age (≥ 22 weeks), adherence and toxicity parameters are acceptable. Upon satisfactory completion of the PK study, cross-over to the alternate regimen (Step 2, also 2 weeks) will occur immediately afterwards. The second 12 hour PK study will be scheduled to be done on Day 28 if adherence and toxicity parameters are acceptable, and conclude the treatment portion of the study. The minimum study duration for P1069 is 8 weeks (4 weeks on study drug treatment, 4 weeks of safety follow-up). A maximum of 8 weeks on study treatment will be allowed for repeat PK studies and study calendar adjustments for toxicity, if needed. Four weeks of safety follow up will bring the maximum study duration to 12 weeks.

9.2 Pharmacokinetic (PK) Evaluation

9.21 ZDV, 3TC and NVP plasma levels

Eligibility for the PK studies:

- ≥ 22 weeks of age
- 100% adherence to the study treatment regimen in the 72 hours prior to the PK study, as described in Section 3.0

1st Intensive PK study

DOT as previously defined in this study, will be done during the 24 hours immediately prior to the PK studies. The times of all study drug doses will be recorded (note the subject must swallow (or crush, if unable to swallow) the GPO-VIR® Z30 tablet(s) with water.

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 12 hour-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 (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, a predose blood sample (2 mL) will be obtained prior to the directly observed morning dose. The recommended dose of the specified study drugs will be administered and the time and method recorded. Blood samples (2 mL each) will be obtained at 0.5, 1, 2,
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 and then repeat the entire PK study. The maximum blood volume drawn cannot exceed the allowable amount (see Section 9.22).

2nd Intensive PK Study

Subjects will be monitored again for study drug adherence and documentation of the doses in the 72 hours prior to the second PK study. On Day 28 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 of administration (tablet-i.e. swallowing or crushing) 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 in the previous section. Evaluability is defined in Section 9.4.

Replacement of subjects will be allowed if blood samples are unevaluable due to damage during shipment or for unforeseen circumstances (see Section 4.8 and 9.4). If a limited amount of blood is available for a specific timepoint/blood draw sample, measurement of the nevirapine concentration is the first priority.

9.22 Rescheduling PK studies

The PK study will be delayed if:

- Adherence parameters are not acceptable (Sections 3.0, 3.1 and 3.2). This should be a rare event given the adherence monitoring plan in the 72 hours prior to the day of the intensive PK. 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.

- The PK study will be deferred as needed if there is an intercurrent acute illness that may be affected by the study or may affect the study outcome.

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 the 72 hours of adherence monitoring prior to the sampling). The maximum blood volume drawn cannot exceed the amount allowed.

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

- Exceeding the allowable amount of cumulative blood volume drawn (8 mL/kg in 8 weeks). The time to reschedule will need to be at least a 4 week interval.

- 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.)

9.23 Analytical methodology

Measurement of NVP, 3TC and ZDV 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 ZDV and 3TC (Simultaneous Determination of 3TC, ddI, ZDV; ZDV, and ABC in Human Plasma by Reversed-Phase UV HPLC: supplied by Dr. Courtney Fletcher, University of Colorado, (relocating to Nebraska). This assay has been validated in the PK laboratory in Chiang Mai and its sensitivity is 25 ng/mL for ZDV and 3TC. These limits are sufficient to accurately characterize the AUC for all GPO-VIR® Z30 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 ZDV, 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 done by GlaxoSmithKline. Zidovudine concentrations will fall below the limit of detection at ~8 hours after drug intake (C₈) due to the very rapid elimination rate of ZDV. 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

9.3.1 PK Parameters

Following the blood sample collection during the intensive PK sampling visits, samples will be shipped from the participating Thai sites to the PHPT-IRD Pharmacology laboratory in Chiang Mai via authorized courier within one week. Analysis of plasma drug levels (ZDV, 3TC and NVP) will be completed and results reported via the LDMS within four (4) weeks of receiving the samples at the laboratory.

The plasma concentrations of ZDV, 3TC and NVP following administration of the GPO-VIR® Z30 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 (Cₘₐₓ) and time of the maximum observed concentration in plasma (Tₘₐₓ)
- Minimum concentration of drug in plasma (Cₘᵢₙ)
- Average concentration of drug in plasma at steady state (Cₐᵥ), which can be calculated by the following equation:
  \[ C_{av} = \frac{AUC}{\tau} \]  Where \( \tau \) is the dosing interval

- Half-life (T₁/₂) will also be estimated for 3TC and ZDV.
- Pharmacokinetic parameters will be presented by weight group and by mode of administration (swallowed, crushed/taken with 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.
9.32 Initial PK Analysis-First 10 Subjects

An initial noncompartmental pharmacokinetic analysis for ZDV, 3TC and NVP will be performed after the first 10 subjects have completed both PK sampling visits. This analysis is to prevent the possibility of continuing to enroll subjects in the study when the pediatric tablet has appreciably substandard bioavailability.

To address this possibility, target thresholds for ZDV, 3TC and NVP will be examined. The target values for the expected AUC are: 2.8 mcg*hr/mL for ZDV \textsuperscript{20}, 4.43 mcg*hr/mL for 3TC \textsuperscript{46} and 63.6 mcg*hr/mL for NVP \textsuperscript{45, 47}.

The GPO-VIR®Z30 drug exposure would be too high if the 90% CI for ZDV, 3TC or NVP AUC lies entirely above twice the target mean AUC value.

The GPO-VIR®Z30 drug exposure would be too low if the upper bound of the 90% CI lies entirely beneath the ½ target mean AUC value.

Subject enrollment will not be stopped during this analysis.

For this preliminary analysis, plasma drug levels (ZDV, 3TC and NVP) measurement will be performed real-time. The noncompartmental pharmacokinetic analysis will be completed within one week of data assembly and presented to the study team, IMPAACT leadership and DAIDS. Based on these results, enrollment may be stopped as soon as the decision is made by the study team and Medical Officer. A decision on whether or not to modify study drug doses will then be made by the study team and Medical Officer.

Pharmacogenomic analysis:

P1069 will utilize buccal swabs to collect a subject sample for the pharmacogenomic assay; and use the CYP2B6 genotyping method according to procedures (Cytology brush and DNA extraction, PCR amplification, restriction enzyme digestion, electrophoresis and interpretation) provided by Dr. Chanin Limwongse at Siriraj Hospital. Participating Thai sites will batch ship these samples to Siriraj Hospital, toward the end of the study. (See the P1069 LPC for details).
9.4 Evaluable Subjects

For a subject meeting the adherence requirements (Section 3.0, 3.1 and 3.2) to be included in the estimation of AUC, a predose plasma concentration and at least 5 of the 6 postdose plasma concentrations for 3TC, ZDV 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. 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. Subjects will be replaced according to Section 4.8.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board/Ethics Committee Review and Informed Consent

This protocol, the informed consent document (Appendix III) 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. [Assent is dependent on the requirement of each local
Ethics Committee]. Children will receive information about the research even if they cannot give assent. 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 P1069 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) by the NIAID, IRB/EC, the U.S. Office for Human Research Protections (OHRP), by the MOPH in Thailand or sponsor’s designee.

IMPAACT has been issued a Certificate of Confidentiality by the Department of Health & Human Services, National Institute of Allergy and Infectious Diseases. This Certificate is applicable to all current IMPAACT and former PACTG studies at NIAID and NICHD sites and is in effect until June 30, 2013.

10.3 Study Discontinuation

The study may be discontinued at any time by the IMPAACT Network, NIAID, OHRP, GPO, US or Thai FDA, the site and/or MOPH IRB/EC, or other local
(Thai) governmental regulatory agencies as part of their duties to ensure that research subjects are protected.

10.4 Regulatory Authorities

At the eligible IMPAACT 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 number that is assigned to the study.

In addition to the GCP Guidelines and the U.S. FDA IND #, held by NIAID, P1069 will be conducted in full concordance with the June 2006 Revision of the Ethical Review Committee of the Ministry of Public Health, the Ethical Principles for Medical Research Involving Human Subjects English and Thai versions on file). (http://www.jrecthai.org/html/th/index.php). It will also follow current World Medical Association Declaration of Helsinki, and ICH Tripartite Harmonised Guidelines for Good Clinical Practice (GCP now E6 (R1), see http://www.ich.org).

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT 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 (CDC) and the National Institutes of Health.

All infectious specimens will be sent using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) as well as specific requirements of the host country for specific instructions required for ground transportation within that country.
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 IMPAACT/PACTG.DATABASE.rmd.

   Ref Type: Catalog

   Ref Type: Catalog


Ref Type: Report

Ref Type: Catalog


Ref Type: Catalog

Ref Type: Catalog

Ref Type: Catalog


Ref Type: Catalog


37. Aurpibul L, Puthanakit T, Sirisanthana T, Sirisanthana V. Substitution of stavudine with zidovudine in HIV-infected children receiving HAART does not result in clinically significant hematologic changes. 4th International AIDS Society Conference, Sydney, Australia. 7-22-2007. Ref Type: Abstract


40. Saitoh A, Sarles E, Capparelli E et al. CYP2B6-516 genetic variants affect the pharmacokinetics of nevirapine and clinical responses in HIV-1-infected children receiving HAART. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, California Abstract 735. 2-6-2007. Ref Type: Abstract

41. Boehringer Ingelheim Corp. Viramune package insert. 2004. Ref Type: Catalog


47. Boehringer Ingelheim Pharmaceuticals. Package insert for nevirapine. 2007. Ref Type: Catalog
# APPENDIX I
## SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>EVALUATIONS</th>
<th>Study-Drug Treatment</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Early Discontinuation</th>
<th>Day 56 Off-Tx F/U for Safety 1</th>
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</tr>
<tr>
<td>History &amp; Physical exam</td>
<td>X X</td>
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<td>Assessment: HIV-related symptoms</td>
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<td></td>
<td>X</td>
<td>X X X X</td>
</tr>
<tr>
<td>Safety Assessment by telephone</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence Assessment/dose monitoring by telephone</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X X X X</td>
</tr>
<tr>
<td>Directly Observed Therapy (DOT)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X X X X</td>
</tr>
<tr>
<td>Hematology (lavender top)</td>
<td>1 mL</td>
<td>Day 14</td>
<td></td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>Chemistries (red or green top)</td>
<td>2 mL</td>
<td></td>
<td></td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Pregnancy Test (urine)-females only</td>
<td>X (X)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets (lavender top)</td>
<td>1 mL (1 mL)</td>
<td></td>
<td></td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>Intensive PK (lavender top)</td>
<td>14 mL</td>
<td></td>
<td></td>
<td></td>
<td>14 mL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>(X)</td>
<td></td>
<td></td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Pharmacogenomics (buccal swab-can be taken at any visit)</td>
<td>X</td>
<td></td>
<td></td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME</td>
<td>4 mL</td>
<td></td>
<td></td>
<td>17 mL</td>
<td></td>
</tr>
</tbody>
</table>

Blood volume in parentheses: only done if needed. Evaluations in parentheses, only if not done previously or if indicated
1. Evaluations should be completed within 14 days prior to study entry except CD4+ counts, which must be obtained within 30 days prior to study entry. Document current regimen (NVP + 2 NRTIs), including doses, method of administration and adherence assessment at screening. Day 0-enrollment and randomization to a treatment group.

2. **History:** current regimen, concomitant medications, significant non-HIV diagnoses, signs and symptoms ≥Grade 1. History includes appropriate reporting for AEs, SAEs, or EAEs since the previous visit. **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. For Step 2-see Section 5.0 and Appendix II.

3. Adherence for eligibility for the PK study must be 100% in the 72 hours immediately prior to the PK Study. The tablet/liquid count should be done on the PK day, see Appendix II. Subjects will be monitored carefully by the site staff to assess complete adherence to the study medication. Admission to the hospital prior to the PK study is up to the site. 
   3a: A telephone call 7 days after each new treatment begins, and after the 2nd PK visit, (see #12) will be done to check on adverse events.
   3b: A dosage calendar/phone calls will be used for the 24-72 hours prior to the PK study day (Day 11-12, and 25-26—See Section 3.0). These records will be used to document eligibility for the 1st PK study (ideally Day 14); entry into Step 2; and the 2nd PK study (ideally Day 28) per study visit scheduling. See Section 9.0 Pharmacology Plan for rescheduling. **Home visits and/or phone contact** to check on adherence (caregiver/medication calendar during the PK eligibility period on each study treatment regimen will be provided by the sites).
   3c: **DOT is as defined in the study (i.e. by a clinical study staff member), and will be done 24 hrs prior to each PK study (Day 13, 27, respectively) and on the PK days (Day 14, 28).**

4. **Hematology:** (CBC, cell differential, platelet count). 1 mL Vacutainer® EDTA (lavender top) tube. CBC will be drawn after the last PK blood sample, on PK study visit days. Draw the minimum amount of blood required, and process per the local laboratory.

5. **Chemistries:** [Local Laboratory]. Blood urea nitrogen (BUN), AST (SGOT), ALT (SGPT), ALP, serum creatinine, amylase, lipase and electrolytes, 2 mL Vacutainer® (no additive, red top tube or heparinized-green top tube may be used). Chemistries on PK study visit days will be drawn after the last PK blood sample. Draw the minimum amount of blood required. Use laboratory ULN values, Grade amylase per the supplemental Table-see Section 6.1.

6. **Pregnancy Test:** [Local laboratory]. 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. Tests will be done, as part of the admission visit for the PK studies, and may be done at early discontinuation and the final study visit, if indicated.
APPENDIX I (Cont.)

7. **Lymphocyte subsets**: [Local laboratory]. CD4/8+ T-cell counts and percentage. Process according to the P1069 Laboratory processing Chart (LPC).

8. **12-hour intensive PK**: Day 14, 28: Subject must be ≥22 weeks of age for the first PK. PK visit window: schedule 2-3 weeks after onset of study drug treatment in each Step. Admission to the hospital, either the morning of, or the evening before-per site/subject scheduling preference (return all study drug medication bottles).

   For repeat PK, see Section 9.22. Refer to Section 6.1 to reschedule, if delays are due to toxicity. Process according to the P1069 LPC; PK samples will be shipped to the Pharmacology Lab, Chiang Mai University, LDMS code 251.

9. **Urinalysis**: [Local laboratory]. Done only if indicated, see #11 below and the P1069 LPC.

10. **Pharmacogenomic sample**: Buccal (cheek) swab. Samples to be analyzed at Siriraj Hospital-LDMS Code 258. Procedure as detailed in the P1069 LPC.

11. **Early discontinuation (toxicity only)**: Subjects will remain on study and be followed and data collected until the toxicity resolves or until 4 weeks after stopping the study drugs, 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 (females of child bearing potential only). For early discontinuation for subject refusal, family moving, etc., the final study visit evaluations will be as indicated.

12. **Safety Follow up**: A phone call will be made to each subject a week (7 days) after stopping study drugs (i.e. after the 2nd PK is completed), to check for adverse events. For subjects that are off-study treatment, a safety F/U visit for P1069 will be scheduled about 4 weeks after the last PK visit. This visit can be coordinated in conjunction with clinical visits (standard of care schedule, NAPHA Program treatment regimen, minimum every 3-4 weeks).

   For insufficient blood draws priorities are as follows:

   1) Safety (hematology, chemistries)
   2) Pharmacokinetics †
   3) Immunology

   † If the PK sample volume is insufficient to measure all 3 study drug concentrations, NVP will be the priority.
APPENDIX II
STUDY DRUG ADMINISTRATION PROCEDURES

GPO-VIR® Z30 Pediatric Tablets

The GPO-VIR® Z30 tablet is specifically formulated to be swallowed (it is film-coated). It should be swallowed with water whenever possible. If children are unable or refuse to swallow the tablet(s), they will be allowed to crush and then swallow them with water. The tablet is scored, to facilitate division into halves. Children and their caregivers will be instructed on how to 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. For children in Groups 2-4, weight is not expected to change in two weeks. For Group 1, however, if the change in weight is greater than 10% from Day 0 (increase or decrease) at the cross-over to Step 2, use the closest corresponding dose to the new weight. If the weight change is less than or equal to 10% from Day 0, use the Day 0 dose.

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 (place the required tablet number 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 ZDV 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:** Will be evaluated during each study visit that the subject is on study drugs. Tablet/liquid counts will be done by the pharmacist on the PK study days. 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 % = \( \frac{\text{number of pills taken}}{\text{number of pills expected to be taken}} \times 100 \)
Table 1. GPO-VIR® Z30 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® Z30 [ZDV/3TC/NVP] Pediatric Tablet</th>
<th>Liquid Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of Tablet(s) per dose</td>
<td>ZDV dose 10 mg/mL</td>
</tr>
<tr>
<td>1</td>
<td>6-6.9</td>
<td>(5-12)</td>
<td>2</td>
<td>60 mg (6 mL)</td>
</tr>
<tr>
<td></td>
<td>7-8</td>
<td></td>
<td>3</td>
<td>90 mg (9 mL)</td>
</tr>
<tr>
<td>2</td>
<td>&gt;8-11.9</td>
<td>(9-12)</td>
<td>3</td>
<td>90 mg (9 mL)</td>
</tr>
<tr>
<td></td>
<td>12-16</td>
<td></td>
<td>4</td>
<td>120 mg (12 mL)</td>
</tr>
<tr>
<td>3</td>
<td>&gt;16-16.9</td>
<td>(9-12)</td>
<td>4</td>
<td>120 mg (12 mL)</td>
</tr>
<tr>
<td></td>
<td>17-19.9</td>
<td></td>
<td>5</td>
<td>150 mg (15 mL)</td>
</tr>
<tr>
<td></td>
<td>20-23</td>
<td></td>
<td>6</td>
<td>180 mg (18 mL)</td>
</tr>
<tr>
<td>4</td>
<td>&gt;23-24.9</td>
<td>(8-12)</td>
<td>6</td>
<td>180 mg (18 mL)</td>
</tr>
<tr>
<td></td>
<td>25-30</td>
<td></td>
<td>7</td>
<td>210 mg (21 mL)</td>
</tr>
</tbody>
</table>

For Step 1 study drug dosages will be based on weight at Day 0, according to this table. For Group 1, if the subject’s weight changes by more than 10% (either increase or decrease) from baseline for Step 2, use the dose that corresponds to the new weight. If the weight change is less than or equal to 10% from Day 0, use the Day 0 dose. Groups 2-4: the weight is not expected to change, so the Day 0 weight value will be used for Step 2.
APPENDIX II (Cont.)

For Liquid Count: The research pharmacist will utilize a conversion table for each liquid study drug based on the density or specific gravity* (g/mL) of the particular study drug. The pharmacist will weigh each bottle (empty and full) separately, before it is dispensed. These weights (g) are recorded in the pharmacy log. When the bottle is returned, it will be re-weighed using the same gram scale. The difference in the weight of each bottle (full-returned weight) will be calculated and recorded in the pharmacy log. This weight difference will be converted to volume (mL) consumed using the conversion tables. The volume expected to be consumed will be calculated from dosage (in mL) and number of doses taken if subject adherence had been perfect (number of doses per day x number of days of therapy since dispensing). The pharmacist will record the date of the first dose consumed from the bottle(s) and number of doses consumed that first day as well as the number of doses on the return day to get an accurate number of expected doses. The adherence percentage will be calculated for each drug as follows:

\[
\text{Adherence} \% = \frac{\text{volume of study drug consumed}}{\text{expected volume of study drug consumed}} \times 100
\]

*lamivudine (3TC) oral solution 10 g/mL, specific gravity = 1.08 g/mL, empty bottle 26 g ± 1 g
*nevirapine (NVP) suspension, specific gravity = 1.10 g/mL
*zidovudine (ZDV) oral solution, specific gravity =1.17-1.23 g/mL, use avg. of 1.2 g/mL

DOT and Dosage Administration Calendar: Caregivers will be provided with a diary, or similar record for medications for P1069 per local site procedures (certified translations). Phone verification (within 2 hrs of the morning/evening dose schedule) by the study staff will be done at least twice in the 72 hour period prior to the PK study visit. DOT by the staff is done on Day 13 and 27. Phone contact/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), phone contact (to assure that study drugs are taken correctly and that there are no adverse reactions) will be made as indicated in Appendix I. After the initial contact, other phone follow-up (i.e. the caregiver may be provided with a cell phone), or a home visit, if needed will be done, as determined appropriate by the initial assessment by the home visit team. Hospital Admissions: Children will be admitted the morning of the PK study, or the previous evening, if more convenient. Hospital dosing records will be used for adherence assessment on the day of each PK study (Day 14 and 28). To be included in the PK study, children must be 100% adherent in the past 72 hours (6 doses) ensured by DOT for all the doses or telephone confirmation for the 4 doses and DOT for the last 2 doses. Admission to the hospital/clinic earlier than indicated in the Schedule of Evaluations for each Step may be an option to address non-adherence, problems with taking study drugs as directed, or to accommodate travel from distant areas, so that eligibility for the PK study can be ensured.
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”, as used in this consent form, is also meant to apply to “your child”, as needed.

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® Z30 for children. This study will compare this pediatric tablet to the liquid anti-HIV drugs available to treat your child, such as nevirapine (NVP or Viramune®), zidovudine (ZDV or AZT or Retrovir®) 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 ZDV, are in your child’s blood and how long they stay in your child’s blood. The new GPO-VIR® Z30 tablet for children has been made so that NVP, 3TC and ZDV can be taken together, all at once.

This study will see if there is any difference between the tablets and the liquids, and see if the tablet works just as well. This study will also see if there are any bad reactions with either the tablet or liquid medications. This is the first time the GPO-VIR® Z30 tablet will be tested in humans. The Z30 tablet is new and is based on the same anti-HIV drugs that GPO makes for adults and older children.

This study will also try to see if how your child’s body handles the study drugs is related to your child’s DNA (called pharmacogenetics). In some people certain gene (DNA) changes can affect the way a drug works. The DNA testing for P1069 will only look at this gene type, to detect a very specific gene type that might change the effectiveness of the HIV drugs being used in this study. A sample of DNA (taken from cheek cells, from inside your child’s mouth) will be tested.

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

Screening:
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, (such as nevirapine) 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 teaspoon (4 mL) of blood drawn for routine tests to make sure it is safe for your child to be in this study. The number of CD4+ T-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 (4 mL) of urine will be needed. If a girl is pregnant, she will not be able to be in 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

The study entry visit will be done within about 14 days after screening. It may also be done soon after, or at the same visit as screening, if all the tests are fine. If another visit after screening, is needed, your child will have another physical exam and a review of medical history and HIV symptoms. Blood will be taken (1 mL), only if it is needed (if the doctor does not have earlier results) for the measurement of CD4+ T-cells. If your child is a girl who could have become pregnant, another urine pregnancy test may be done.

Your child will be randomly assigned, a process like flipping a coin, into one of two treatment groups. One group will take the new GPO-VIR® Z30 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 ZDV), as those that are in the GPO-VIR® Z30 tablet(s), every 12 hours. A single sample of your child’s DNA may be taken at this study visit (or it may be taken at another study visit), but only one sample is needed. This sample will be taken with a swab (from the inside of the cheek) for the DNA (pharmacogenetic) test. A small brush will be used to collect cells from the mouth. This study visit should only take 1-2 hours.

The study staff will work with you and your child to make sure that you and your child know how to take these study drugs the right way. A tablet crusher will be given to you to use, if your child cannot easily swallow the tablets. Syringes with labels for your child when taking the liquid study drugs and instructions, will be given to you by the study staff. A medication calendar will be given to you, to keep track of the dose and time of day your child should take the study drugs.

On Study Drugs

The treatment part of P1069 is four (4) weeks long. Each Group of children will change the form of the study drugs, (tablets to liquids or liquids to tablets), after 2 weeks. Your child will be scheduled to come to the clinic before the end of these two weeks. The study staff will make sure your child takes the study drugs the right way during the monitoring period (3 days before the PK study visit). They will do this by giving you a study drug calendar, calling you on the phone to remind you and maybe visiting your home, if your child is having problems with the study drugs. 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 3 more days (or longer, if your doctor thinks it is better), and then check again. There will be at least two clinic visits, while you are on the study drugs.

Before the PK Study:

Your child may be admitted to the hospital the night before to be ready for the PK study the next morning, or early in the morning of the PK day, depending on how the site can schedule it with you and your child.

At this admission 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. You will also bring back the study drug calendar or similar tool that was provided to you by the site staff. 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. This should take about an hour or so. If your child has had her first menses, a pregnancy test will be done.

If your child has taken all the study drugs the right way, your child will be admitted to the hospital for the 12 hour special blood tests (called a pharmacokinetic study, or PK study for short) to measure the study drugs in his/her blood.

PK Study

Your child must be old enough for the PK study (at least 22 weeks of age). For each PK study, your child will have a total of about 1 tablespoon (17 mL) of blood drawn over 12 hours. A small needle connected to a plastic tube that allows blood to be drawn more than once, 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 without 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 ½ a teaspoon of blood (2 mL) will be taken. Less than one teaspoon (3 mL) of blood will be drawn for the routine tests, as part of the last sample.

If there are no problems, your child can go home after the first PK study. The study staff will give you and your child instructions and new study drugs, before you leave the hospital. For example, if your child took the tablet(s), then you will be given the liquid study drugs for your child to take, after the PK study. If your child was taking the liquid study drugs, then the new study drug would be the tablet(s).

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.
After about 2 Weeks on the new Study Drugs

A second PK study will be done on the new study drugs. The study staff will call you by phone, to see how your child is doing, and if there are any problems taking the new form of the study drugs.

An admission visit will be scheduled, before the 2nd PK day, the same way as for the 1st PK study. Your child may be admitted the night before to be ready for the PK study the next day, or early in the morning of the PK day, depending on how the site can schedule it with you and your child.

You will bring the remaining study drugs, and study drug calendar with you. There will be a physical exam. If your child is a girl who could become pregnant, another urine pregnancy test will be done. This should only take an hour or so. If your child took the study drugs the right way, the 2nd PK study will be done.

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.

2nd PK Study:

This 12-hour PK study will be done the same way as the first one. 7 samples of blood will be taken. The last blood sample will include less than one teaspoon (3 mL) of blood for the routine tests, as part of the last sample and an extra amount (1 mL) for a CD4+ cell count to make sure your child does not have any problems at the end of the 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, there are no more study visits on the study drugs.

Off study:

Your child will take the anti-HIV drugs he/she was taking before Day 0 of the P1069 study, unless your child’s doctor changes them. The staff will call you/your child about a week (7 days) after the last PK day to see if there are any problems or bad reactions. GPO has agreed to provide access to the new tablet, if it will benefit your child.

Last Safety Follow up Visit:

About 3 weeks after the phone follow-up (about 4 weeks after the last PK day), there will be a final safety follow-up visit (at about 4 weeks). This visit will include a physical exam, history, check of HIV-related symptoms and about one teaspoon (4 mL) of blood
APPENDIX III (Cont.)

drawn for routine tests and to measure your child’s CD4+ count again. A routine urine test may be done, if needed. If your child is a girl who could have become pregnant, another urine pregnancy may be done. This visit will take the same time, about an hour or so, as your child’s normal clinic visit.

Early Discontinuation/Off Treatment Follow-up:

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 (4 mL) of blood collected for routine tests, and CD4+ measurements. A routine urine test may be done, if needed. Another physical exam, history and check on HIV-related symptoms, will be done. If your child is a girl who could have become pregnant, another urine pregnancy test may be done.

You should tell your child’s nurse or doctor before your child takes any non-study drugs, medications, herbal 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. This safety follow-up visit will be scheduled at about 4 weeks, after your child stopped taking the study drugs.

Other Information:

Storage of blood and DNA samples:

Some of your child’s blood (if there is any leftover from tests required in this study) may be stored. The special test (that tells if your child’s DNA could have an effect on how the study drugs are used by your child’s body) will be done using some of your child’s cells that contain DNA. These cells are taken by a swab from the inside your child’s mouth, in the cheek area. After the tests are run, there may be some leftover DNA. If it is stored, your child’s identity will be protected. The sample(s) may be used for future IMPAACT 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 (like the DNA tests) 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.

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.

**Blood and DNA Samples for P1069:**

* I agree to allow my child’s blood and DNA samples to be stored for use in future IMPAACT/DAIDS and MOPH-approved, HIV-related research studies. [I understand that this may include pharmacogenetic testing, as described for P1069]*

______________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 IMPAACT/other network-DAIDS-approved, HIV-related research.

**HOW MANY CHILDREN WILL TAKE PART IN THIS STUDY?**

About 48 Thai children will take part in this study.
APPENDIX III (Cont.)

HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child will be in this study for about 8 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 IMPAACT Network, National Institutes of Health (NIH), Office of Human Protections (OHRP), the drug company supporting this study [Government Pharmaceutical Organization (GPO)], the US or Thai FDA, the site’s and/or Ministry of Public Health (MOPH)-Thailand’s Institutional Review Board (IRB) or Ethics Committee (EC), or other (Thai) governmental regulatory agencies 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® Z30 pediatric tablets and/or the Retrovir®, 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 doctors will not be able to continue to provide your child with the GPO-VIR® Z30 pediatric tablets and/or the Retrovir®, 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 will be able to obtain them. GPO has agreed to provide the fixed-
dose combination (FDC) product until full approval by the Thai Ministry of Public Health, if it is considered in the child’s best interest.

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 for blood drawing enters the body. A heparin lock is a tube placed in the vein which can stay in the vein a longer time so blood samples can be taken without more needle sticks. The 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

Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

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 zidovudine (ZDV)]

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.
APPENDIX III (Cont.)

Lamivudine (3TC, EPIVIR®)
GlaxoSmithKline

The following side effects have also been associated with use of lamivudine:
If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if lamivudine is stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

- Headache
- Feeling tired
- Dizziness
- Numbness, tingling, and pain in the hands or feet
- Depression
- Trouble sleeping
- Rash
- Upset stomach, vomiting, nausea, loose or watery stools
- 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.
- Abnormal pancreatic and liver function blood tests

Zidovudine (RETROVIR®)
GlaxoSmithKline

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

- Decrease in the number of white blood cells that help fight infection
- Decrease in the number of red blood cells that may cause weakness, dizziness, and fatigue
- Muscle aches, weakness, and wasting
- Headache
- Upset stomach
- Vomiting
- Decrease in appetite
- Vague overall feeling of discomfort
- Lack of energy
- Feeling tired
- Sleeplessness
- Heartburn
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) [nevirapine (NVP)]

Nevirapine (NVP, VIRAMUNE®)
*Boehringer Ingelheim Pharmaceuticals, Inc.*

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

Hypersensitivity reactions (“allergic reaction”) may occur. These reactions are rarely fatal. The symptoms that you may 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.

Muscle break down causing muscle aches or pains has been observed in some people experiencing skin and/or liver reactions associated with nevirapine.

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.
APPENDIX III (Cont.)

Nevirapine (NVP, VIRAMUNE®) Continued

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.

In addition to the serious side effects listed above, additional side effects include:
- Fever
- Headache
- Upset stomach (nausea, vomiting)

Fixed Dose Combinations (FDCs) of the above drugs

The GPO-VIR® Z30 tablet for children is a new formulation that has not been tested in humans before. The risks are similar to the risks listed above for the drugs in GPO-VIR® Z30: zidovudine, lamivudine and nevirapine. If you have questions concerning possible GPO-VIR® side effects, please ask the study staff at your child’s site.

GPO-VIR® Z30 (Nevirapine, Lamivudine and Zidovudine Pediatric Combination tablets)

*Government Pharmaceutical Organization (Thailand)*

The major adverse effects include:
- tingling, burning, numbness or pain in the hands and feet
- pancreatitis (nausea, vomiting severe abdominal or stomach pain)
- skin rash, mild to moderate (eruption, with or without itching)
- severe and life-threatening skin reactions (e.g. Stevens-Johnson syndrome).

Other effects include: diarrhea, inability to sleep, headache, fever, bone marrow depression, anemia (decrease in the number of red blood cells that may cause weakness, dizziness, and tiredness, joint aches and pains, muscle aches and pains, abnormal liver function test results, hepatitis (inflammation of the liver which may be caused by an infection or a chemical agent).

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 such as female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm during the study. Condoms alone are considered adequate. Hormonal birth control alone (e.g. pills, shots, or slow release inserts placed under the skin) would not be considered adequate. 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® Z30 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 IMPAACT eligible 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.
APPENDIX III (Cont.)

Your child’s records may be reviewed by the participating sites’ IRB/EC, US Food and Drug Administration (FDA), Thai FDA, Thai Ministry of Public Health (MOPH), National Institutes of Health (NIH), Office of Human Research Protections (OHRP), study staff, study monitors, the drug company supporting this study (GPO) 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 about 700 Baht for food allowance and to cover travel expenses for each clinic visit.

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

**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.

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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<tbody>
<tr>
<td>Participant’s Legal Guardian (print) (As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’s Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
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APPENDIX IV

Protocol P1069 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 Zidovudine (ZDV), Lamivudine (3TC) and Nevirapine (NVP) as GPO-VIR® Z30 Pediatric tablet vs. the Individual Liquid Formulations in HIV-Infected Children ≥ 5 months to <13 years of age in Thailand.

Eligible Children:
- HIV infected Thai infants and children, age: ≥ 5 months (20 weeks) to <13 yrs, weight: 6 to 30 kg
- 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)
- There are two parts to this study. Each part lasts 2 weeks and has a pharmacokinetic or PK study visit, at the end. The PK study is to check the levels of study drugs in the blood.
- Children must be able to come and stay in the hospital for the 12-hour PK study because the blood is drawn over several hours). Children must be at least 22 weeks old for the PK study

Purpose:
- To look at how the GPO-VIR® Z30 pediatric tablet (based on the same anti-HIV medications that will be taken as liquids), is absorbed in the body, compared to the liquid doses.
- To compare the tablet and liquid medication and see how safe and tolerable they are.
- All children will take both kinds of anti-HIV medications (tablets and liquids), at different times in the study.

Length of Study and Number of Participants:
- About 8 weeks (4 weeks of treatment: 2 weeks each for tablets, 2 weeks for liquids) + 4 weeks safety follow up
- A minimum of 31 to maximum 48 children will be enrolled in this study

Medications Involved:
- GPO-VIR® Z30 pediatric tablet (a combination of ZDV, 3TC & NVP) that is swallowed with water (it can also be crushed and taken with water for younger children).
- Zidovudine (ZDV or AZT); Lamivudine (3TC) and Nevirapine (NVP) liquid medications
- All medications are taken twice a day (every 12 hours) by mouth, without food
- The number of tablets or amount of liquid medications will be based on the child’s weight.
Visit/Study Requirements:

- **Screening visit:** History and Physical Exam, lab tests, CD4 T-cell count, 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.

- **Entry:** Children will be randomized to a treatment group, the GPO-VIR® Z30 pediatric tablet or ZDV, 3TC, and NVP liquids. Phone calls and a dosage calendar will be used (home visits may be used) to make sure that the study medication is taken on schedule. (If there are problems, the hospital scheduling may be changed).

- **Special test:** Cells will be taken from inside each participant’s cheek (using a swab), for a DNA sample. A special type of test (using this DNA sample) will be taken once, at one of the clinic visits, from each participant. These samples will not be looked at, until the end of the study.

- **The first PK study visit is scheduled at the end of the second week of study treatment.** There will be 7 sampling points during each PK study to see if the treatment is working. Same tests as screening, but no CD4 T-cell count.

- **Switching study drugs:** After the first PK visit is done, all children will switch the forms of the medication they are taking (tablets to liquids OR liquids to tablets). Phone calls and a dosage calendar will be used, similar to the first 2 weeks. Another PK study is done at the end of Week 4, after 2 weeks on the different form of the medication. Same tests as the screening visit.

- **After the last PK study, the study treatment will be over.** The study staff will talk to you about how to obtain these medications, if needed, once the study ends.

- **Safety Follow-Up:** A phone call for safety follow up will be made by the staff about a week after starting new study drugs and a week after the last PK visit; a final study visit is scheduled about 3 weeks after the phone call, to monitor the children. Same tests as the screening visit, a urine test may be done, if needed.

- **Extra visits, including home visits or another clinic visit 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.

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*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.**

Final Version Date: 03/28/08