IMPAACT P1071

Phase I/II Open-Label Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of Vicriviroc (SCH-417690) a Novel CCR5 Antagonist in Combination Regimens in HIV-infected Antiretroviral Therapy Experienced Children and Adolescents

A Multicenter, International 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:
Schering-Plough

IND # 69,661, held by Division of AIDS, NIAID

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Version 2.0
FINAL
06/05/09
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
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<tr>
<td>ARV</td>
<td>Antiretroviral</td>
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<tr>
<td>AUC</td>
<td>Area under the plasma concentration profile over time of dosing interval</td>
</tr>
<tr>
<td>$C_{\text{min}}$</td>
<td>Plasma concentration at the end of the 24 hour dosing interval.</td>
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<tr>
<td>CRPMC</td>
<td>Clinical Research Products Management Center</td>
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<tr>
<td>DAIDS</td>
<td>Division of AIDS (United States)</td>
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<tr>
<td>DMC</td>
<td>Data Management Center</td>
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<td>DSMB</td>
<td>Data Safety and Monitoring Board</td>
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<tr>
<td>EAE</td>
<td>Expedited Adverse Event</td>
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<tr>
<td>GM</td>
<td>Geometric mean</td>
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<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
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<td>IB</td>
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<td>IRB</td>
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<td>NIH</td>
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<td>NOAEL</td>
<td>No observable adverse effects level</td>
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<td>OBT</td>
<td>Optimized Background Therapy</td>
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<td>PACTG</td>
<td>Pediatric AIDS Clinical Trials Group</td>
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<td>QD</td>
<td>Once daily</td>
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<td>RCC</td>
<td>Regulatory Compliance Center</td>
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<td>SADR</td>
<td>Suspected Adverse Drug Reaction</td>
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<td>SDMC</td>
<td>Statistical and Data Management Center</td>
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<td>SMC</td>
<td>Study Monitoring Committee</td>
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<tr>
<td>VCV</td>
<td>Vicriviroc</td>
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SUMMARY OF CHANGES FOR IMPAACT P1071 VERSION 2.0

All changes from Version 1.0 appear in boldface type in Version 2.0 of the protocol, including correction of typographic errors, updated information, and other changes that do not affect regulatory or study subject consent. Information from Letter of Amendment #1 is included.

The following is a summary list of the changes made in the protocol:

**Roster**
1. Protocol Team Roster was updated to include new team members and correct member information.

**Schema**
2. The minimum number of subjects for Stage I was changed to 48 subjects (12 subjects per cohort). The minimum number of subjects for Stage II was changed to 52 subjects. This change has also been made throughout the protocol for consistency.
3. The age ranges for Stage I, Cohorts I, II, and III has been changed as follows: Cohort I: ≥ 12 years to <19 years, Cohort II: ≥6 years to < 12 years, and Cohort III: ≥ 6 years to < 12 years. This change has also been made throughout the protocol for consistency.

**Background and Rationale**
4. Section 1.2, Rationale-Background information was added to the end of the first paragraph about the enhanced version of the Trofile™ HIV co-receptor assay.
5. Section 1.21, Rationale for Dose Selection Criteria - The second sentence of the second paragraph is changed to read: Since HIV-infected adult patients showed a favorable virologic response when their steady-state $C_{min} > 100$ ng/mL, the PK target for treating pediatric patients is to achieve $C_{min} > 100$ ng/mL for all subjects.

**Study Design**
6. Section 3.2, Step I-The reference to the Trofile™ HIV co-receptor assay was updated to indicate that the enhanced version of the assay will be used. This change has been also been made throughout the protocol for consistency.
7. Language was added to the third paragraph of section 3.31 to state that dose adjustments will be made based on a mini-cohort. This change has been made throughout the protocol for consistency.
8. Language was added to the third paragraph of section 3.31 to change parameters that would warrant repeat PK sampling.

**Selection and Enrollment of Subjects**
9. The following language has been added to the title of section 4.2 and to the Table of Contents: (In addition to the inclusion criteria in Step I).
10. The second sentence of Section 4.7 was revised to read, “A Site Implementation Plan (SIP) will be required from each international site and subunit participating in the study.

11. Inclusion criterion 4.22 - The first sentence inside the parenthesis was changed to read, “(NNRTI’s other than etravirine will be excluded). Change also appears in 3.3, 4.6, and 6.32.

12. Sections 4.44 and 4.5 - Instead of referring to NNRTI’s, the following drug names were added: efavirenz, nevirapine, and delavirdine.

Study Treatment

13. The titles of Tables 6-9 were revised to indicate that dosing will be based on mini-cohorts.

14. Tables 10 and 11 were added for Cohorts III and IV dose adjustments if the respective mini-cohorts have a median Cmin < 130 ng/mL and > 400 ng/mL respectively.

Subject Management

15. The first three sentences in the note in section 6.3 have been deleted.

16. Language was added to section 6.3 to state that Vicriviroc levels will be assayed after the last subject in each mini-cohort has completed their 14-20 day intensive PK visit and the protocol team has evaluated the results.

17. Language has been added to section 6.3 to change the procedures in Stage I if the target PK and safety parameters are not met by the mini-cohort.

Adverse Event Reporting

18. Section 7.0 has been updated with revised adverse event reporting language per DAIDS guidance.

Statistical Considerations

19. Section 8.0 has been updated to include changes described in the study design and a clear description of an independent study monitoring committee that will be formed to review the study as needed.

Clinical Pharmacology

20. Sections 9.2 and 9.31 have been revised based on mini-cohort dosing strategy. All references to individual dose adjustments have been removed. Change also appears in Tables 6-9 and Appendix II.

Schedule of Evaluations

21. Appendix IA: Expanded CCR5 flow cytometry has been added to the following visits: Step I, Step II entry, week 48 and Confirm Virologic Failure. Total blood volume and Footnote #13 for these visits have been adjusted accordingly.

DAIDS Sample Informed Consent

22. The DAIDS Sample Informed Consent has been revised based on the increased blood volumes for lymphocyte subsets.
Phase I/II Open-Label Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of Vicriviroc (SCH-417690) a Novel CCR5 Antagonist in Combination Regimens in HIV-Infected Antiretroviral Therapy Experienced Children and Adolescents

**DESIGN:** Phase I/II, multi-center, open-label, two stage, age-stratified, intensive PK non-comparative study.

**SAMPLE SIZE:**
Step I: Screen approximately 280 subjects to evaluate co-receptor tropism.

Step II - Treatment: Includes 140 subjects to yield 100 evaluable subjects.
Stage I: A minimum of 48 subjects (12 per cohort)
Stage II: A minimum of 52 subjects, with at least 10 subjects from each cohort

**POPULATION:** HIV-1-infected antiretroviral treatment experienced children and adolescents ≥ 2 years to <19 years of age at participating IMPAACT sites in the U.S., South Africa, Brazil, and Argentina.

**STRATIFICATION:** If R5-tropic virus is found, subjects will be stratified into one of the following age cohorts. In Step II, Stage I there will be a minimum of 12 subjects in each age cohort.

- Cohort I: ≥12 years to <19 years of age, to receive tablet formulation of VCV*
- Cohort II: ≥6 years to <12 years of age, to receive tablet formulation of VCV*
- Cohort III: ≥6 years to <12 years of age, to receive liquid formulation of VCV
- Cohort IV: ≥2 years to <6 years of age, to receive liquid formulation of VCV

* Note that these subjects must have weight ≥ 25 kg since they will receive tablet formulation.
REGIMEN: Vicriviroc will be available in tablet form in dose strengths of 20 or 30 mg and in liquid form at a concentration of 1 mg/mL.

Dosing for Step II, Stage I will begin at approximately 0.8 mg/kg in tablet formulation (for Cohorts I and II) or liquid formulation (for Cohorts III and IV) once a day in combination with an optimized regimen including a ritonavir boosted protease inhibitor and at least one other antiretroviral drug. Subjects’ virus must be susceptible (per genotyping results) to the ritonavir-boosted protease inhibitor that is selected for the optimized regimen. Opening of Cohort III will be dependent on safety and PK data from mini-cohort II. Opening of Cohort IV will be dependent on safety and PK data from mini-cohort III. The starting dose for Step II, Stage II in Cohorts I, II, III and IV will be dependent on the safety and pharmacokinetic (PK) data available from Stage I in each cohort.

TREATMENT DURATION: 48 weeks plus 5 years after initial VCV exposure per subject on the selected dose.

STUDY DURATION: 48 weeks per subject followed by follow up until 5 years after Step II initiation. See section 5.34.

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**Figure 1. P 1071 Study Design**
OBJECTIVES:

Primary:

1. In Stage I, to evaluate the short term safety and tolerability of vicriviroc in combination with optimized background therapy which includes a ritonavir-boosted protease inhibitor in HIV-infected, treatment experienced children and adolescents.
2. In Stage I, to determine the multidose pharmacokinetics of vicriviroc in combination with optimized background therapy which includes a ritonavir-boosted protease inhibitor, and to determine the dose of vicriviroc that achieves a target $C_{\text{min}}$ in children and adolescents.
3. In Stage II, to evaluate the long term safety and tolerability of the optimized dosage of vicriviroc in combination with optimized background therapy which includes a ritonavir-boosted protease inhibitor in HIV-infected, treatment experienced children and adolescents.

Secondary:

1. In Step I, to investigate the predictors of co-receptor tropism among antiretroviral-experienced children and adolescents who undergo screening for P1071.
2. To evaluate the antiviral activity of vicriviroc given with an optimized background therapy by measuring viral load response in antiretroviral therapy experienced children and adolescents at 24 and 48 weeks.
3. To evaluate the immunologic activity of vicriviroc given with an optimized background therapy by measuring changes in CD4 cell count and percent from baseline to weeks 24 and 48.
4. To assess specific alterations in the HIV-1 envelope and polymerase genomes that are associated with vicriviroc and antiretroviral resistance in those experiencing virologic failure, virologic breakthrough or co-receptor phenotype switch.
5. To evaluate whether co-receptor usage changes over time in children and adolescents who experience virologic failure and virologic breakthrough during vicriviroc treatment (R5 $\rightarrow$ R5X4 $\rightarrow$ X4).
6. To explore covariates that may alter response to a vicriviroc-containing regimen including vicriviroc exposure, clinical status, immunologic status, age, race/ethnicity, and pharmacogenomics.
7. To determine if CCR5 expression or CCR5 genetic variants and other immunologic factors alter the pharmacokinetics or response to vicriviroc.
1.0 INTRODUCTION

1.1 Background

Triple combination antiretroviral therapy (ART), including a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), has become the standard treatment of HIV-infected adults and children. Effective antiretroviral therapy results in a reduction in viral load with a concomitant increase in the CD4 cell count that has been associated with declining morbidity and mortality in HIV-infected adults and children (1-3). However, poor adherence, drug toxicities, and drug resistance further complicate HIV management. Therefore, children and adolescents who have manifested multiple class intolerance and/or harbor drug-resistant virus have an unmet medical need. The development of drugs that block other targets in the HIV life cycle are critically important if treatments are to be available for children and adolescents who have failed or are unable to tolerate currently available antiretrovirals (4).

The chemokine receptor CCR5 is utilized as a co-receptor for HIV entry into CD4 cells and represents a new target for drug development (5). It is well known that genetic variants alter the rate of HIV disease progression and that individuals with the homozygous deletion in the CCR5 coding gene (CCR5Δ32/Δ32) are rarely infected with HIV and appear to have no immunologic deficit (6). Therefore, the use of CCR5 antagonists provides a novel antiretroviral target and could expand the anti-HIV therapeutic armamentarium. Co-receptor tropism assays measure the ability of the HIV envelope to use CCR5 or CXCR4 for viral entry. Viral populations analyzed in tropism assays are classified into CCR5 or R5-tropic, CCR5 and CXCR4 or R5/X4-tropic and CXCR4 or X4-tropic (7). Analysis of viral tropism, performed using the Trofile™ assay (Monogram Biosciences, Inc. South San Francisco, CA) was recently carried out on 402 HIV-infected treatment naïve patients and on 161 treatment experienced patients at the Chelsea and Westminster Hospital in London. Among the HIV treatment naïve subjects, 81% harbored R5-tropic viruses and 19% carried either R5/X4-tropic or X4-tropic viruses. Among 161 treatment experienced subjects, 77% had R5-tropic, 22% had R5/X4-tropic or mixed R5 and X4- tropic viruses and only 0.7% carried exclusive X4-tropic viruses (8). The ACTG 5211 protocol studied co-receptor use among 391 antiretroviral experienced adult subjects. Fifty percent harbored an R5-tropic virus, 46% had dual-tropic or mixed tropic viruses that used both CCR5 and CXCR4 coreceptors and 4% had X4-tropic viruses (9). Comparable analyses in treatment experienced children have not been done. However by means of the MT-2 cell line expressing CXCR4, studies in children under 7 years of age treated with zidovudine monotherapy have shown that 63% harbored non-syncytium inducing viruses (CCR5 tropic viruses) and 37% harbored syncytium inducing viruses (CXCR4 tropic viruses) and infants were invariably infected with NSI, CCR5 tropic virus (10;11). Similar to what has been observed in adults, children
harboring non-syncytium inducing viruses (CCR5 tropic viruses) have a higher CD4 cell percentage, 16% compared to 5% among those harboring syncytium inducing viruses (CXCR4 tropic viruses) (10). Another study among perinatally infected children being enrolled on a protease inhibitor (ritonavir or nelfinavir) based highly active antiretroviral therapy (HAART) regimen had baseline and follow up co-receptor usage determination using a human osteosarcoma cell line expressing CCR5 or CXCR4 chemokine receptors (12). Children were divided in 3 groups after a mean of 28 months on HAART. Complete responders had viral load suppression to <50 copies/ml, partial responders had a mean viral load reduction of 0.9 log$_{10}$ and non-responders had a viral load reduction of <0.5 log$_{10}$. Among the complete responders, 6 subjects had a baseline R5 tropic virus and only 1 had X4 tropic virus. The follow-up sample while on HAART had invariable R5 tropic virus. Among the partial responders, 6 subjects had a baseline R5 tropic virus and 4 had X4 tropic virus. The follow-up sample while on HAART had R5 tropic virus only. Among the 3 non-responders, all had baseline R5 tropic viruses, while during follow up 3 and 2 subjects had R5 and X4 tropic viruses respectively, suggesting that children failing a protease inhibitor containing regimen are more likely to have dual/mixed tropic virus than children with successfully controlled viral replication while on HAART (12).

Vicriviroc (SCH-417690), a novel CCR5 antagonist, has potent in vitro activity and demonstrated activity against CCR5 (R5) tropic strains of HIV from different regions of the world, harboring the clades B, C, D, A, E and G with an IC$_{90}$ between 0.45 nM and 18 nM (13). Vicriviroc is a small molecule compound with a molecular weight of 650 Da, has high bioavailability and is 84% protein bound in human plasma (13). Since most treatment experienced patients harbor viruses with resistance mutations to reverse transcriptase (RT) and protease (PR) inhibitors, the antiviral activity of vicriviroc was tested against a panel of viruses harboring single or multiple mutations in the RT and PR genes. In addition, isolates containing enfuvirtide (T-20) associated mutations in the gp41 envelope protein were evaluated. Vicriviroc effectively inhibited infection by viruses resistant to one or more RT or PI as well as viruses with multiple drug resistance phenotype. Vicriviroc was also equally inhibitory against viruses harboring gp41 mutations associated with T-20 resistance, with an EC$_{90}$ comparable to those of the wild-type control virus (13). Previous studies have suggested that amino acid changes in the V3 loop of HIV gp120 confer reduced susceptibility to CCR5 antagonists (14). P1071 will evaluate HIV envelope genotypic sequences in subjects experiencing virologic breakthrough or virologic failure on vicriviroc.

Important host genetic variants have been reported to determine the variability in drug response. Several enzymes in liver and intestine have crucial roles in transport and metabolism of various drugs. Among them, enzymes of cytochrome P450 (CYP) play a significant role in pharmacokinetics (PK) of different classes of drugs (15). Recent pharmacogenomic studies have shown that several
important single nucleotide polymorphisms (SNPs) influence the activity and bioavailability of antiretrovirals in children, including nelfinavir and efavirenz.

Several SNPs have been reported to change the levels of enzymes and their substrates for CYP3A4 and CYP2C9. SNPs for the genes encoding for CYP3A4 and CYP2C9 could play an important role to influence the pharmacokinetics of CCR5 antagonist which leads to different clinical responses to CCR5 inhibitors combining with other antiretrovirals.

1.11 Current status of antiretroviral treatment in children and adolescents in South Africa

There are approximately 1 million births in South Africa each year. With a 29.1% HIV seroprevalence rate in pregnant women in 2006, almost 300,000 infants are exposed to HIV each year. In the absence of intervention to prevent mother-to-child transmission of HIV, the vertical transmission rate is estimated to be between 30-40%. Current estimates indicate that only 14.6% of pregnant women in South Africa receive treatment to reduce mother-to-child HIV transmission; therefore, a significant number of children in South Africa will still acquire HIV via vertical transmission and be in need of HAART.

South Africa has an estimated 300,000 HIV-infected children; if one assumes that about 40% will qualify for HAART then at least 120,000 qualify immediately. However, as of September 2006 only about 21,000 children have initiated HAART by the national antiretroviral roll-out program.

The Harriet Shezi Clinic in Soweto, near Johannesburg, is the largest pediatric HIV clinic in the country. The clinic has initiated HAART in more than 2,000 children, most of whom were perinatally infected. The Harriet Shezi Clinic alone has at least 150 children over the age of 2 years who have detectable HIV viral load more than six months after initiating HAART.

A study from the Sinikithemba clinic, a family centered HIV clinic in KwaZulu-Natal, recently reported on the outcome of 151 children who initiated HAART. The Sinikithemba cohort exhibited a high degree of virologic suppression with 84% and 80% suppression at 6 and 12 months, respectively. In another report from Cape Town, 69% of 264 children initiating HAART had a VL < 400 at 12 months. These studies revealed that between 20 and 31% of children will have virologic failure 12 months after starting HAART in South Africa.
A growing percentage of HIV-infected children requiring treatment are accessing antiretroviral therapy. Among the IMPAACT sites in South Africa, the number of children failing 1st and 2nd line regimens is likely to increase over the next year. Therefore it is very important to adequately investigate new therapeutic agents for HIV-infected children and adolescents outside of North America and Europe where both viral and host characteristics may be different.

1.12 Current status of antiretroviral treatment in children and adolescents in Brazil

Brazil has more than one third of the total number of people living with HIV in Latin America. Brazil’s epidemic has changed over the years to be an epidemic of heterosexual transmission with a ratio between men and women decreasing from 26 infected men for each woman in 1985 to 1.5 in 2006 (www.unaids.org). There are approximately 220,000 HIV-infected women of childbearing age in Brazil. Consequently, despite prevention programs to decrease mother-to-child transmission, it is expected that the number of HIV-infected children in need of treatment will increase (www.unaids.org).

In 1995, Brazil became the first developing country to achieve universal access to HIV treatment via its national health-care system (www.unaids.org). Many of the 7,000 children and adolescents currently on treatment are on salvage regimens. A survey conducted with the five NICHD-sponsored IMPAACT sites in October 2007 indicated that there are 185 children between 6 and 19 years of age and 25 children between 2 and 6 years of age that would be eligible for Step I of P1071. Assuming that overall 50% would qualify for Step II by harboring R5 tropic viruses, at least 100 children and adolescents would be eligible for Step II enrollment at Brazilian sites (J. Pinto, personal communication).

1.13 Current status of antiretroviral treatment in children and adolescents in Argentina

According to UNAIDS, the HIV rate in Argentina is 9.4/100,000 inhabitants and unprotected sex has become the main route of HIV transmission (www.unaids.org). An estimated four in five new HIV diagnoses in 2007 were attributed to unprotected sexual intercourse (mainly heterosexual) and 3.4% of new infections occur perinatally (www.unaids.org). More than 65% of the estimated 134,000 people living with HIV are concentrated in Buenos Aires, the capital city, and its metropolitan area. The inversion of male to female ratio, from 92:1 in 1987 to 1.5:1 in 2007 is a shared characteristic with most Latin-American
countries (www.unaids.org). Nationwide, there are 4,035 cases of HIV infection in children under age 13. Most of these children have acquired the infection through perinatal exposure. Surveillance during 2005 in Buenos Aires including the metropolitan area showed the following data: among 1,807 cases of HIV/AIDS in children and adolescents, 90% had been caused by perinatal transmission. The median age was 9 years and 50.8% were female. Most of the children and adolescents had experienced AIDS events (80.3%), had at least one hospitalization (69%), and were on antiretroviral treatment (80%) (www.unaids.org). Since 1990, a national law has guaranteed the access to diagnosis, prevention and treatment services in Argentina. Hospital General de Agudos J. M. Ramos Mejia is a public institution which provides pediatric clinical care and treatment to 60 HIV-infected children and adolescents. A recent close watch of the efficacy of their regimens has shown virologic failure in up to 50% of children and adolescents. Almost every child experiencing virologic failure has reduced options to receive optimal antiretroviral treatment. It is anticipated that the number of children and adolescents on follow-up will increase in the near future because a specific outreach program has been implemented (Dr. Silvina Ivalo, personal communication).

1.14 Preclinical Experience with Vicriviroc

In preclinical studies, the only dose-limiting toxicity of vicriviroc in all species studied was seizures. No observable adverse effects levels (NOAEL) were identified in each species, and a plasma concentration of 4670 ng/mL was determined to be the threshold below which no seizures occurred in any species. In Phase 1 studies with 10 mg vicriviroc in the presence of ritonavir, the peak plasma concentration of vicriviroc ranged from 105 to 174 ng/mL. Based on the linear pharmacokinetics of this compound, we expect a three fold increase in plasma concentrations with the 30 mg dosage. These levels are well below the seizure threshold of 4670 ng/mL.

Male and female fertility and early embryonic or fetal development in rats and monkeys were not affected at any dose. A transient decrease in body weight in newborn rats was noted in one preclinical study, but no permanent long-term effects on growth, development or reproductive capability of newborn rats in adulthood were observed in this study. Clinical observations at high doses in monkeys included tonic-clonic seizure, vomiting, soft feces and/or diarrhea and a decrement in body weight (24).

Negative results for vicriviroc were obtained in bacterial mutagenicity assays, a human peripheral blood lymphocyte assay, and a mouse
micronucleus assay. There were no effects observed in studies of single oral doses of vicriviroc on cardiovascular, central nervous system (CNS), respiratory, renal and gastrointestinal function that would warrant concern at doses up to 40 mg/kg in monkeys, 20 mg/kg in dogs and 30 mg/kg in rats. Weak inhibition of the cardiac delayed-rectifier hERG or IKr (IC$_{50}$ of 5.8 µM, or approximately 4 µg/mL) occurred at a level much higher than the maximum plasma concentration of 0.3 µg/mL anticipated with doses used in this study. A thorough QT study conducted in human volunteers according to FDA guidelines yielded no evidence of prolongation of QT interval. The risk to humans associated with the vicriviroc exposures anticipated in this protocol is therefore considered to be very low.

1.15 Clinical Experience with Vicriviroc

Vicriviroc was evaluated in a phase II study in HIV-infected treatment experienced adults harboring the R5-tropic virus (25). This protocol enrolled 118 CCR5-tropic HIV-infected adults with plasma HIV RNA levels ≥ 5000 copies/mL despite receiving a standard, 3-drug ritonavir-boosted protease inhibitor ART regimen. Subjects were randomized to vicriviroc 5, 10 or 15 mg once daily (QD) or placebo which was added to their current ART regimen for 14 days to assess the antiviral activity provided by the added vicriviroc, after which time the subject’s background regimen was optimized by the investigator based on the resistance profile of their virus documented during screening. The optimized background mandated a ritonavir-boosted protease inhibitor. The final regimen continued for an additional 46 weeks or until virologic failure or other reason for discontinuation occurred.

One hundred eighteen (118) subjects were enrolled over the course of 17 months; 92% were males; 20% were black, 12% Hispanic, 66% white and 2% other race. The median age was 46 years, with 46% of subjects between 41 and 50 years of age. The median baseline HIV RNA was 4.56 log$_{10}$, with 29% >5.0 log$_{10}$. The median CD4 count was 146 cells/µL, with 19% having a CD4 cell count of < 50 cells/µL and 34% having >200 cells/µL. One-third of enrolled subjects were enfuvirtide-experienced. There were no significant safety issues to indicate a need for change in the protocol. The Safety Monitoring Committee recommended discontinuation of the 5 mg QD arm in October, 2005, based on suboptimal antiviral activity and emergence of X4-tropic viruses. These subjects were dose-escalated to 15 mg QD. The trial was unblinded in March, 2006, due to the observation of malignancies in several subjects receiving vicriviroc. As no clear association between the malignancies and vicriviroc could be ascertained, the trial continued to completion in
October, 2006 (25). Roll-over to open label vicriviroc 15 mg QD was accepted by the majority of subjects.

Vicriviroc was recently evaluated in a Phase II dose finding study of HIV-infected treatment experienced adults harboring the R5-tropic virus (VICTOR-E1). This protocol enrolled 116 CCR5-tropic HIV-infected adults with plasma HIV RNA levels ≥ 1000 copies/mL despite receiving a standard 3-drug ART regimen. Subjects were randomized on Day 1 to 20 or 30 mg vicriviroc once daily or placebo. The subject’s background therapy was optimized on Day 1 based on the resistance profile of their virus during screening, and was mandated to include a ritonavir-boosted protease inhibitor. The subjects continued treatment for 48 weeks, or until virologic failure or other reason for discontinuation occurred.

One hundred sixteen (116) subjects were enrolled over the course of 4 months; 78% were males and 68% were white, well distributed across the dose groups. The mean age was 45 years, ranging between 27 and 68 years of age. The mean baseline HIV RNA was 4.55 log₁₀, ranging between 2.20 and 6.34 log₁₀. The mean CD4 count was 202 cells/µL in the vicriviroc groups (3-730 cells/uL) and 226 cells/uL in the placebo group (2-692 cells/uL). Of subjects randomized to the vicriviroc groups, 24% had enfuvirtide as part of their optimized background therapy (OBT), compared to 14% of placebo subjects. There were no significant safety issues to indicate a need for change in the protocol. Of the 86 subjects who completed the study, 98% consented to roll-over to open label vicriviroc 30 mg QD after Week 48. Of the 30 subjects who discontinued study prior to Week 48, the majority (63%) were placebo recipients, of which the majority (73%) were discontinued for meeting the criteria for virologic failure.

1.151 Efficacy

Significant antiviral activity of both doses of vicriviroc, compared with placebo was demonstrated at the Week 24 and 48 interim analyses. With continued dosing in combination with an optimized background regimen containing a ritonavir-boosted PI, sustained viral suppression was demonstrated over the full 48 weeks. The magnitude of antiviral effect, by standard measures, is shown in Table 1.
Table 1. Antiviral Activity:

<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>24 week data</th>
<th>48 week data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VCV 30 mg N (%)</td>
<td>VCV 20 mg N (%)</td>
</tr>
<tr>
<td>≥ 1.0 log decline</td>
<td>30 (77)</td>
<td>30 (75)</td>
</tr>
<tr>
<td></td>
<td>26 (67)</td>
<td>25 (62)</td>
</tr>
<tr>
<td>&lt; 400 copies</td>
<td>28 (72)</td>
<td>30 (75)</td>
</tr>
<tr>
<td></td>
<td>25 (64)*</td>
<td>24 (60)*</td>
</tr>
<tr>
<td>&lt; 50 copies</td>
<td>25 (64)</td>
<td>23 (57)</td>
</tr>
<tr>
<td></td>
<td>23 (59)*</td>
<td>20 (50)*</td>
</tr>
</tbody>
</table>

* Based on TLOVR analysis: sustained confirmed full suppression (<400 or <50 copies/mL) through Week 48. (FDA Guidance for Industry: Antiretroviral Drugs Using Plasma HIV RNA Measurements - Clinical Considerations for Accelerated and Traditional Approval, October 2002)

These data supported the 30 mg QD dose to be taken forward into Phase III studies in CCR5-tropic adults based on its tolerability and antiviral efficacy (26).

1.152 Pharmacokinetics and Pharmacodynamics (PD)

Population PK modeling was developed by pooling steady state PK data from healthy subjects as well as sparse data from HIV-infected patients. A two-compartment PK model adequately described vicriviroc PK in treatment experienced HIV-infected patients receiving Ritonavir-boosted PI-containing regimens.

The results showed linear PK across doses ranging from 20-30 mg QD. Summary statistics of steady state $C_{\text{min}}$ and AUC values for various vicriviroc doses are presented in Table 2. It was also observed that AUC and $C_{\text{min}}$ values were highly correlated as shown in Figure 2 (Week 48 data included).
Table 2: Summary statistics of VCV PK in Study P03672 with Treatment Experienced HIV-Infected Patients (Including Week 48)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Subject Number</th>
<th>C_{min} (ng/mL)</th>
<th>AUC (hr*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>40</td>
<td>148 (90% CI 135-162)</td>
<td>4113 (90% CI 3796-4457)</td>
</tr>
<tr>
<td>30 mg</td>
<td>39</td>
<td>194 (90% CI 176-214)</td>
<td>5521 (90% CI 5074-6010)</td>
</tr>
</tbody>
</table>

a: LS Means based on log transformed data  
b: 90% confidence interval based on log transformed data

Figure 2: Correlation of Steady-state C_{min} and AUC Values

Since AUC and C_{min} values were highly correlated, C_{min} values were used to explore the relationship between exposure and viral response. When C_{min} data were grouped into different categories, the highest response rates (<50 copies HIV RNA/mL and <400 copies HIV RNA/mL) were observed.
copies HIV RNA/mL) were observed in patients with $C_{\text{min}} > 100$ ng/mL (Figures 3 and 4). These results indicate that patients with $C_{\text{min}} > 100$ ng/mL are associated with favorable viral responses.
1.16 Drug Interaction Studies

Vicriviroc is a CYP3A4 substrate and metabolism is impacted by agents that inhibit or induce this enzyme system. Co-administration of ritonavir, a potent CYP3A4 inhibitor, significantly increases vicriviroc exposure and half-life and decreases total body clearance. Drug interactions between vicriviroc 10 mg twice daily (BID) and ritonavir at 100 mg, 200 mg, and 400 mg BID were studied in healthy HIV-negative volunteers. All ritonavir doses had a similar effect increasing the vicriviroc $C_{\text{max}}$ by 2-4 fold and the AUC by 4-6 fold and $C_{\text{min}}$ by 7-9 fold at 14 days. Vicriviroc had no effect on the ritonavir pharmacokinetics. In the presence of ritonavir, vicriviroc is rapidly absorbed with a dose related increase in exposure when dosed up to 100 mg and has a long terminal-phase half-life (23 hours) which supports once-daily dosing. In a multiple-dose drug interaction study in HIV uninfected healthy volunteers, following 14 days of oral vicriviroc 10 mg BID with or without 600 mg QD of efavirenz, vicriviroc $C_{\text{max}}$ was reduced by 66%, the $AUC_{0-12}$ was reduced by 80% and the half life decreased from 23 to 11 hours. However, there was no effect on the efavirenz pharmacokinetics.

Single doses of up to 250 mg of vicriviroc alone have been administered in the clinic. The highest multiple-doses administered have been 200 mg
vicriviroc QD alone and 150 mg vicriviroc with 100 mg ritonavir QD. The highest vicriviroc exposures available to date are from dosing 150 mg vicriviroc QD with ritonavir for 14 days (in the thorough QT study), which resulted in a mean C_{max} (range) of 1380 ng/ml (1070 to 1720 ng/mL). Thus far all doses have been safe and well tolerated. In the presence of ritonavir, vicriviroc steady state was attained by day 14 with a 5-fold mean accumulation over the first dose. Both renal and hepatic pathways are active in vicriviroc elimination (24). Drug interaction studies that have been conducted include all currently marketed ritonavir-boosted protease inhibitors (lopinavir, atazanavir, indinavir, fosamprenavir, saquinavir, nelfinavir, darunavir and tipranavir), as well as efavirenz, ritonavir/efavirenz, tenofovir, and Combivir® (27). There were no significant changes in vicriviroc plasma concentrations when combined with the ritonavir-boosted protease inhibitors mentioned, other than the effects observed with ritonavir alone.

Vicriviroc can be given with or without food, as overall AUC is not changed after a high-fat meal. In addition, there was no interaction when an antacid was co-administered with vicriviroc.

A pharmacokinetic-pharmacodynamic (PK-PD) disease model was developed to describe short and long-term antiviral activity of vicriviroc (28). This model was based on clinical data from a 14 day vicriviroc monotherapy study and a long term study of vicriviroc in combination with Combivir® in treatment naïve subjects. This PK-PD model suggests that higher vicriviroc dosages have enhanced antiviral activity with a 2 log_{10} copies/mL viral load decline at 48 weeks supporting the use of ritonavir enhanced 30 mg of vicriviroc once a day (28). Data from Schering-Plough reveals that both AUC_{24} and C_{min} are directly correlated with viral load decline. Preliminary data from a similar study in healthy volunteers revealed that 30 mg of VCV (with ≥100 mg RTV) yielded a mean AUC_{24} and C_{min} of 6342 ng*hr/mL and 197 ng/mL, respectively (24).

1.17 Safety

Vicriviroc has been studied in approximately 500 human subjects in Phase 1 clinical pharmacology studies and in more than 300 HIV-infected subjects in Phase 2 trials. Vicriviroc has been well tolerated in all studies to date. No hepatotoxicity (as has been seen with aplaviroc) or other drug-specific toxicity has been reported. To date, there have been reports of malignancies in 11 subjects enrolled in treatment experienced vicriviroc studies. Ten (10) of these cases were in subjects exposed to vicriviroc; 1 subject was diagnosed while taking placebo (case of squamous cell
carcinoma). Malignancies in the 10 vicriviroc subjects include: 3 cases of Hodgkin’s lymphoma (one of which was in a subject with previous Hodgkin’s lymphoma); 2 cases of non-Hodgkin’s lymphoma (one of which was in a subject with previous Hodgkin’s lymphoma); 3 cases of Kaposi’s sarcoma (two recurrent, and one new in a subject diagnosed concomitantly with Hodgkin’s lymphoma); 1 gastric adenocarcinoma; 1 basal cell carcinoma; and 1 squamous cell carcinoma. There have been no reports of malignancies from Phase I healthy volunteer studies or Phase II treatment-naïve vicriviroc studies.

Additional details about specific benefits and risks for subjects participating in this clinical trial may be found in the Schering-Plough Investigator’s Brochure for Vicriviroc (2008).

1.2 Rationale

There is an unmet medical need for novel and potent antiretroviral therapy for HIV-infected patients who are experiencing drug resistance or toxicity, or who are failing their current antiretroviral regimen. These patients are often heavily pre-treated and have very limited therapeutic options. Drugs with new mechanisms of action, such as the HIV entry inhibitors, demonstrate activity even in subjects with resistance to currently available reverse transcriptase and protease inhibitors. Vicriviroc, a CCR5 co-receptor antagonist, is a potent and selective entry inhibitor of R5 tropic virus. Subjects will be screened during Step I for co-receptor tropism using Trofile™, the coreceptor use assay (Monogram Biosciences, Inc., South San Francisco, CA). This assay amplifies the full-length env-coding sequence from HIV-1 RNA in subjects’ plasma by reverse transcriptase-polymerase chain reaction. The resulting amplicon is used to generate pseudotyped defective HIV-1 recombinants that carry the HIV gag, pol and regulatory genes and a luciferase reporting gene in place of env gene, under control of the HIV-1 long-terminal repeat (LTR). Infectivity of the resultant viral stocks is assessed in cell lines that express CD4+ and CCR5 or CXCR4 by measuring luciferase activity. R5, R5/X4 dual mixed tropic or X4 tropic designations are verified by blocking co-receptor- mediated infection using specific antagonists (29). Recently, an enhanced version of the Trofile™ HIV co-receptor tropism assay with greater sensitivity to detect CXCR4-using viruses has been introduced to replace the original assay for subjects being considered for treatment with CCR5 antagonists (30;31). Only children with R5-tropic virus will be enrolled in Step II (treatment).

The purpose of this initial vicriviroc pediatric study is to gain insight on short and long term safety data, pharmacokinetics, and efficacy in HIV-1 infected children and adolescents ages 2 years to nineteen years. In addition, this study will
investigate co-receptor tropism and will evaluate factors associated with virologic failure in a vicriviroc treated pediatric population.

1.21 Rationale for Dose Selection Criteria

The goal of the approach to dose selection is to determine a pediatric dose that approximates adult exposure observed at the 30 mg dose in the presence of ritonavir to be consistent with adult dosing in Phase II studies.

Vicriviroc at 30 mg dose in the presence of ritonavir yields mean AUC_24 and C_{min} of 6342 ng*hr/mL and 197 ng/mL, respectively. Since HIV-infected adult patients showed a favorable virologic response when their steady-state C_{min} > 100 ng/mL, the PK target for treating pediatric patients is to achieve C_{min} > 100 ng/mL for all subjects.

1.22 Rationale for targeting vicriviroc PK as surrogate of virologic efficacy despite variability in the CCR5 cellular receptor expression

Expression of CCR5 receptors on the surface of CD4 lymphocytes appears to be constant for a given individual, but to vary quite significantly among individuals (32-34). While many factors, including age, may influence the number of CCR5 expressing cells, the density of CCR5 expression in the cell membrane seems to be very stable across a spectrum of age for an individual.

In a study that evaluated CCR5 receptor occupancy by a receptor antagonist as a predictor of drug efficacy, the authors reported that close to complete occupancy of all receptors is required to induce a significant decrease in viral load; that CCR5 receptor occupancy is not a direct measure of drug inhibitory activity; and that maximum CCR5 receptor occupancy was achieved with very low doses of the drug studied (35). One possible explanation for this finding is the high affinity of a drug for the CCR5 receptor. Based on their results, the authors concluded that routine monitoring of receptor occupancy as a biomarker for CCR5 antagonist efficacy is not likely to be informative.

Despite the previously-described large inter-individual variability in CCR5 receptor density in the adult population, earlier phase II studies with vicriviroc demonstrated a potent and predictable antiviral activity that correlated with pharmacokinetic exposure. Based on this evidence, we could argue that pediatric subjects, despite anticipated variability in CCR5 receptor density, will show a similar response (36). Studies of three different small-molecule CCR5 receptor antagonists in adults demonstrated mean viral load reduction of ~1.5 logs over a 10 day
exposure to the drugs (25;37-39). In a recent vicriviroc study in treatment
experienced adults who received 30 mg QD in combination with a boosted
protease inhibitor containing optimized background therapy (OBT), the
mean reduction in plasma HIV RNA was ~2.0 log_{10} as compared to ~1.0
log_{10} with OBT alone. This magnitude of effect also correlated strongly
with PK exposure (26). Taking into account the correlations between PK
exposure and efficacy, in spite of wide inter-patient variability in CCR5
receptor density, it seems likely that a similar correlation will exist in
children. However, this will need to be confirmed with documented
antiviral activity.

To define the appropriate dose of vicriviroc for pediatric patients, efficacy
will be monitored by plasma HIV RNA levels and CD4 counts and
correlated with the observed PK exposure. It is reasonable to study
initially pediatric doses that are expected to approximate the PK exposure
achieved in adults receiving the recommended 30 mg QD dose. A decline
of ~2 log_{10} in HIV RNA as was seen in adults would be expected to be
associated with the appropriate pediatric dose. This protocol provides for
adjustment of VCV dose level in the event of suboptimal PK exposure.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 In Stage I, to evaluate the short term safety and tolerability of vicriviroc in
combination with optimized background therapy which includes a
ritonavir-boosted protease inhibitor regimen in HIV-infected, treatment
experienced children and adolescents.

2.12 In Stage I, to determine the multidose pharmacokinetics of vicriviroc in
combination with optimized background therapy which includes a
ritonavir-boosted protease inhibitor, and to determine the dose of
vicriviroc that achieves a target $C_{\text{min}}$ in children and adolescents.

2.13 In Stage II, to evaluate the long term safety and tolerability of the
optimized dosage of vicriviroc in combination with optimized background
therapy which includes a ritonavir-boosted protease inhibitor in HIV-
infected, treatment experienced children and adolescents.

2.2 Secondary Objectives

2.21 In Step I, to investigate the predictors of co-receptor tropism among
antiretroviral-experienced children and adolescents who undergo
screening for P1071.
2.22 To evaluate the antiviral activity of vicriviroc given with an optimized background therapy by measuring viral load response in antiretroviral therapy experienced children and adolescents at 24 and 48 weeks.

2.23 To evaluate the immunologic activity of vicriviroc given with an optimized background therapy by measuring changes in CD4 cell count and percent from baseline to weeks 24 and 48.

2.24 To assess specific alterations in the HIV-1 envelope and polymerase genomes that are associated with vicriviroc and antiretroviral resistance in those subjects experiencing virologic failure, virologic breakthrough or co-receptor phenotype switch.

2.25 To evaluate whether co-receptor usage changes over time in children and adolescents who experience virologic failure and virologic breakthrough during vicriviroc treatment (R5 → R5X4 → X4).

2.26 To explore covariates that may alter response to a vicriviroc-containing regimen including vicriviroc exposure, clinical status, immunologic status, age, race/ethnicity, and pharmacogenomics.

2.27 To determine if CCR5 expression or CCR5 genetic variants and other immunologic factors alter the pharmacokinetics or response to vicriviroc.

3.0 STUDY DESIGN

P1071 is a phase I/II, multi-center, open-label, two stage, age-stratified, intensive PK non-comparative study to explore the safety, tolerability, pharmacokinetic profile and antiviral activity of the investigational CCR5 inhibitor vicriviroc in HIV-infected treatment experienced children and adolescents.

Vicriviroc will be administered orally in tablet dose strengths of 20 or 30 mg and in liquid formulation at a concentration of 1 mg/mL. All subjects enrolled into the study will be stratified into the following age groups:

Cohort I: ≥12 years to <19 years of age, to receive tablet formulation of VCV
Cohort II: ≥6 years to <12 years of age, to receive tablet formulation of VCV
Cohort III: ≥6 years to <12 years of age, to receive liquid formulation of VCV
Cohort IV: ≥2 years to <6 years of age, to receive liquid formulation of VCV

Subjects who age out of a cohort during the study or during follow-up will remain in the cohort to which they were assigned at Step II entry.

3.1 Pre-Screening

The following information will be collected during pre-screening: route of HIV acquisition, complete antiretroviral therapy history and duration of each regimen, CDC classification at screening, prior AIDS defining conditions, historical CD4 cell count and percentage nadir, historical peak HIV RNA load, current CD4 cell
count and percentage, CD8 cell count and percentage, HIV RNA load and HIV subtype.

3.2 Step I

Step I is an investigation of predictors of HIV co-receptor tropism in children and adolescents screened for entry into Step II. Each subject’s virus will be screened for co-receptor tropism using the enhanced version of the Trofile™ co-receptor use assay (Monogram Biosciences, Inc., South San Francisco, CA) (29-31). Approximately 280 subjects will enter Step I. In the event that 140 subjects with CCR5 tropic virus are not enrolled into Step II, an additional 30 subjects will be enrolled into Step I. Slots will continue to be opened in Step I in blocks of 30 until 140 subjects are enrolled into Step II. Conversely, if enrollment into Step II is completed prior to enrollment of 280 subjects in Step I, enrollment will be terminated. Subjects enrolled into Step I who are on a failing ART regimen will need to continue on that regimen until eligibility into Step II is confirmed.

Only subjects with R5-tropic virus found in Step I will be eligible to continue to Step II. These participants must have evidence of HIV genotypic drug sensitivity (assay performed by Monogram Biosciences, Inc., South San Francisco, CA) to a boosted protease inhibitor.

3.3 Step II

Step II is composed of Stage I (intensive PK) and Stage II, which are sequential stages and will enroll approximately 140 subjects to yield about 100 evaluable subjects. A minimum of 48 subjects will be enrolled in Stage I (at least 12 per age cohort), and the remaining subjects will be enrolled in Stage II.

Enrollment will begin concurrently for Cohorts I and II on the tablet formulation. Subjects will only be enrolled in these cohorts if their weight is ≥25 kg. OBT will start from day 1 and the site investigator will construe a regimen based on the HIV genotype performed by Monogram Biosciences and on the ART history. The OBT regimen must contain a ritonavir boosted PI to which the subject’s virus is susceptible (by genotype) and at least one other antiretroviral drug. NNRTIs with the exception of etravirine, and maraviroc may not be part of the OBT. Sites are asked to send the proposed OBT regimen by email to the P1071 team (actg.teamp1071@fstrf.org) for final approval; the team will respond within 2 business days. Once a preliminary dose of vicriviroc has been determined based on the intensive PK (Stage I) in mini-cohort II, and provided that the dose is safe, enrollment for Cohorts III and IV on the liquid formulation will proceed sequentially.

3.31 Stage I
Stage I is a dose ranging study designed to explore the pharmacokinetics of vicriviroc at the dosage of approximately 0.8 mg/kg once a day in twelve children and adolescents from each cohort (48 subjects in total). Each cohort will enroll an initial mini-cohort of 4 children. Enrollment to the cohort will pause after the fourth subject enrolls to allow for evaluation of the PK and safety results. As steady state vicriviroc levels will be achieved within 14 days of drug initiation, an intensive pharmacokinetics (PK) evaluation will be performed between days 14 and 20. Vicriviroc levels will be assayed in real time (ideally within two weeks) and the protocol team will evaluate the results. On completion of the intensive PK, children will continue taking the assigned vicriviroc therapy and the OBT. If the mini-cohort PK data are acceptable (see section 9.31) and 4 week safety data are acceptable (see section 8.5), enrollment in Stage I will open to complete a full cohort of approximately 12 children. The starting dose of 0.8 mg/kg once a day is based on comparable dosages used in HIV-infected adults targeting a specific $C_{\text{min}}$ of 197 ng/mL. This is achieved by dosing 30 mg of vicriviroc in a ritonavir containing regimen. The maximum starting dose will be 30 mg QD; if exposure levels are inadequate, dosing maybe increased to a maximum of 40 mg QD. Children and adolescents who have discontinued antiretroviral therapy for at least 4 weeks or who are on a failing regimen will have a HIV genotype and phenotype performed (Monogram Biosciences) and will be enrolled provided their virus is CCR5 tropic and the genotype reveals susceptibility to at least a ritonavir-boosted protease inhibitor.

The initial Stage I dose of vicriviroc will be approximately 0.8 mg/kg for participants in each cohort, with a maximum of 30 mg QD. Cohorts I and II using the tablet formulation will be opened to accrual simultaneously; there is the potential for significantly different rates of accrual between cohorts due to patient availability. If 24 hour intensive PK and/or safety data from a mini cohort in Stage I suggest the initial 0.8 mg/kg needs modification, the study team will review all available information and make a recommendation to modify dosing for Cohorts I and II. In subjects from mini-cohorts requiring dose modifications, an additional intensive pharmacokinetic evaluation will be performed 14-20 days post dose modification. The protocol team may request that a subject in Stage I undergo repeat intensive PK sampling at the same dose if a subject’s results appear to be incomplete and or uninterpretable. Once the dose in mini-cohort II is found to be safe and the PK target is achieved, enrollment in Cohort III will start. Once the dose in mini-cohort III is found to be safe and the PK target is achieved, enrollment will proceed with Cohort IV.
See Appendix II, Algorithm for Cohort Management in Stage I.

3.32 Stage II

Once an optimal dose of vicriviroc is determined for a given age cohort, and provided safety is acceptable, Stage II will open to enrollment for that cohort. Stage II is intended to provide long-term safety, tolerability and efficacy data for vicriviroc given in combination with an OBT regimen. Children and adolescents who have discontinued antiretroviral therapy for at least 4 weeks, or who are on a failing regimen, will have a HIV genotype and phenotype performed (by Monogram Biosciences) and will be enrolled provided their virus is CCR5 tropic and the genotype is susceptible to at least a ritonavir-boosted protease inhibitor. OBT will start from day 1. The site investigator will construe a regimen based on the HIV genotype and the ART history. The OBT regimen must contain a ritonavir boosted PI to which the subject’s virus is susceptible (by genotype). Sites must send their proposed OBT regimen to the P1071 team via email (actg.teamp1071@fstrf.org) for final approval; the team will respond within 2 business days. Stage II subjects will complete 48 weeks of exposure at the selected dose for that cohort.

Approximately 52 to 80 additional subjects will be enrolled into Stage II. A minimum of 10 children will be accrued into each Stage II cohort up to a maximum of 20 subjects. Additional subjects may be allowed to enroll into a given Stage II Cohort past the 20 subject cap only after protocol team approval. The protocol team approval is contingent on satisfying the minimum enrollment in the younger Stage II age cohorts.

Refer to the Schedule of Evaluations (Appendices I-A and I-B) and the Algorithm for Cohort Management (Appendix II) for additional details.

3.33 Follow-up

All subjects exposed to vicriviroc will be followed until 5 years after initial exposure. Visits will be every 3 months for subjects on study drug and every 6 months for subjects who discontinue study provided vicriviroc. See Appendices I-A and I-B for details.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria for Step I

4.11 Age ≥2 years to <19 years at study entry.
4.12 Past or current documentation of a confirmed diagnosis of HIV-1 infection defined as two separate peripheral blood specimens from different days, and each specimen must be positive. The two positive results may have been obtained in any combination of the following:

- Positive HIV-1 ELISA or licensed HIV-1 rapid antibody test and confirmatory HIV-1 Western Blot or IFA (at age > 18 months)
- For subjects in countries without access to Western blot or IFA: Positive HIV-1 ELISA or licensed HIV-1 rapid antibody test and confirmatory rapid test from a different test kit
- HIV-1 RNA viral load > 1000 copies/mL plasma
- Positive HIV-1 DNA PCR or HIV-1 p24 antigen assay or HIV-1 culture

4.13 Treatment experienced subjects:

- Children or adolescents on an unchanged therapeutic regimen for at least 12 weeks and experiencing virologic failure defined as having a HIV RNA viral load ≥ 1,000 copies/mL and without evidence of progressive viral load decline on current regimen. Progressive virologic decline refers to a decrease in viral load of >0.75 log_{10} over 12 weeks prior to Step I entry.

OR

- Subjects on no treatment for ≥4 weeks but with history of virologic failure as defined above on a prior therapeutic regimen. (Therapeutic regimen refers to triple drug combination therapy.)

4.14 Subjects who, by ARV history and/or previous genotypic or phenotypic testing results, are likely to have virus that is sensitive to at least one ritonavir boosted protease inhibitor.

4.15 HIV-1 plasma RNA viral load greater than or equal to 1,000 copies/ml within 90 days of Step I entry.

4.16 Able to swallow study medication, provided as tablets or liquid formulation specific to cohort requirement.

4.17 Parent, legal guardian or subject able and willing to provide signed informed consent and to have the subject followed at the clinic site.

4.18 Female subjects who are sexually active and potentially able to become pregnant, must have a negative pregnancy test within 3 days of Step I entry, and must use two methods of birth control while on study and
during follow up, until 3 months after discontinuing study-provided vicriviroc. Acceptable methods of birth control include hormonal contraceptives, condoms (male or female), diaphragm or cervical cap with spermicide, or IUD.

4.19 Male subjects who are sexually active must agree not to attempt to impregnate a female, or to participate in sperm donation programs. Males engaging in sexual activity that could lead to pregnancy must use a condom until one month after discontinuing vicriviroc.

4.2 Inclusion Criteria for Step II (In addition to the inclusion criteria in Step I)

4.21 Subject’s plasma HIV tested at Step I by the enhanced version Trofile™ assay must be R5 tropic virus only.

4.22 Genotypic sensitivity to enable the subject to take optimized background therapy consisting of at least a ritonavir-boosted protease inhibitor, in addition to the study drug. (NNRTIs other than etravirine will be excluded. OBT must include at least one other antiretroviral but viral sensitivity is not required.) Optimized background therapy must be submitted to the protocol team via email (actg.teamp1071@fstrf.org) for approval.

4.23 Female subjects who are sexually active and potentially able to become pregnant, must have a negative pregnancy test within 3 days of Step II entry.

4.3 Exclusion Criteria for Step I

4.31 Presence of any currently active AIDS defining illness or history of malignancy.

4.32 Subjects with a history of a seizure disorder that requires current anti-seizure medication for control or who, in the opinion of the investigator, are at risk for seizures. A history of febrile seizures alone is not an exclusion criterion.

4.33 Known Grade ≥3 of any of the following laboratory tests within 90 days of Step I entry: neutrophil count, hemoglobin, platelets, AST, ALT, lipase, creatinine.

4.34 Any vaccinations 14 days prior to Step I, or scheduled to occur within 14 days prior to entry into Step II, and the week 24 and 48 visits in Step II.
4.35 Subjects who are pregnant or breastfeeding. (Infants who are receiving breastfeeding are allowed to enroll.)

4.36 Subjects with allergy/sensitivity to study drug or its excipients.

4.37 Subjects who are taking any Step II disallowed medications (see section 4.6) and who are unable or unwilling to discontinue them at least one week prior to entering Step II.

4.4 **Exclusion Criteria for Step II**

4.41 All exclusion criteria listed above for Step I.

4.42 Subjects harboring dual or mixed tropic virus (R5/X4) or X4 virus or non phenotypable virus.

4.43 Current or anticipated use of any disallowed medications (see Section 4.6).

4.44 Use of **efavirenz, nevirapine and delavirdine** for 21 days prior to Step II initiation.

4.5 **Concomitant Medication Guidelines**

Background therapy drugs can include any commercially-available antiretroviral medication (except maraviroc), one of which is a ritonavir boosted PI. **Efavirenz, nevirapine and delavirdine** are allowed only in Step I, but won’t be allowed in Step II or for 21 days prior to Step II initiation.

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the Disallowed Medications section. It is the responsibility of the investigator to check on potential drug-drug interactions between background antiretroviral therapy and other concomitant therapies before placing a subject on a specific medication.

4.51 **Required Medications**

Ritonavir. The suggested doses for ritonavir are:

- The RTV enhancing dose in Kaletra® is 57.5 mg/m² or 100mg/1.74m².
- The RTV dose used with atazanavir is 100mg/m² up to 100mg.
- The RTV doses with tipranavir are 115-150 mg/m².
- For amprenavir or fosamprenavir the RTV dose is 150-200mg/m² up to 200mg.
4.52 Immunizations

Commercially available immunizations according to standard of care may be given to study subjects, but not 2 weeks prior to Step I or Step II visits, or either of the points in the study at which key data analysis will be performed (i.e., Week 24 and Week 48).

4.6 Disallowed Medications during Step II

Subjects should not receive any of the following medications during Step II and for NNRTIs (other than etravirine) for 21 days prior to Step II.

- Anti-seizure medications (prescribed for known seizure disorder)
- Interferons
- Interleukin-2
- Systemic glucocorticoids at supraphysiologic doses for ≥7 consecutive days
- Phenothiazines (eg, chlorpromazine, prochlorperazine, promethazine); trimethobenzamide
- Immunosuppressants or immunomodulators
- Cytotoxic agents or cancer chemotherapy
- Ribavirin, rifampin
- Cocaine (heavy use, in the opinion of the investigator)
- Drugs (therapeutic or recreational) with potential for withdrawal seizures, including, but not limited to, heavy use of alcohol
- Entecavir (Baraclude®)
- Efavirenz, nevirapine, delavirdine
- Maraviroc, or other CCR5 antagonists

The following exceptions to the above list are permitted:

- Neurontin (gabapentin), valproate, Lamictal (lamotrigine) or other anticonvulsants may be used for any indication other than seizures.
- Benzodiazepines such as Valium (diazepam), Ativan (lorazepam), and Xanax (alprazolam) may be used for anxiety if there are no plans to discontinue the medication over the course of the study. Subjects using these medications must be warned not to discontinue their use without medical consultation.
- A single dose of Versed (midazolam) may be used for sedation in subjects undergoing procedures in a monitored setting.
- Chlorpromazine and promethazine can be used as antiemetic medications, as long as the subject has received similar doses in the past without extrapyramidal side effects.
- Intravenous Immunoglobulin (IVIG) when clinically indicated.
Note: No seizure activity attributable to vicriviroc has occurred in clinical studies to date. However, seizures have occurred in animal species at very high plasma concentrations of vicriviroc. Agents that cause seizures or have the potential of lowering seizure threshold should be used with caution and only if no satisfactory alternatives are available.

4.7 Enrollment Procedures

Prior to implementation of this study, each site must have the protocol document and the consent form approved by the local Institutional Review Board (IRB)/Ethics Committee (EC). A Site Implementation Plan (SIP) will be required from each international site and subunit participating in the study. The plan must be submitted to the Protocol Team for review and approval before protocol registration can occur. Each site must complete the protocol registration process through the DAIDS Regulatory Compliance Center (RCC) Protocol Registration Office before subjects can be enrolled in this study. Subject enrollment is done through the Data Management Center (DMC) Subject Enrollment System (SES). Written informed consent for study participation must be obtained before any study related procedures are performed.

4.71 Pre-Screening

Sites must utilize the IMPAACT Screening System to obtain a unique screening number for each potential study subject. Sites must then send an e-mail to the team at actg.teamp1071@fstrf.org with the individual’s screening number and the cohort to which they want to enroll, after careful review of Step I inclusion criteria. The protocol team will authorize the site (via e-mail) to proceed with the screening evaluations if there is a slot available. As a reminder, potential subjects should remain on their pre-study failing ARV regimens until the genotype and phenotype requirements are completed and they begin to take their study assigned ARV regimen (Section 6.32).

4.72 Screening

After receiving team authorization, the site has a maximum of 14 days from the date the screening slot is granted to enroll to step one and complete the screening visit. If the participant is not enrolled, the screening number will expire and the process will repeat.

4.8 Co-enrollment Procedures

Co-enrollment is permitted except for protocols that would violate the exclusion criteria and where permitted by local/country regulations; a list of protocols in
which co-enrollment is pre-approved will be provided via email and on the P1071 web page. All co-enrollments onto treatment protocols not on the pre-approved list require the assent of the protocol chairs of IMPAACT P1071 and the co-enrollment protocols.

4.9 Replacement of Subjects

Subjects who enroll in Step II, Stage I will be replaced if:
- The subject discontinues prior to completion of the intensive PK evaluations,
- The subject’s intensive PK data are unevaluable,
- The subject requires treatment with disallowed medications (unless this is due to an adverse event that may be indicative of safety failure),

OR
- The subject becomes pregnant.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

At Step II entry, subjects will be enrolled into four age cohorts:

Stage I

Cohort I: ≥12 - < 19 years and ≥ 25 kg will receive vicriviroc tablets at approximately 0.8 mg/kg orally every 24 hours (see Table 3) with a ritonavir-boosted protease inhibitor containing regimen.

Cohort II: ≥6 - < 12 years and ≥ 25 kg will receive vicriviroc tablets at approximately 0.8 mg/kg orally every 24 hours (see Table 3) with a ritonavir-boosted protease inhibitor containing regimen.

Cohort III: ≥ 6 - < 12 years will receive vicriviroc liquid formulation at approximately 0.8 mg/kg orally every 24 hours (see Table 4) with a ritonavir-boosted protease inhibitor containing regimen.

Cohort IV: ≥2 - <6 years will receive vicriviroc liquid formulation at approximately 0.8 mg/kg orally every 24 hours (see Table 5) with a ritonavir-boosted protease inhibitor containing regimen.

Initial dosing will not exceed 30 mg QD, but may increase to a maximum of 40 mg QD if initial exposure is inadequate. See Tables 3, 4 and 5 for initial dose at approximately 0.6-0.8 mg/kg/day for mini-cohorts I-IV. For mini-cohorts
with median $C_{\text{min}} < 130$ ng/ml, the adjusted dose will be between 0.8-1.2 mg/kg/day (see Tables 6, 8 and 10). For mini-cohorts with median $C_{\text{min}} > 400$ ng/ml, the adjusted dose will be between 0.34 and 0.6 mg/kg/day (see Tables 7, 9 and 11). Note that weight should be measured at each visit; dose adjustments for growth should be made as needed.

Note: If the protocol team determines that the initial dose of 0.8 mg/kg is not appropriate, sites will be notified via email. If dose adjustments are required, the pharmacist must receive a new prescription for an adjusted dose from Tables 6, 7, 8, 9, 10 and 11. If the protocol team determines that a cohort dose adjustment is required and the appropriate dose is not included in the tables below, an updated dosing table will be provided via protocol amendment. Please refer to section 6.3 for cohort dosing management. Full cohort dose adjustments will be made as described in section 9.31.
Initial Dose Tables for Stage I:

Table 3: Stage I Initial Dose of vicriviroc tablet doses with a target dose of approximately 0.8 mg/kg once daily for Cohorts I and II in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Initial Dose (mg)</th>
<th>Number and Strength of Vicriviroc Tablet(s) to Administer for Each Dose Once Daily</th>
<th>Dose Range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥25 kg - 34 kg</td>
<td>20 mg</td>
<td>1 x 20 mg tablet</td>
<td>0.59-0.8 mg/kg</td>
</tr>
<tr>
<td>&gt;34 kg</td>
<td>30 mg</td>
<td>1 x 30 mg tablet</td>
<td>≤0.87 mg/kg</td>
</tr>
</tbody>
</table>

Table 4: Stage I Initial Dose of vicriviroc oral solution doses with a target dose range of approximately 0.6 mg/kg - 0.8 mg/kg once daily for Cohort III in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Initial Dose of Vicriviroc Oral Solution</th>
<th>Volume of Vicriviroc Oral Solution to Administer Once Daily on Cohort III</th>
<th>Dose Range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10 kg - 14 kg</td>
<td>8 mg</td>
<td>8 mL</td>
<td>0.57 - 0.8 mg/kg</td>
</tr>
<tr>
<td>&gt;14 kg - 20 kg</td>
<td>12 mg</td>
<td>12 mL</td>
<td>0.6 - 0.85 mg/kg</td>
</tr>
<tr>
<td>&gt;20 kg – 25 kg</td>
<td>16 mg</td>
<td>16 mL</td>
<td>0.64 - 0.8 mg/kg</td>
</tr>
<tr>
<td>&gt;25 kg – 30 kg</td>
<td>18 mg</td>
<td>18 mL</td>
<td>0.6 - 0.72 mg/kg</td>
</tr>
<tr>
<td>&gt;30 kg – 34 kg</td>
<td>21 mg</td>
<td>21 mL</td>
<td>0.62 - 0.7 mg/kg</td>
</tr>
</tbody>
</table>
Table 5: Initial Dose of vicriviroc oral solution doses with a target dose range of approximately 0.6 mg/kg – 0.8 mg/kg once daily for Cohort IV in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Targeted Dose of Vicriviroc Oral Solution</th>
<th>Volume of Vicriviroc Oral Solution to Administer Once Daily in Cohort IV</th>
<th>Dose Range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥7 kg – 8 kg</td>
<td>5 mg</td>
<td>5 mL</td>
<td>0.63 – 0.71 mg/kg</td>
</tr>
<tr>
<td>&gt;8 kg – 9 kg</td>
<td>6 mg</td>
<td>6 mL</td>
<td>0.67 – 0.74 mg/kg</td>
</tr>
<tr>
<td>&gt;9 kg – 10 kg</td>
<td>6.5 mg</td>
<td>6.5 mL</td>
<td>0.65 – 0.71 mg/kg</td>
</tr>
<tr>
<td>≥ 10 kg – 11 kg</td>
<td>7.5 mg</td>
<td>7.5 mL</td>
<td>0.68 – 0.74 mg/kg</td>
</tr>
<tr>
<td>&gt;11 kg – 12 kg</td>
<td>8 mg</td>
<td>8 mL</td>
<td>0.67 – 0.72 mg/kg</td>
</tr>
<tr>
<td>&gt;12 kg – 13 kg</td>
<td>8 mg</td>
<td>8 mL</td>
<td>0.62 – 0.66 mg/kg</td>
</tr>
<tr>
<td>&gt;13 kg – 14 kg</td>
<td>9 mg</td>
<td>9 mL</td>
<td>0.64 – 0.69 mg/kg</td>
</tr>
<tr>
<td>&gt;14 kg – 15 kg</td>
<td>9 mg</td>
<td>9 mL</td>
<td>0.6 – 0.64 mg/kg</td>
</tr>
<tr>
<td>&gt;15 kg – 16 kg</td>
<td>10 mg</td>
<td>10 mL</td>
<td>0.63 – 0.66 mg/kg</td>
</tr>
<tr>
<td>&gt;16 kg – 17 kg</td>
<td>11 mg</td>
<td>11 mL</td>
<td>0.65 – 0.68 mg/kg</td>
</tr>
<tr>
<td>&gt;17 kg – 18 kg</td>
<td>11 mg</td>
<td>11 mL</td>
<td>0.61 – 0.64 mg/kg</td>
</tr>
<tr>
<td>&gt;18 kg – 19 kg</td>
<td>12 mg</td>
<td>12 mL</td>
<td>0.63 – 0.66 mg/kg</td>
</tr>
<tr>
<td>&gt;19 kg – 20 kg</td>
<td>12 mg</td>
<td>12 mL</td>
<td>0.6 – 0.63 mg/kg</td>
</tr>
<tr>
<td>&gt;20 kg – 21 kg</td>
<td>13 mg</td>
<td>13 mL</td>
<td>0.62 – 0.65 mg/kg</td>
</tr>
<tr>
<td>&gt;21 kg – 22 kg</td>
<td>14 mg</td>
<td>14 mL</td>
<td>0.64 – 0.66 mg/kg</td>
</tr>
<tr>
<td>&gt;22 kg – 23 kg</td>
<td>14 mg</td>
<td>14 mL</td>
<td>0.61 – 0.63 mg/kg</td>
</tr>
<tr>
<td>&gt;23 kg – 24 kg</td>
<td>15 mg</td>
<td>15 mL</td>
<td>0.63 – 0.65 mg/kg</td>
</tr>
<tr>
<td>&gt;24 kg – 25 kg</td>
<td>15 mg</td>
<td>15 mL</td>
<td>0.6 – 0.62 mg/kg</td>
</tr>
<tr>
<td>&gt;25 kg – 26 kg</td>
<td>16 mg</td>
<td>16 mL</td>
<td>0.62 – 0.64 mg/kg</td>
</tr>
<tr>
<td>&gt;26 kg – 27 kg</td>
<td>17 mg</td>
<td>17 mL</td>
<td>0.63 – 0.65 mg/kg</td>
</tr>
<tr>
<td>&gt;27 kg – 28 kg</td>
<td>17 mg</td>
<td>17 mL</td>
<td>0.61 – 0.63 mg/kg</td>
</tr>
<tr>
<td>&gt;28 kg – 29 kg</td>
<td>18 mg</td>
<td>18 mL</td>
<td>0.62 – 0.65 mg/kg</td>
</tr>
<tr>
<td>&gt;29 kg – 30 kg</td>
<td>19 mg</td>
<td>19 mL</td>
<td>0.63 – 0.66 mg/kg</td>
</tr>
</tbody>
</table>

Adjusted Dose Tables for Stage I

Table 6: Adjusted Dose for mini-cohorts with a median $C_{min} < 130$ ng/mL on vicriviroc tablet formulation (Cohorts I and II) in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Adjusted Dose from Table 3</th>
<th>Number and Strength of Vicriviroc Tablet(s) to Administer for Each Dose Once Daily</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 7: Adjusted Dose for mini-cohorts with a median $C_{\text{min}} > 400 \text{ ng/mL}$ on vicriviroc tablet formulation for Cohorts I and II in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Adjusted Dose from Table 3</th>
<th>Number and Strength of Vicriviroc Tablet(s) to Administer for Each Dose Once Daily*</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;25 kg - 34 kg</td>
<td>15 mg</td>
<td>*(A)</td>
<td>0.44-0.59 mg/kg</td>
</tr>
<tr>
<td>&gt;34 kg</td>
<td>20 mg</td>
<td>1 x 20 mg tablet</td>
<td>0.34-0.58 mg/kg</td>
</tr>
</tbody>
</table>

*(A) Subject will need to be moved to Cohort III and take liquid formulation.

Table 8: Adjusted Dose of vicriviroc oral solution doses for mini-cohorts with a median $C_{\text{min}} < 130 \text{ ng/mL}$ with a target dose range of approximately 0.8 mg/kg – 1.2 mg/kg once daily for Cohort III in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Targeted Dose of Vicriviroc Oral Solution</th>
<th>Volume of Vicriviroc Oral Solution to Administer Once Daily on Cohort III</th>
<th>Dose Range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10 kg - 14 kg</td>
<td>12 mg</td>
<td>12 mL</td>
<td>0.86 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;14 kg - 20 kg</td>
<td>17 mg</td>
<td>17 mL</td>
<td>0.85 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;20 kg – 25 kg</td>
<td>24 mg</td>
<td>24 mL</td>
<td>0.96 – 1.19 mg/kg</td>
</tr>
<tr>
<td>&gt;25 kg – 30 kg</td>
<td>30 mg</td>
<td>30 mL</td>
<td>1 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;30 kg – 34 kg</td>
<td>36 mg</td>
<td>36 mL</td>
<td>1.06 – 1.2 mg/kg</td>
</tr>
</tbody>
</table>
Table 9: Adjusted Dose of vicriviroc oral solution doses for mini-cohorts with a median C\textsubscript{min} > 400 ng/mL with a target dose range of approximately 0.4 mg/kg – 0.6 mg/kg once daily for Cohort III in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Targeted Dose of Vicriviroc Oral Solution</th>
<th>Volume of Vicriviroc Oral Solution to Administer Once Daily on Cohort III</th>
<th>Dose Range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10 kg – 14 kg</td>
<td>6 mg</td>
<td>6 mL</td>
<td>0.43 – 0.59 mg/kg</td>
</tr>
<tr>
<td>&gt;14 kg – 20 kg</td>
<td>8.5 mg</td>
<td>8.5 mL</td>
<td>0.43 – 0.6 mg/kg</td>
</tr>
<tr>
<td>&gt;20 kg – 25 kg</td>
<td>11.5 mg</td>
<td>11.5 mL</td>
<td>0.46 – 0.57 mg/kg</td>
</tr>
<tr>
<td>&gt;25 kg – 30 kg</td>
<td>14 mg</td>
<td>14 mL</td>
<td>0.46 – 0.56 mg/kg</td>
</tr>
<tr>
<td>&gt;30 kg – 34 kg</td>
<td>16 mg</td>
<td>16 mL</td>
<td>0.47 – 0.53 mg/kg</td>
</tr>
</tbody>
</table>

Table 10: Adjusted Dose of vicriviroc oral solution doses for mini-cohorts with a median C\textsubscript{min} < 130 ng/mL with a target dose range of approximately 1 mg/kg – 1.2 mg/kg once daily for Cohort IV in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Targeted Dose of Vicriviroc Oral Solution</th>
<th>Volume of Vicriviroc Oral Solution to Administer Once Daily in Cohort IV</th>
<th>Dose Range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥7 kg – 8 kg</td>
<td>8.5 mg</td>
<td>8.5 mL</td>
<td>1.06 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;8 kg – 9 kg</td>
<td>9.5 mg</td>
<td>9.5 mL</td>
<td>1.06 – 1.17 mg/kg</td>
</tr>
<tr>
<td>&gt;9 kg – 10 kg</td>
<td>10.5 mg</td>
<td>10.5 mL</td>
<td>1.05 – 1.15 mg/kg</td>
</tr>
<tr>
<td>≥10 kg – 11 kg</td>
<td>12 mg</td>
<td>12 mL</td>
<td>1.09 – 1.19 mg/kg</td>
</tr>
<tr>
<td>&gt;11 kg – 12 kg</td>
<td>13.5 mg</td>
<td>13.5 mL</td>
<td>1.13 – 1.22 mg/kg</td>
</tr>
<tr>
<td>&gt;12 kg – 13 kg</td>
<td>14.5 mg</td>
<td>14.5 mL</td>
<td>1.12 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;13 kg – 14 kg</td>
<td>16 mg</td>
<td>16 mL</td>
<td>1.14 – 1.22 mg/kg</td>
</tr>
<tr>
<td>&gt;14 kg – 15 kg</td>
<td>17 mg</td>
<td>17 mL</td>
<td>1.13 – 1.21 mg/kg</td>
</tr>
<tr>
<td>&gt;15 kg – 16 kg</td>
<td>18 mg</td>
<td>18 mL</td>
<td>1.13 – 1.19 mg/kg</td>
</tr>
<tr>
<td>&gt;16 kg – 17 kg</td>
<td>19 mg</td>
<td>19 mL</td>
<td>1.12 – 1.18 mg/kg</td>
</tr>
<tr>
<td>&gt;17 kg – 18 kg</td>
<td>20.5 mg</td>
<td>20.5 mL</td>
<td>1.14 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;18 kg – 19 kg</td>
<td>22 mg</td>
<td>22 mL</td>
<td>1.16 – 1.22 mg/kg</td>
</tr>
<tr>
<td>&gt;19 kg – 20 kg</td>
<td>23 mg</td>
<td>23 mL</td>
<td>1.15 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;20 kg – 21 kg</td>
<td>24.5 mg</td>
<td>24.5 mL</td>
<td>1.17 – 1.22 mg/kg</td>
</tr>
<tr>
<td>&gt;21 kg – 22 kg</td>
<td>25 mg</td>
<td>25 mL</td>
<td>1.14 – 1.18 mg/kg</td>
</tr>
<tr>
<td>&gt;22 kg – 23 kg</td>
<td>26.5 mg</td>
<td>26.5 mL</td>
<td>1.15 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;23 kg – 24 kg</td>
<td>28 mg</td>
<td>28 mL</td>
<td>1.17 – 1.21 mg/kg</td>
</tr>
<tr>
<td>&gt;24 kg – 25 kg</td>
<td>29 mg</td>
<td>29 mL</td>
<td>1.16 – 1.2 mg/kg</td>
</tr>
<tr>
<td>&gt;25 kg – 26 kg</td>
<td>30 mg</td>
<td>30 mL</td>
<td>1.15 – 1.2 mg/kg</td>
</tr>
</tbody>
</table>
Table 11: Adjusted Dose of vicriviroc oral solution doses for mini-cohorts with a median C_{min} > 400 ng/mL with a target dose range of approximately 0.4 mg/kg – 0.6 mg/kg once daily for Cohort IV in Stage I

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>Targeted Dose of Vicriviroc Oral Solution</th>
<th>Volume of Vicriviroc Oral Solution to Administer Once Daily in Cohort IV</th>
<th>Dose Range (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥7 kg – 8 kg</td>
<td>4 mg</td>
<td>4 mL</td>
<td>0.5 – 0.57 mg/kg</td>
</tr>
<tr>
<td>&gt;8 kg – 9 kg</td>
<td>4.5 mg</td>
<td>4.5 mL</td>
<td>0.5 – 0.56 mg/kg</td>
</tr>
<tr>
<td>&gt;9 kg – 10 kg</td>
<td>5 mg</td>
<td>5 mL</td>
<td>0.5 – 0.55 mg/kg</td>
</tr>
<tr>
<td>&gt;10 kg – 11 kg</td>
<td>5.5 mg</td>
<td>5.5 mL</td>
<td>0.5 – 0.54 mg/kg</td>
</tr>
<tr>
<td>&gt;11 kg – 12 kg</td>
<td>6 mg</td>
<td>6 mL</td>
<td>0.5 – 0.54 mg/kg</td>
</tr>
<tr>
<td>&gt;12 kg – 13 kg</td>
<td>6.5 mg</td>
<td>6.5 mL</td>
<td>0.5 – 0.54 mg/kg</td>
</tr>
<tr>
<td>&gt;13 kg – 14 kg</td>
<td>7 mg</td>
<td>7 mL</td>
<td>0.5 – 0.53 mg/kg</td>
</tr>
<tr>
<td>&gt;14 kg – 15 kg</td>
<td>7.5 mg</td>
<td>7.5 mL</td>
<td>0.5 – 0.53 mg/kg</td>
</tr>
<tr>
<td>&gt;15 kg – 16 kg</td>
<td>8 mg</td>
<td>8 mL</td>
<td>0.5 – 0.53 mg/kg</td>
</tr>
<tr>
<td>&gt;16 kg – 17 kg</td>
<td>8.5 mg</td>
<td>8.5 mL</td>
<td>0.5 – 0.53 mg/kg</td>
</tr>
<tr>
<td>&gt;17 kg – 18 kg</td>
<td>9 mg</td>
<td>9 mL</td>
<td>0.5 – 0.53 mg/kg</td>
</tr>
<tr>
<td>&gt;18 kg – 19 kg</td>
<td>9.5 mg</td>
<td>9.5 mL</td>
<td>0.5 – 0.53 mg/kg</td>
</tr>
<tr>
<td>&gt;19 kg – 20 kg</td>
<td>10 mg</td>
<td>10 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
<tr>
<td>&gt;20 kg – 21 kg</td>
<td>10.5 mg</td>
<td>10.5 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
<tr>
<td>&gt;21 kg – 22 kg</td>
<td>11 mg</td>
<td>11 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
<tr>
<td>&gt;22 kg – 23 kg</td>
<td>11.5 mg</td>
<td>11.5 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
<tr>
<td>&gt;23 kg – 24 kg</td>
<td>12 mg</td>
<td>12 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
<tr>
<td>&gt;24 kg – 25 kg</td>
<td>12.5 mg</td>
<td>12.5 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
<tr>
<td>&gt;25 kg – 26 kg</td>
<td>13 mg</td>
<td>13 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
<tr>
<td>&gt;26 kg – 27 kg</td>
<td>13.5 mg</td>
<td>13.5 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
<tr>
<td>&gt;27 kg – 28 kg</td>
<td>14 mg</td>
<td>14 mL</td>
<td>0.5 – 0.52 mg/kg</td>
</tr>
</tbody>
</table>

Stage II

The starting dose for Stage II in Cohorts I, II, III and IV will be dependent on the safety and PK data available from Stage I in all 4 cohorts.

Weight ranges were determined using National Center for Health Statistics (NCHS) Growth Charts at the 5th percentile for the youngest age and the 95th percentile for the oldest age of each cohort.
5.11 Duration

Subjects will be enrolled into one of four cohorts. Once a Cohort has been filled in Stage I and the optimal dose of vicriviroc for that Cohort is determined, Stage II will open for that Cohort and subjects will complete 48 weeks of vicriviroc study drug regimen at the final dose for that Cohort. All subjects who have been on vicriviroc study drug regimen will be followed for safety and efficacy up until 5 years after initiation of vicriviroc study drug regimen.

5.2 Drug Formulation

This study will evaluate two different formulations of vicriviroc: the tablet formulation containing 20 mg and 30 mg and the liquid formulation, vicriviroc oral solution at a concentration of 1 mg/mL described below.

Vicriviroc maleate oral solution is an aqueous-based, sugar-free, cherry-flavored liquid formulation supplied by Schering-Plough. The oral solution contains vicriviroc maleate at a concentration of 1 mg/mL, and contains the following inactive ingredients: citric acid monohydrate, sodium citrate dihydrate, sucralose, sorbitol, sodium benzoate, xanthan gum, and cherry flavor. The solution pH is approximately 4.3. The solution is packaged into 120 mL amber glass bottles. Both Vicriviroc maleate tablet formulation and oral solution should be stored at controlled room temperature: 20 - 25º C (68 - 77º F).

It is expected that the bioavailability of the oral solution will be similar to that of vicriviroc maleate tablets because vicriviroc maleate is a highly soluble (tablets dissolve very rapidly: greater than 80% dissolution in 10 minutes is typically observed with 0.1N HCl as the dissolution medium), and highly permeable drug substance.

5.3 Drug Supply, Distribution and Pharmacy

5.31 Study Product Acquisition

Vicriviroc 20 mg and 30 mg tablets and vicriviroc solution at a concentration of 1 mg/mL in bottles will be provided by Schering-Plough. Vicriviroc will be available through the NIAID Clinical Research Products Management Center. The IMPAACT pharmacist can obtain the study products for this protocol by following instructions in the manual, Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, in the section on Study Product Control.

Other components of the ARV regimen will not be supplied by P1071.
5.32 Study Product Accountability

The IMPAACT pharmacist is required to maintain complete records of all study products received from the NIAID Clinical Research Products Management Center and subsequently dispensed. All unused study products must be returned to the NIAID Clinical Research Products Management Center after the study is completed or terminated. The 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.

5.33 Study Product Dispensing

Vicriviroc 20 mg and 30 mg tablets and vicriviroc solution at a concentration of 1 mg/mL should be dispensed to subjects in a container with a child resistant lid.

Subjects must bring back to clinic all used study product bottles and ALL unused study drug at each visit.

5.34 Extended Follow Up for Safety

For subjects who complete 48 weeks of study and are continued on study drug, vicriviroc will be provided in a follow-up period involving visits every 3 months up until 5 years after initial vicriviroc exposure after Step II initiation in P1071. Subjects who discontinue study-provided vicriviroc will continue to be followed every 6 months up until 5 years after initial vicriviroc exposure after Step II initiation in P1071. These subjects will be treated as medically appropriate as determined by their primary care providers. Provided that the overall data for the study drug appear to be generally favorable, subjects who complete the study and who appear to have benefited from receiving study drug will be provided vicriviroc until the study drug is accessible from a commercial source. IMPAACT and Schering will develop the appropriate mechanism to do this.

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, dated December 2004 (available at http://rcc.tech-res-intl.com), will be used for screening eligibility and for grading toxicities when
specifically noted below. Alternate explanations for clinical or laboratory abnormalities that may at first appear to be related to the study agent must be explored.

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator. 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 edition of the Harriet Lane Handbook for normal ranges/values and document this for monitoring purposes. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2 or baseline.

The protocol team should be contacted via email at actg.teamp1071@fstrf.org within 24 hours for any ≥Grade 3 toxicities. Anticipated toxicities resulting from components of the HAART regimen will be managed by the subject's clinician, in discussion with the study team, according to best clinical practice including dose reductions when indicated. Within class changes and in rare cases, across class changes, will be allowed for toxicity after consultation with the protocol team. Hypersensitivity reaction to abacavir should be noted as such and should be managed by the subject’s clinician according to standard clinical practice.

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 probably not related or not related to study drug may not result in study drug interruption. Any AEs known to be associated with HIV infection or AIDS must be reported in the same manner as AEs not associated with HIV infection. Where the etiology is clearly HIV-related, the relationship will be judged to be “not related” to study drug. General guidelines for study drug suspected adverse drug reactions (SADRs) are provided below.

### 6.11 Reporting

- All toxicities ≥ Grade 1 should be recorded on Case Report Forms (CRFs) at each visit.
- Seizures of any grade will be assessed for relationship to study drug.
- All other toxicities ≥ Grade 3 will be assessed for relationship to study drug.

**Grade 3 or 4 –**

- The protocol team must be notified of study drug SADRs within 24 hours at actg.teamp1071@fstrf.org.
The investigator should attempt to confirm any unexpected laboratory test results as soon as possible but always within 72 hours to determine if the result was spurious.

Expedited Adverse Event (EAE) reporting must be done within 72 hours of the initial result if the value is confirmed or if confirmatory results are not available within 72 hours.

For subjects receiving atazanavir, if bilirubin is grade 3 or higher with AST/ALT < 2.5 times ULN and there are no clinical symptoms other than jaundice or icterus, continue study drug and other antiretrovirals unless the clinician feels that continuing study drug would be harmful to the subject. Repeat AST/ALT weekly until it can clearly be established that AST/ALT is not increasing.

6.2 Management

Grade 1 - Continue study drug; routine monitoring.

Grade 2 - Continue study drug; monitor closely with more frequent visits when clinically indicated.

Grade 3 – Continue study drug while awaiting confirmatory results unless the clinician believes that remaining on study drug would be unsafe.

If Grade 3 abnormalities are confirmed, the study drug and concomitant antiretroviral therapy should be withheld until the abnormalities are Grade 2 or below unless the clinician, with the approval of the study team and the DAIDS medical officer of record, 1) believes that withholding antiretroviral therapy (including study drug) would be harmful to the subject; or 2) believes there is an alternative explanation for the observed toxicity; or 3) believes grade 3 toxicity is not dangerous for the patient (e.g. increased bilirubin with atazanavir).

Grade 4 - Hold study drug and concomitant antiretrovirals immediately unless the clinician, with the approval of the study team and the DAIDS medical officer of record, believes that withholding antiretroviral therapy (including study drug) would be harmful to the subject and that continuing them would pose little additional risk. Attempt to confirm any unexpected laboratory results as soon as possible, but always within 72 hours of the event to determine if these results were spurious. The protocol team should be notified of the results at actg.teamp1071@fstrf.org.

For confirmed drug related Grade 4 SADRs, study medication should be permanently discontinued. For Grade 4 adverse events that are determined to be
unrelated to study drug, the investigator should contact the team to determine when study drug may be safely resumed.

All antiretroviral therapy (including study drug) should be started or stopped together whenever possible; except when one antiretroviral agent can be substituted for another within class, after the relationship of the toxicity to study drug or other ART has been determined.

Seizures: In the event of a seizure, vicriviroc must be discontinued and, following emergency treatment and control of the seizure, a full medical evaluation must be undertaken to determine the etiology of the seizure. Recommended evaluations include, but may not be limited to: vicriviroc plasma/cerebrospinal fluid (CSF) concentration, computed tomography (CT) scan (± magnetic resonance imaging [MRI]), electroencephalogram (EEG), electrocardiogram (ECG), blood chemistry/electrolytes evaluation, blood/CSF exam for infection and/or malignancy, and as appropriate, additional tests to rule out toxoplasmosis, West Nile Virus or HSV. After the occurrence of a seizure, vicriviroc may be resumed ONLY if a clear etiology is determined and the investigator and protocol team concur that the single seizure has not predisposed the subject to recurrence, and the subject does not require anti-seizure medication.

6.21 Follow-up of Abnormal Events and Laboratory Values

All abnormal clinical events and laboratory values occurring in enrolled subjects will be followed closely until resolution. The urgency and frequency of repeat evaluations will depend on the clinical significance of the specific abnormality. Study clinicians will provide appropriate clinical management of adverse events according to their best medical judgment and local practice. For any persistent Grade 3 or 4 clinical or laboratory study drug SADRs, evaluations should be repeated approximately weekly (or more frequently if necessary) until toxicity falls below Grade 2 or returns to baseline, and as appropriate thereafter. Alternate explanations will be sought for all clinical and laboratory abnormalities.

6.3 Study Management Plan

The protocol team will maintain a web page through the DMC informing sites as to the availability of enrollment slots per cohort. The protocol team, including the chairs, medical officers, pharmacist, and pharmacologist, will respond to sites who contact the team with questions regarding toxicity management, dose modifications, or other issues within one business day of receiving site questions. Team responses will include the entire team.
All vicriviroc dose modifications will be recommended by the protocol team. The protocol team will review the Stage I data for each cohort to determine whether a dose adjustment is required, before opening enrollment to a full cohort. The study team will review the complete set of Step II, Stage I dose finding data for each full cohort and make a dose recommendation which must be approved by the DAIDS Medical Officer, IMPAACT representatives and Schering-Plough representatives. Once all agree, Step II, Stage II opens to enrollment.

Note: Subjects who screen to enter Stage I of their age cohort but can not enroll because the slots are full will be given first priority to enroll on Stage II.

6.31 Cohort Dosing Management

Stage I

Stage I will begin with enrollment of 4 subjects from each age cohort. Enrollment to the cohort will pause upon entry of the fourth subject. These 4 subjects will be treated with vicriviroc at approximately 0.8 mg/kg in addition to an optimized background therapy (OBT) containing a boosted protease inhibitor (as described in section 6.32). As steady state vicriviroc levels will be achieved within 14 days of drug initiation, an intensive pharmacokinetics evaluation will be performed between days 14 and 20. Vicriviroc levels will be assayed after the last subject in each mini-cohort has completed their 14-20 day intensive PK visit and the protocol team will evaluate the results. Immediately after completion of the intensive PK, subjects will continue taking the assigned vicriviroc dosage and the OBT. If the PK data are acceptable (see section 9.31) and 4 week safety data are acceptable (see section 8.51), enrollment in Stage I will open to complete a full cohort of approximately 12 subjects. If the target PK and/or safety parameters are not met by this mini-cohort, the dose for the original mini-cohort will be modified and a new mini-cohort will be accrued at the adjusted dose and an intensive PK evaluation will be performed 14-20 days post dose modification. If the new mini-cohort PK data is acceptable (section 9.31) and 4 week safety data are acceptable (section 8.51), enrollment into Stage I will open to complete the full cohort of 12 subjects. If the full cohort of 12 fails to meet the target PK and/or safety parameters, a new mini-cohort of 4 will be enrolled on a modified dose and the process will repeat.

Once PK and safety data are available for the full cohort of 12 subjects, the study team will recommend a Stage II dose for that age cohort. The recommended dose must be approved by the DAIDS Medical Officer, IMPAACT and Schering-Plough prior to use in Stage II. If on review of all PK and safety data from the full cohort the dose is not acceptable, the
process will repeat and a dose will be adjusted for the full cohort as described in section 9.31

Approximately 12 subjects per cohort are needed in Stage I to provide data for the Stage II dose selection. Enrollment will open simultaneously in Cohorts I and II. Once the dose for mini-cohort II is found to be safe and the PK target is achieved, enrollment in Cohort III will open. Once the dose for mini-cohort III is found to be safe and the PK target is achieved, enrollment in Cohort IV will proceed. Subjects opting to discontinue in Stage I prior to completion of intensive PK will be replaced for PK purposes only.

Stage II

Stage II is intended to provide long-term safety, tolerability and efficacy data for vicriviroc given in combination with an OBT. Enrollment into each age cohort of Stage II will progress independently. At least 10 additional subjects at the selected dose (passing the Stage I safety/PK dose-finding guidelines) will be enrolled into Stage II of each cohort. The remaining subjects will be enrolled in Stage II without restriction to age or vicriviroc formulation; however an effort will be made to enroll all age groups. Treatment duration of Stage II is 48 weeks per subject on the selected dose and the selected drug formulation.

6.32 Optimization of background ARV regimen

All subjects must be prescribed an optimized background therapy (OBT) beginning on Day 1 of Step II (Stage I or II) to be taken concomitantly with vicriviroc. Each subject’s OBT is to be chosen by the site investigator and approved by the study team, based on results of genotype testing, the subject’s history of prior antiretroviral use, and drug toxicity. OBT must include at least 1 active, ritonavir-boosted protease inhibitor (suggested dose between 57.5 mg/m² and 115 mg/m², as specified in section 4.51) and at least 1 other antiretroviral. Other CCR5 antagonists and NNRTIs with the exception of etravirine may not be a component of the background regimen.

The subject’s OBT must remain unchanged for the duration of Step II until week 48 of the study, unless a change is approved by the P1071 study team. Discontinuation or replacement of an ART component(s) with another drug in the same class (ie. saquinavir for indinavir) will be permitted at the discretion of the site investigator for management of intolerance or toxicities. However, OBT must always include at least 1
active ritonavir boosted PI and at least 1 other antiretroviral, aside from vircriviroc as described above. The study team must be informed of these changes at actg.teamp1071@fstrf.org. Subjects who are experiencing virologic failure as defined in section 6.33 at or after week 24 may have their regimen re-optimized, at the discretion of the site investigator, based on the HIV genotypic and phenotypic resistance testing performed at the time of virologic failure. The subject may continue on study, on or off study drug as described in section 6.33.

6.33 Virologic Failure

Virologic failure in this study is defined as:

- a decrease in HIV RNA of < 1.0 log10 between enrollment into Step II and week 8, and confirmed at week 12. If not confirmed at week 12, subject can continue on study on treatment and will not be considered a virologic failure. (An exception is made if at week 8, there is a <1.0 log10 decrease but the plasma HIV RNA measures < 400 copies/mL.)

OR

- HIV RNA > 400 copies/mL starting at Week 24 or beyond on 2 consecutive measurements at least 1 week apart;

OR

- virologic rebound starting at Week 12 or beyond that is defined as:
  - HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL; or
  - > 1.0 log10 increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart). For the purposes of this study, nadir is defined as the lowest HIV RNA while on study drug.

Subjects who are confirmed virologic failures as defined above will have genotype/phenotype and tropism testing completed to determine viral tropism at the time of failure. Subjects whose viral tropism has switched to X4 or dual/mixed R5/X4 virus may not continue on study drug. Subjects who are confirmed virologic failures may, at the discretion of the site investigator and with the approval of the protocol team:

- Be taken off study drug, and continue on study until week 48, with the long term follow up;
OR

- Have background therapy re-optimized; with the subject remaining on study drug (if the subject’s viral tropism has not switched to X4 or R5/X4).

The protocol team will notify the FDA of any subjects who are confirmed virologic failures and opt to continue on study drug.

6.4 Criteria for Treatment Discontinuation

- The subject requires treatment with disallowed medications
- Drug toxicity that requires permanent study drug discontinuation as defined in Section 6.1
- Pregnancy. In the event that a subject becomes pregnant, sites are encouraged to register the subject’s pregnancy in the Antiretroviral Pregnancy Registry (http://www.apregistry.com/reg.htm (In US, Canada: 1-800-258-4263, international: 910-256-0238.)
- The subject experiences virologic failure and has a trofile assay result indicating a co-receptor switch to X4 or dual mixed tropic virus.

In the event of treatment discontinuation, the subject (or parent/legal guardian if the subject is < 18 years) will be asked to continue on study/off study drug until 5 years after initial vicriviroc exposure.

6.5 Criteria for Study Discontinuation

- The subject or legal guardian refuses further treatment and/or follow-up evaluations.
- The investigator 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.
- The study is cancelled at the discretion of IMPAACT, the IRB, FDA, NIAID, OHRP, or Schering-Plough.

7.0 EXPEDITED ADVERSE EVENT REPORTING TO DAIDS

The adverse events (AEs) that must be reported in an expedited fashion to DAIDS Regulatory Compliance Center (RCC) Safety Office include all serious adverse events (SAEs) as defined by ICH guidelines regardless of relationship to the study agent(s).
A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization\(^1\)
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above must also be reported in an expedited timeframe to DAIDS. Such determination may be made through medical or scientific judgment [ICH E2A]

In addition to reporting all SAE’s as defined above, other events that sites must report in an expedited fashion include all malignancies, seizures and hepatotoxocities [≥ Grade 3 clinical or laboratory (AST, ALT, bilirubin except for subjects on atazanavir) hepatotoxocities, whether or not symptomatic or related to study drug].

The death of any subject after enrollment or within 30 days of study completion, regardless of the cause, must be reported within 1 working day of first becoming aware of the death. After the 30-day period, deaths need to be reported only as part of long-term follow-up studies. If an autopsy is performed, the report must be provided. Reports of all deaths must be communicated as soon as possible to the appropriate IRB or EC and/or reported in accordance with local law and regulations.

For all SAE’s submitted to RCC, sites must file an updated SAE report to RCC with the final or stable outcome (Status Code p. 5 of the EAE form) unless the SAE reported in the initial EAE form already had a final or stable outcome.

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\(^1\) Per ICH SAE definition, hospitalization itself is not an adverse event, but is an outcome of the event. Thus, hospitalization in the absence of an adverse event is not regarded as an AE, and is not subject to expedited reporting.

The following are examples of hospitalization that are not considered to be AEs:
- Protocol-specified admission (e.g. for procedure required by study protocol)
- Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
- Diagnostic admission (e.g. for a work-up of an existing condition such as persistent pretreatment lab abnormality)
- Administrative admission (e.g. for annual physical)
- Social admission (e.g. placement for lack of place to sleep)
- Elective admission (e.g. for elective surgery)
The study agents for which relationship assessments are required is vicriviroc.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, must be used and is available on the DAIDS RCC Web site: http://rcc.tech-res.com/eaeh.htm.

The protocol-defined expedited event reporting period for this protocol 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 a period of 5 years after initiation of Stage II, if the subject continues on study drug.

After the end of the protocol-defined reporting period defined above, sites must report clinical events that are serious, unexpected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

The timelines and mechanisms for reporting all the events listed above 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 (and in study manual of Operations (MOP), if applicable).

Sites using the DAERS internet-based reporting system for submission of EAEs to DAIDS will follow DAERS processes as outlined in DAERS training information. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within DAERS application itself.

If the site cannot use DAERS to report an AE on an expedited basis, the AE 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 (and the study MOP if applicable), and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please continue to contact the RCC.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase I/II study with primary objectives of assessing the safety and pharmacokinetics of vicriviroc administered to HIV-infected children and adolescents within the age range of ≥2 years to <19 years. The sample will be stratified into the following age groups: Cohort I (≥12 to <19 years of age on
tablet formulation), Cohort II (≥6 to <12 years of age on tablet formulation), Cohort III (≥6 to <12 years of age on liquid formulation) and Cohort IV (≥2 to <6 years of age on liquid formulation). A minimum of 12 subjects will be enrolled into each cohort in Stage I of the study for purposes of dose finding. Additional subjects will be enrolled into Stage II of the study and treated at the doses determined optimal for their cohorts on the basis of Stage I results. The total sample will include 100 evaluable patients who have been treated exclusively at the doses judged to be optimal for their age cohorts.

The study will be monitored intensely by the protocol team, which will review safety and pharmacokinetic data at least twice a month during the dose finding stage (Stage I) with the aim of determining the optimal dose for each cohort while protecting patient safety. In addition a P1071 Independent Study Monitoring Committee, composed of three clinicians and a statistician independent of the P1071 protocol team, and Schering-Plough will oversee the study. In accordance with IMPAACT and DAIDS procedures, this committee will be composed of one clinician from the IMPAACT Protocol Development and Monitoring Committee, two clinicians appointed by the IMPAACT Primary Therapy Scientific Committee associated with the network but not directly involved in the conduct of study and an independent statistician appointed by the IMPAACT Statistical and Data Management Center. Members of the P1071 Independent Study Monitoring Committee will have 1) no financial interest in the study; 2) no planned authorship in publication of study results; and 3) no involvement in the conduct of the study.

Initial tests of safety and PK will examine data from the first 4 subjects (mini-cohort) of Cohorts I and II (tablet formulation) to determine whether Cohorts III and IV (liquid formulation) will be allowed to open. These tests will proceed as follows: The starting dose administered to the first four subjects of the first 2 mini-cohorts will be evaluated on the basis of PK data, based on a blood sample taken 14-20 days after the start of therapy on that dose. For the mini-cohort meeting PK targets, safety will be evaluated on the basis of all available data collected through the fourth week on that dose. For the mini-cohort failing to meet PK targets and requiring a dose adjustment, safety will be evaluated on the basis of data gathered until the time of the visit at which the dose is adjusted. This will ensure that, for the mini-cohort needing dose adjustment, adverse events attributed to the starting dose must have occurred while the patients were still on that dose. However, this also means that for such subjects the safety of the starting dose may be assessed on the basis of less than 4 weeks of study drug exposure.

The overall safety and PK data of the first 4 subjects on a given cohort will be evaluated with respect to the safety guidelines specified in Section 8.5 and the PK guidelines specified in Section 9. If the first 4 subjects of Cohort I meet both sets
of guidelines, then 8 additional subjects will be accrued to this cohort. Likewise, if the first 4 subjects of Cohort II meet both sets of guidelines, then 8 additional subjects will be accrued to this cohort. Cohort III will open to accrue the mini cohort only when the first 4 subjects enrolled into Cohort II (mini-cohort) meet both sets of guidelines. Cohort IV will be opened to accrue the mini-cohort once the mini-cohort III has passed the safety and PK guidelines. If the first 4 subjects in the first two cohorts fail either the safety or the PK guidelines in this initial test, then the starting dose will be adjusted in the appropriate direction, (upwards for inadequate PK values - see section 9.31; downwards for safety failure), if this is feasible. Four new subjects will be treated at the new dose, and an initial evaluation of safety and PK will be made on the basis of data from these subjects. The evaluation will proceed as described above. In the final assessment of Stage I results, the starting dose of a fully accrued cohort (N = 12) will be evaluated on the basis of safety and pharmacokinetic guidelines. Failure with respect to the safety and/or PK guidelines will result in a dose adjustment within this cohort, with the starting dose adjusted in the appropriate direction, if this is feasible. New subjects will be started on the new dose and evaluations will proceed as described above.

Once the dose finding procedures have been completed for each cohort, the protocol team will review all safety and PK data and will make final recommendations concerning the doses to be administered during Stage II of the study. These recommendations will be reviewed by the P1071 Independent Study Monitoring Committee described above, as well as by DAIDS representatives, the Scientific Oversight Committee of the IMPAACT Network and Senior Scientific Management at Schering-Plough, the pharmaceutical sponsor of the study. The purpose of this review process will be to take account of all available information in determining whether the dose finding algorithm has converged on the best doses for further study in Stage II or whether adjustments are needed.

Subjects accrued to Stage II of the study will be administered the doses determined for their age cohorts. For purposes of analysis, data from these subjects will be combined with the data from the Stage I subjects who have been treated at the optimal doses determined for their cohorts and who have not required dose adjustments, such that their total exposure to the study drug has been at the optimal dose. Sensitivity analyses will be performed in the primary analysis to determine whether the exclusion of patients whose doses have been adjusted creates a selection bias which impacts upon any results.

Accrual will proceed until at least 100 evaluable subjects are available for the weeks 24 and 48 safety analyses, some coming from Stage I and some from Stage II. For this analysis “evaluable” will be defined as: having been treated only on the dose determined to be optimal for a given age cohort and having either
completed 24 (or 48) weeks of exposure to the study drug or having been classified as a safety failure, due to an adverse event occurring during the first 24 (or 48) weeks of treatment. Although the primary safety analyses will focus on the effects of exposure to the optimal dose level for 24 and 48 weeks, secondary analyses will include all safety data collected from first patient exposure until the end of the study. This will include data representing the final dose for each cohort, as well as data gathered during the dose finding stage which may represent exposure to doses which have failed. This will also include data from patients whose individual doses have been adjusted, with results broken down by the times at which different dose levels were taken.

8.2 Endpoints and Outcome Measures

8.21 Primary Endpoints:

8.211 Toxicity

- Termination from treatment due to a suspected adverse drug reaction (SADR) judged to be at least possibly attributable to the study medication

- Adverse events of Grade 3 or higher severity

8.212 Pharmacokinetics

Failure to meet PK targets (specified in Section 9)

8.22 Secondary endpoints

8.221 Virologic failure, defined as: a) failure to achieve at least a 1 log drop in HIV RNA or HIV RNA <400 copies/mL by week 8, with failure confirmed at week 12, or b) HIV RNA >400 copies/mL on 2 consecutive measurements at week 24 and beyond, or c) virologic rebound starting at week ≥ 12, defined as HIV RNA >400 copies/mL on 2 consecutive measurements after initial response with viral load <400 copies/mL, OR >1.0 log10 increase in HIV RNA above nadir level on 2 consecutive measurements (nadir = lowest HIV RNA while on study drug)

8.222 Changes in co-receptor tropism from R5 at Step I and/or baseline to R5/X4 or X4 at virologic failure as measured by the enhanced version of the Trofile™ assay

8.23 Primary response variables
Pharmacokinetic parameters, including AUC, $C_{\text{min}}$, $C_{\text{max}}$, $T_{\text{max}}$

8.24 Secondary response variables
- Plasma HIV RNA PCR (copies/mL)
- CD4 counts and percent
- Polymerase genome and envelope sequence

8.3 Randomization and Stratification

There will be no randomization. In Step II, subjects will be enrolled in 4 cohorts as described in Section 8.1.

8.4 Sample Size and Accrual

Total accrual will depend upon the number of subjects who must be accrued to yield 100 evaluable subjects for purposes of the primary safety analyses. There is some uncertainty concerning the number needed to complete the dose finding procedures in Stage I and the number who may be lost to follow-up for reasons other than treatment failure. Each successful cohort on Stage I will include 12 subjects, all or almost all of whom will have been treated continuously on the dose that has been chosen for Stage II. This will yield approximately 48 subjects from Stage I who will contribute to the evaluation of the optimal dose. We will accrue additional patients in Stage II to ensure 100 evaluable subjects who have been treated only on the optimal dose. An additional constraint is that this group from Stage II must include at least 10 subjects from each of the 4 age/formulation cohorts. In total, it is anticipated that 140 (Stage I + Stage II) subjects may need to be enrolled in the protocol to yield 100 evaluable subjects for the weeks 24 and 48 safety analyses.

8.5 Safety Guidelines for the Evaluation of Stage I Starting Doses

The attribution of relationship of serious adverse events to study drug for the purposes of employing the start, stop and pause rules will be by consensus among the site investigator, the study team (which includes representatives from Schering-Plough) and the DAIDS medical officer of record. If unanimous agreement between them cannot be established, the relevant data will be reviewed by the P1071 Independent Study Monitoring Committee, which will make the final judgment concerning the relationship between study drug and the adverse event. Within this committee the decision will be determined by the majority opinion of the P1071 Independent Study Monitoring Committee clinicians. Gradation of relationship will use the following terminology: Not related, Probably not related, Possibly related, Probably related or Definitely
related. An event judged to be at least possibly related to the study treatment will be considered to be a Suspected Adverse Drug Reaction (SADR) for purposes of the dose finding algorithm which follows.

8.51 Safety Guidelines for the First Four Subjects Started at a Given Dose Level in Each Stage I Cohort

For each Cohort, the frequency of adverse reactions to the starting dose of the study medication will be evaluated on the first 4 subjects. The data will extend to the week 4 visit for subjects in the mini-cohort not requiring dose adjustment or until the visit on which the dose for the mini-cohort is adjusted, as described above. Further accrual into this cohort will be contingent upon meeting the following safety guidelines:

If any of the first 4 subjects has a life threatening SADR or any Grade 4 event that is probably or definitely attributable to the study medication or 2 or more subjects have terminated study drug due to a grade 3+ at least possibly treatment related SADR, stop accrual into this dose group until a safety review by the study team is conducted. All of the relevant safety and pharmacokinetic data will be reviewed to determine whether it is safe to continue the attempt to find an optimal dose for this cohort. If the team determines that it is safe to proceed, it will make specific changes in dosing and monitoring procedures which may be recommended. If there are any concerns regarding safety, the P1071 Independent Study Monitoring Committee will then review all of the relevant safety and pharmacokinetic data, along with the recommendations of the protocol team, and will determine whether and under what conditions further dose finding activities for this cohort may proceed.

The Protocol will only proceed if this review has led to a recommendation that it is safe to do so and the team, including the study chair, medical officer and Schering-Plough representatives, agree. The safety review may lead to a recommendation that the dose be de-escalated. Before implementing such a recommendation, the study team will review the PK data to determine whether a lower dose is likely to achieve adequate drug exposure.

If none of the first 4 subjects has experienced a life-threatening SADR or a Grade 4 event that is probably or definitely attributable to the study medication and fewer than 2 of these 4 subjects have terminated study drug due to a grade 3+ at least possibly treatment related SADR, then this cohort has passed the initial safety guidelines. If these 4 subjects also meet the PK guidelines, accrue 8 more subjects to this cohort and evaluate the
safety and PK results of the overall cohort of 12 subjects.

Given the small sample sizes within each cohort, the information available for preliminary safety decisions will be imperfect. Two types of sampling errors are possible: 1) in a cohort where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines; 2) in a cohort where the true rate of toxicity is low enough that further exposure to the current starting dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study medication were used extensively among the patient population at the dose level under question. The hypothetical situations presented in Table 8 range from conditions under which a given dose level would cause a high incidence of severe and life threatening SADRs to conditions under which severe SADRs would be relatively rare and would not be life threatening. For each of these hypothetical situations, we assume that a sample of 4 subjects is drawn from the patient population and that the safety guidelines, summarized above, are followed.

Table 8: Probability of Failing Dose Escalation Guidelines Under Potential Rates of True Toxicity

<table>
<thead>
<tr>
<th>True Toxicity Rates</th>
<th>Probability of Failing Safety Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Life Threatening SADR that would result in Tx discontinuation, excluding Grade 4 events probably or definitely attributable to study medication</td>
<td>Life Threatening SADR or Grade 4 events probably or definitely attributable to study medication</td>
</tr>
<tr>
<td>.50</td>
<td>.00</td>
</tr>
<tr>
<td>.50</td>
<td>.05</td>
</tr>
<tr>
<td>.50</td>
<td>.25</td>
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<td>.00</td>
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<td>.00</td>
<td>.05</td>
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<tr>
<td>.00</td>
<td>.25</td>
</tr>
</tbody>
</table>

Table 8 shows (e.g.) that there is a 78 % chance of failing the safety guidelines under conditions in which the true rate of life-threatening
toxicity is 5% and the rate of non-life threatening SADR is 50%. Assuming that it would be undesirable to accrue additional subjects at a dose that had these true rates of adverse events, the 22% chance of NOT failing the safety guidelines would represent the probability of error. The table also shows that there is a 1% chance of failing, when the true rate of non-life threatening SADR is only 5% and the true rate of life threatening SADR is zero. Assuming that the potential benefits associated with exposing additional subjects to this dose of the drug would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

8.52 Safety Guidelines for the Total Group of Twelve Subjects Started at a Given Dose Level in Each Stage I Cohort

The final safety guidelines applied to a given starting dose of the study medication within a cohort will make use of data from all subjects started at that dose. The data will extend to the week 4 visit for subjects in the cohort which does not require dose adjustment or until the visit on which the dose is adjusted, as described above. If none of these subjects has experienced a life-threatening SADR or a Grade 4 event that is probably or definitely attributable to the study medication and no more than 25% terminated study treatment due to grade 3+ at least possibly treatment related SADR, then this starting dose will pass the safety guidelines for the cohort under investigation.

If any of these subjects has a life threatening SADR or any Grade 4 event that is probably or definitely attributable to the study medication or more than 25% terminated study treatment due to grade 3+ at least possibly treatment related SADR, this starting dose will fail the safety guidelines for the cohort under investigation. Should this occur the protocol team will review all of the relevant safety and pharmacokinetic data in an attempt to determine whether it is safe to continue the attempt to find an optimal dose for this cohort. If the team determines that it is safe to proceed, it will make specific changes in dosing and monitoring procedures which may be recommended. If there are any concerns regarding safety, the P1071 Independent Study Monitoring Committee will then review all of the relevant safety and pharmacokinetic data, along with the recommendations of the protocol team, and will determine whether and under what conditions further dose finding activities for this cohort may proceed.

8.6 Analyses

8.61 Summary of Dose Finding Data:
The analysis of dose finding data will consist of descriptive statistics summarizing the safety and PK data from the dose finding phase of the study. (See Section 9 for PK analysis). The safety data will be broken down by cohort and will present the results of the safety evaluations applied to each starting dose tested within each cohort, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each cohort, every adverse event of Grade 3 or higher will be listed, along with subject demographics, the dose prescribed to the patient at the time of the event and the protocol team’s assessment of the probability that this event was due to the study treatment (not related, possibly related, probably related or definitely related).

8.62 Analysis of Data Representing Exposure to the Doses Judged to be Optimal for Each Cohort

These analyses will be stratified by Age Cohort. The findings will be presented in both in aggregate and broken down by cohort, with estimates bounded by 95% confidence limits. Given that the small sample sizes within cohorts will provide limited power for statistical tests of differences across age cohorts, interpretation of the results will depend upon whether differences across cohorts are great enough to be considered to be clinically significant. If no such differences are observed, then the clearest interpretation of the findings will come from the aggregated data, where analyses will have the greatest statistical precision. However, if results vary across cohorts to a clinically important extent, interpretation of results should take into account the issues represented by the stratification factor.

8.621 Primary Analyses (performed on data through the week 24 and 48 visit)

Pharmacokinetics

(See Section 9)

Safety

The primary safety analysis will include only subjects whose starting doses have been those judged to be optimal for their cohorts. Stage I subjects whose doses have been adjusted for inadequate PK will be excluded. Stage I subjects who have been removed from treatment or have had their doses reduced due to
toxicities while on the optimal dose will be included and treated as safety failures in the primary safety analysis. Sensitivity analyses will be performed to determine whether the exclusion of subjects whose doses have been adjusted creates a selection bias which impacts upon any results.

Each subject’s safety data will be summarized as: the worst grade of adverse event experienced during the first 24 weeks (and 48 weeks) of exposure to the optimal dose of the study treatment and the worst grade of adverse event judged to be at least possibly due to study treatment during this time period. Frequency distributions of these safety outcomes will be presented in the aggregate and broken down by age. Listings of all Grade 3+ events will be provided, broken down by type of toxicity (hepatic, hematologic, etc.).

The proportions of subjects experiencing Grade 3+ adverse events will be presented in aggregate and broken down by age cohort, with these proportions bounded by exact 95% confidence intervals. Similar analyses will present the proportions of subjects exhibiting Grade 3+ events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.

Table 9 presents exact 95% confidence intervals around various potential rates of Grade 3+ adverse events which might be observed in a total sample of 100 evaluable subjects, a sample of 12 subjects representing a minimal sample that might be accrued within any age stratum and two potential sample sizes that might occur if subgroups are analyzed (N = 30, N=70). This table indicates that confidence intervals will be quite wide around the minimal sample size of 12 subjects within a given stratum, but would be reasonably precise around samples of 70-100 subjects.

Table 9: Percent of Subjects Experiencing Grade 3+ Adverse Events (or Grade 3+ Adverse Events Attributed to the Study Medication) with Exact 95% Confidence Intervals

<table>
<thead>
<tr>
<th>N</th>
<th>% With Grade 3+ Adverse Events</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0%</td>
<td>0% -- 26%</td>
</tr>
<tr>
<td>30</td>
<td>0%</td>
<td>0% -- 12%</td>
</tr>
<tr>
<td>70</td>
<td>0%</td>
<td>0% -- 5%</td>
</tr>
<tr>
<td>100</td>
<td>0%</td>
<td>0% -- 4%</td>
</tr>
</tbody>
</table>
8.622 Key Secondary Analyses

Viral Load

HIV RNA (copies/mL) outcomes will be analyzed at weeks 24 and 48. At both of these time points the primary definition of virologic success will require subjects to have achieved and maintained 1-log drops from baseline or viral loads of <400 copies/mL. A secondary, more stringent definition of virologic success, which requires that subjects achieve and maintain viral loads of <50 copies/mL, may also be utilized. Patients meeting the definition of virologic failure described in Section 8.221 will be treated as failures in these analyses. The proportions of subjects meeting each of the criteria for virologic success at each of these time points will be bounded by exact 95% confidence intervals, and will be presented both in the aggregate and broken down by age cohort.

Table 10 presents exact 95% confidence intervals around various potential rates of virologic success which might be observed in a total sample of 100 evaluable subjects or in subsamples of various sizes (N=12, 30, 70). Subjects whose OBT is changed after initial optimization will be considered to be treatment failures in these analyses, unless the change is one specifically allowed by the protocol (See Section 6.32).
Table 10: Percent of Subjects Meeting Criterion for Virologic Success with Exact 95% Confidence Intervals

<table>
<thead>
<tr>
<th>N</th>
<th>% Undetectable RNA</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>10%</td>
<td>0.2% -- 38%</td>
</tr>
<tr>
<td>30</td>
<td>10%</td>
<td>2% -- 27%</td>
</tr>
<tr>
<td>70</td>
<td>10%</td>
<td>4% -- 20%</td>
</tr>
<tr>
<td>100</td>
<td>10%</td>
<td>5% -- 18%</td>
</tr>
<tr>
<td>12</td>
<td>30%</td>
<td>10% -- 65%</td>
</tr>
<tr>
<td>30</td>
<td>30%</td>
<td>15% -- 49%</td>
</tr>
<tr>
<td>70</td>
<td>30%</td>
<td>20% -- 42%</td>
</tr>
<tr>
<td>100</td>
<td>30%</td>
<td>21% -- 40%</td>
</tr>
<tr>
<td>12</td>
<td>50%</td>
<td>19% -- 81%</td>
</tr>
<tr>
<td>30</td>
<td>50%</td>
<td>31% -- 69%</td>
</tr>
<tr>
<td>70</td>
<td>50%</td>
<td>38% -- 62%</td>
</tr>
<tr>
<td>100</td>
<td>50%</td>
<td>40% -- 60%</td>
</tr>
<tr>
<td>12</td>
<td>70%</td>
<td>35% -- 90%</td>
</tr>
<tr>
<td>30</td>
<td>70%</td>
<td>51% -- 85%</td>
</tr>
<tr>
<td>70</td>
<td>70%</td>
<td>58% -- 80%</td>
</tr>
<tr>
<td>100</td>
<td>70%</td>
<td>60% -- 79%</td>
</tr>
<tr>
<td>12</td>
<td>90%</td>
<td>62% -- 99.8%</td>
</tr>
<tr>
<td>30</td>
<td>90%</td>
<td>73% -- 98%</td>
</tr>
<tr>
<td>70</td>
<td>90%</td>
<td>80% -- 96%</td>
</tr>
<tr>
<td>100</td>
<td>90%</td>
<td>82% -- 95%</td>
</tr>
</tbody>
</table>

CD4:

Change in CD4 count and percent from baseline to weeks 24 and 48 will be bounded by 95% confidence intervals and presented both in the aggregate and broken down by age cohort.

Viral Coreceptor Phenotype:

Among all patients enrolled in Step I, the prevalence of detectable coreceptor phenotype, R5 tropic, R5/X4 mixed and X4 tropic viruses will be evaluated. The extent to which coreceptor phenotype in Step I is associated with Step I CD4 cell count, HIV RNA, and age will be evaluated. The association of Step I coreceptor phenotype and nadir CD4, HIV subtype, number of
ART regimens, and years of ART will be evaluated. At the time of virologic failure, the extent of change from Step I and/or baseline R5 tropic virus to R5/X4 mixed or to X4 tropic virus as detected by the enhanced version Trofile™ assay will be evaluated.

HIV Drug Resistance:

Correlation between baseline HIV genotypic and phenotypic drug resistance and subsequent virologic failure will be evaluated. Subjects will be screened for HIV genotypic and phenotypic drug resistance to the OBT and to vicriviroc (envelope sequence) at virologic failure.

8.7 Monitoring

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 safety data, and make decisions regarding SADRs that are needed to protect subjects from undue risk. In addition the IMPAACT Network will appoint a P1071 Independent Study Monitoring Committee to provide impartial reviews in situations where patient safety is in question, as described above.

The safety and tolerability of the study agent will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. It is required that the data required for the toxicity reports 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 Data Management Center (DMC) will be reviewed and discussed by the Protocol Team on conference calls held at least every 2 weeks, and by the P1071 Independent Study Monitoring Committee under conditions specified above. Data on accrual, pharmacokinetics and toxicity will be reviewed.

Adverse events will be monitored, not only in the dose finding stage of the study, but throughout the follow-up period. If the protocol team identifies any potentially treatment-related toxicities, which may compromise subject safety, it will determine whether the study needs to be suspended or modified. Should this occur, the P1071 Independent Study Monitoring Committee will review all relevant data and will determine whether, and under what conditions, the study will be allowed to proceed.

8.7.1 Rules for Suspending Accrual to Assess Safety Following an Adverse Event
Accrual will be temporarily suspended if any subject has a life threatening Suspected Adverse Drug Reaction (SADR) or any Grade 4 event that may not be judged to be life-threatening but is judged to be probably or definitely attributable to the study medication. Following temporary suspension of accrual, the team will further review the safety data within 48 hours of notification of the event to determine if continuation of accrual is appropriate. If the team, including the study chair, the DAIDS medical officer of record and Schering-Plough representatives agree that the study drug is likely to be safe for additional subjects, they may allow accrual to resume. The P1071 Independent Study Monitoring Committee will be informed of this decision, and the study will not reopen without the approval of this committee. Regulatory agencies will be notified of the event and the team’s decision after this review of the safety data has taken place.

8.72 Accrual Rate Evaluation

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team will monitor feasibility quarterly, first based on site registration and then on accrual. Initially, the team will monitor site registration quarterly to ensure that an adequate number of sites have registered to complete the protocol. If less than one-third of eligible sites have registered after the protocol has been approved for 6 months, the team will re-assess the feasibility of the protocol and the reasons why sites have not registered, and will amend the protocol accordingly. Once one-third of eligible sites have registered, the team will assess accrual on a quarterly basis. If any Stage I cohort has not accrued half its subjects within 6 months of opening, the team will identify the reasons for lack of accrual and possibly amend the protocol accordingly.

8.73 Extended Follow-Up for Safety

Every subject exposed to vicriviroc through P1071 will have clinical follow up every 3 months for subjects on study-provided drug and every 6 months for subjects off study-provided vicriviroc. This will be done for a total of five years after Step II initiation for long term safety, sponsored by Schering-Plough as part of P1071.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

The clinical pharmacology objectives are:
1. To determine the multidose pharmacokinetics of vicriviroc in the presence of a ritonavir-boosted PI in HIV-infected children and adolescents.

2. To determine the dose of vicriviroc that achieves a target $C_{\text{min}}$ in children and adolescents.

3. To collect sparse concentration-time data and construct a pediatric population pharmacokinetic model for vicriviroc to be used to assess drug-exposure, variability and the covariates that impact vicriviroc disposition and response (age, pharmacogenetics).

9.2 Primary and Secondary Data

Stage I Subjects

Demographic data, dosing history, and sample collection times will be collected. Stage I for each age cohort will have intensive pharmacokinetic evaluations, performed after the first 14-20 days of therapy. Blood samples will be drawn pre-dose and 1, 2, 3, 4, 6, 8, 12 and 24 hours post dosing. This intensive pharmacokinetic evaluation will be repeated at week 24 however, the vicriviroc dose will not be modified. Pre-dose samples will collected at weeks 8 and 16. Plasma vicriviroc and ritonavir concentrations will be measured in all intensive PK samples, and the boosted PI in the regimen will be measured in the Pre-dose and 24 hours post dose samples. Ritonavir concentrations will be measured as a secondary measure of adherence to ART. In subjects requiring dose modifications (due to mini-cohort dose adjustment or in subject’s whose PK data is incomplete or uninterpretable), an additional intensive pharmacokinetic evaluation will be performed 14-20 days post dose modification.

A pharmacokinetic evaluation will be collected at any needed visit for confirmation of virologic failure. This will be drawn at a random time in relation to the latest vicriviroc dose, with the dose date and time recorded.

All PK samples will be registered in the Lab Data Management System (LDMS) database. Stage I vicriviroc and ritonavir sample assays and pharmacokinetic calculations will be performed after the last subject in each mini cohort has completed their 14-20 day intensive PK visit. The measurement of the PI concentrations of the regimen will be performed in batched mode throughout the study.

A non-compartmental pharmacokinetic analysis will be performed on all of the Stage I vicriviroc and ritonavir concentration data generated from the week 2 and 24 intensive samplings. Calculated pharmacokinetic parameters will include: area-under-the-curve ($\text{AUC}_2$), maximum plasma concentration ($C_{\text{max}}$), time to
C_{\text{max}} (T_{\text{max}}), \text{apparent clearance (CL/F), apparent volume of distribution (V/F)} \text{ and minimum plasma concentration (C}_{\text{min}}). AUC_{\tau} \text{ will be determined using the linear trapezoidal method. } C_{\text{max}} \text{ and } T_{\text{max}} \text{ will be taken directly from the observed concentration-time data. Data will be summarized based on both Cohort and overall. All doses evaluated will be included.}

Stage II Subjects

Stage II subjects will have timed PK samples collected at study weeks 2, 8, 16, 24 and 48 visits. For Stage II subjects these sparse samples will be collected at 2-5 hours post dose (weeks 8 and 16) or at 10-14 hours post dose (weeks 2, 24 and 48). These sparse PK samples will be assayed for vicriviroc, ritonavir and the boosted PI in the regimen in batched mode throughout the study. A pharmacokinetic evaluation will be collected at any needed visit for confirmation of virologic failure. This will be drawn at a random time in relation to the latest vicriviroc dose, with the dose date and time recorded.

The entire pharmacokinetic dataset collected in Stages I and II will be combined and used in a vicriviroc population pharmacokinetic analysis with the program NONMEM. An open one-compartment with first order absorption and allometric scaling for clearance and volume parameters will be employed as the base model. Alternative and more complex models will be evaluated as indicated by the data. The influence of covariates on vicriviroc disposition will be assessed. Specifically age, height, weight, sex, ethnicity, ritonavir exposure, concomitant agents, laboratory measurements and CYP450 and drug transporter SNPs will be evaluated for their impact on vicriviroc pharmacokinetics. Empiric Bayesian post-hoc estimates of apparent clearance, apparent volume of distribution and drug exposure will be determined and may be used for further exploratory analysis.

Intra-subject variability will also be quantified as an assessment of adherence. Observed vicriviroc concentrations (DV) will be compared to individual predicted (IPRED) concentrations and the log ratio determined as Ln (DV/IPRED). Study visits where the absolute value of this ratio is ≥ 0.7 (approximately 50% of 200% of predicted) will be labeled as a non-adherent visit. As a second method for using PK data to assess adherence will be based on the 90% CI for pre-dose concentrations from the intensive PK derived model. IPRED pre-dose concentrations that are below the model derived 90% CI will be labeled as a non-adherent visit by this method. Similar assessment of protease inhibitor concentrations will be explored depending on the frequency of use of specific concomitant protease inhibitors. These designations will be compared with other measures of adherence. In addition, the frequency of PK determined non-adherence will be compared with clinical outcomes.
9.3 Study Design, Modeling and Data Analysis

9.31 Vicriviroc PK Dose Determination

Stage I Dosing

This portion of the study utilizes a $C_{\text{min}}$-targeted approach. For Stage I, the average of the pre-dose and 24 hour post dose sample from the intensive PK evaluations will be used as the estimate of $C_{\text{min}}$. The population target median vicriviroc $C_{\text{min}}$ is 200 ng/mL, with the additional goal that nearly all of subjects’ $C_{\text{min}}$ is $> 100$ ng/mL. These targets are based on the adult vicriviroc steady-state $C_{\text{min}}$ seen with 30 mg (197 ng/mL) and the greater virologic response seen in adults with $C_{\text{min}} > 100$ng/mL. The initial pediatric dosing utilized in this study represents a dose of 30 mg in adults scaled (allometric/BSA) to pediatric weights. The goal of the approach to dose selection is to determine a pediatric dose that approximates adult exposure observed at the 30 mg dose in the presence of a ritonavir-boosted protease inhibitor to be consistent with adult dosing in Phase II studies. The initial PK summary evaluation will be performed after PK results from 4 subjects in each cohort are evaluated.

- If the median $C_{\text{min}}$ is $< 130$ ng/mL in the first 4 subjects, the dosing for these subjects will be increased by approximately 33% to 50% with a new minicohort of 4 subjects enrolled at the higher dose, into the intensive sampling cohort. Doses in Cohort I and II will be increased from 20 mg to 30 mg; or from 30 mg to 40 mg (Table 6).

- If the median $C_{\text{min}}$ is $\geq 130$ ng/mL and $\leq 400$ ng/mL, an additional 6 subjects will be enrolled into the intensive sampling cohort.

- If the median $C_{\text{min}}$ is $> 400$ ng/mL, the dosing for the subjects in this mini-cohort will be reduced by approximately 25-33% and a new mini cohort of 4 subjects will be enrolled at the decreased dose, into the intensive sampling cohort. Doses in Cohort I and II will be reduced from 30 mg to 20 mg (Table 7).

- The protocol team may request that a subject undergo repeat intensive PK sampling at the same dose if a subject’s results appear to be incomplete or uninterpretable.

Dose Adjustments

Stage I mini cohorts may have their group vicriviroc doses adjusted based on the median PK results. If a mini cohort has a median
vicriviroc $C_{\text{min}} < 130 \text{ ng/mL}$ during the intensive PK evaluation, the dose for the entire cohort will be increased by 33 to 50% or from 20 mg to 30 mg or from 30 mg to 40 mg for Cohorts I and II. **Cohorts** receiving vicriviroc liquid (Cohorts III and IV) failing to achieve the group exposure criteria will have their dose increased by 50% to 1.2 mg/kg (See section 5.1, Tables 6-11). **Dose adjustments will be made at the mini cohort level.**

Stage II Dosing

Stage II subjects will utilize the dose derived from Stage I. The pharmacokinetic assessments in Stage II will be performed at the end of the study.

10.0 **HUMAN SUBJECTS**

10.1 **Institutional Review Board and Informed Consent**

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

Each site which receives US HHS funding and follows the United States 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 re-signs the consent. The plan should follow all national, local and state guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

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, except as necessary for monitoring by the FDA, the Office for Human Research Protections (OHRP), the NIAID, the local IRB or Ethics Committee, or Schering Plough Corporation.

10.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, the FDA, the IRB or EC, the OHRP, the drug company sponsoring the study, or other governmental agencies as part of their duties to ensure that research subjects are protected.

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 sponsors 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 Centers for Disease Control and Prevention.

All infectious specimens will be sent using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN3373, 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


Ref Type: Catalog


Ref Type: Abstract

Ref Type: Abstract

Ref Type: Abstract


Ref Type: Abstract


## APPENDIX I-A
### SCHEDULE OF EVALUATIONS FOR U.S. BASED SITES

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Pre-Screening</th>
<th>Step I</th>
<th>Step II</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 48</th>
<th>Confirm Virologic failure</th>
<th>Follow-up visits</th>
<th>Off treatment / On study</th>
<th>Early Discontinuation</th>
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## APPENDIX I-A
### SCHEDULE OF EVALUATIONS U.S. BASED SITES

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Pre-Screening⁴</th>
<th>Step I²</th>
<th>Step II</th>
<th>Confirm Virologic failure¹⁷</th>
<th>Follow-up visits¹⁸,¹⁹</th>
<th>Off treatment / On study²⁰</th>
<th>Early Discontinuation</th>
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<tr>
<td>Immunology</td>
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<td>TOTAL BLOOD VOLUMES¹¹</td>
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<th>Step II</th>
<th>Confirm Virologic failure¹⁷</th>
<th>Follow-up visits¹⁸,¹⁹</th>
<th>Off treatment / On study²⁰</th>
<th>Early Discontinuation</th>
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<tr>
<td>Week 2</td>
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<td>Early Discontinuation</td>
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</table>

¹² Lymphocyte subsets: 2 mL every 6 weeks.

¹³ Expanded CCR5 flow: 6 mL every 24 weeks.

¹⁴ Pharmacology:

²⁰ Off treatment / On study: Q 3 Mo for those on treatment and Q 6 Mo for those on study.

²¹ Early Discontinuation: Q 3 Mo for those on treatment and Q 6 Mo for those on study.

³² TOTAL BLOOD VOLUMES: 29-34 mL every 24 weeks.
APPENDIX I-A
SCHEDULE OF EVALUATIONS U.S. BASED SITES

1. Pre-Screening evaluations are based on historical results obtained as part of clinical care within 3 months prior to screening.
2. The Step I evaluations must be performed within 30 days of the pre-screening visit and within 60 days prior to Step II entry.
3. History (signs and symptoms, medications, diagnoses, adverse events) and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], CDC class). Weight should be measured without shoes and with minimal clothing. During Step I only, history will include route of HIV acquisition, AIDS defining conditions, ARV history, and duration of each regimen, historical nadir CD4 cell count and percentage, peak HIV RNA load, current CD4 cell count and percentage, CD8 cell count and percentage.
4. Complete IMPAACT Adherence Module CRF.
5. Hematology should include CBC with differential and platelet count.
6. Chemistries should include AST, ALT, total bilirubin, BUN, electrolytes, glucose, creatinine, total amylase.
7. Lipid profile should include triglycerides and cholesterol. May be drawn in non-fasting state, and apply fasting values. If triglycerides are $\geq$ Grade 2, a complete lipid profile (including triglycerides, cholesterol, HDL and LDL) must be drawn in fasting state as soon as possible.
8. Dipstick urinalysis is sufficient. Abnormal findings should be followed with complete urinalysis and microscopic examination.
9. May be either urine or HCG blood test. Must be performed on all subjects of childbearing potential within 72 hours of enrollment. Pregnancy testing should continue as clinically indicated until 3 months after stopping study-provided vicriviroc.
10. 5 mL will be collected for subjects <6 years of age; 10 mL will be collected for subjects $\geq$6 years of age.
11. Must be performed at DAIDS VQA-certified laboratory.
12. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at DAIDS IQA-certified laboratory.
13. Expanded CCR5 flow - draw 4mL of blood into Streck tube and 2mL into a K2 EDTA tube. Ship both tubes priority overnight to the Children’s Hospital of Philadelphia.
14. Refer to Laboratory Processing Chart (LPC) for complete pharmacology collection and shipping instructions.
15. For subjects enrolled in Step II, Stage I only. Intensive PK sampling time points are pre-dose and 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Blood draws are 3 mL at pre-dose and 24 hours, and 2 mL at all other time points. Intensive PK will be repeated 14-20 days after any dose modifications.
16. For subjects enrolled in Step II, Stage I: Draw 3 mL at weeks 8 and 16 immediately pre-dose.
   For subjects enrolled in Step II, Stage II: Draw 3 mL at the following times:
   - Weeks 8 and 16: 2-5 hours post dose
   - Weeks 2, 24 and 48: 10-14 hours post dose
17. For subjects who meet criteria for virologic failure: Confirm 4 weeks after initial indication of virologic failure. Random PK sample should be collected at this visit, with time since last dose of drug recorded.
18. After Week 48, visits should continue to occur every 3 months for subjects who continue to receive study-provided VCV, and every 6 months for subjects who discontinue study-provided VCV, until 5 years after initiation of Step II.
APPENDIX I-A

SCHEDULE OF EVALUATIONS U.S. BASED SITES

19. For subjects who experience virologic failure and opt to discontinue VCV, if the enhanced version of the Trofile assay shows R5/X4 or X4 tropic virus, an enhanced version of the Trofile assay will be done every 3 months up to 12 months after VCV discontinuation, or until tropism reversal to R5, whichever comes first.

20. Subjects who prematurely discontinue study treatment (prior to week 48) will continue to be followed at scheduled study visits, but only the evaluations listed in this column are required.

21. The team is aware that the total blood volume may be excessive for younger children. Sites should comply with local IRB limitations. The NIH recommends a limit of 3mL/kg per single blood draw and a limit of 7 mL/kg in any 6 week period. Refer to the blood draw priority list below. Note that blood volumes indicate the range for subjects depending on age and Step assignment; not all subjects have all blood draws listed.

For insufficient blood draws, priorities are as follows:

(1) Hematology
(2) LFTs
(3) Pharmacology
(4) Virology
(5) Lymphocyte subsets
(6) Lipid profile
(7) Stored plasma and cells
(8) Expanded CCR5 flow
### APPENDIX I-B

**SCHEDULE OF EVALUATIONS FOR SITES OUTSIDE THE U.S.**

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Step I</th>
<th>Step II</th>
<th>Confirm Virological failure</th>
<th>Follow-up visits</th>
<th>Off treatment/On study</th>
<th>Early Discontinuation</th>
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<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td>Q 3 Mo</td>
<td>Q 6 Mo</td>
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<tr>
<td>Informed Consent</td>
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<td>History</td>
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*Note: CLINICAL EVALUATIONS and LABORATORY EVALUATIONS are subject to change based on ongoing clinical trials and regulatory requirements.*
APPENDIX I-B (continued)
SCHEDULE OF EVALUATIONS FOR SITES OUTSIDE THE U.S.

<table>
<thead>
<tr>
<th>Procedures</th>
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<td>Week 24</td>
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<td>Confirm Virologic failure</td>
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<tr>
<td>Follow-up visits</td>
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<td>Q 3 Mo</td>
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<td>Q 6 Mo</td>
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<td>Off treatment/ On study</td>
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<tr>
<td>Early Discontinuation</td>
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<td>TOTAL BLOOD VOLUMES</td>
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</table>

1. Pre-Screening evaluations are based on historical results obtained as part of clinical care within 3 months prior to screening.
2. The Step I evaluations must be performed within 30 days of the pre-screening visit and within 60 days prior to Step II entry.
3. History (signs and symptoms, medications, diagnoses, adverse events) and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], CDC class). Weight should be measured without shoes and with minimal clothing. During Step I only, history will include route of HIV acquisition, AIDS defining conditions, ARV history, and duration of each regimen, historical nadir CD4 cell count and percentage, peak HIV RNA load, current CD4 cell count and percentage, CD8 cell count and percentage.
4. Complete IMPAACT Adherence Module CRF.
5. Hematology should include CBC with differential and platelet count.
6. Chemistries should include AST, ALT, total bilirubin, BUN, electrolytes, glucose, creatinine, total amylase.
7. Lipid profile should include triglycerides and cholesterol. May be drawn in non-fasting state, and apply fasting values. If triglycerides are ≥ Grade 2, a complete lipid profile (including triglycerides, cholesterol, HDL and LDL) must be drawn in fasting state as soon as possible.
8. Dipstick urinalysis is sufficient. Abnormal findings should be followed with complete urinalysis and microscopic examination.
9. May be either urine or HCG blood test. Must be performed on all subjects of childbearing potential within 72 hours of enrollment. Pregnancy testing should continue as clinically indicated until 3 months after stopping study-provided vicriviroc.
10. 5 mL will be collected for subjects <6 years of age; 10 mL will be collected for subjects ≥6 years of age.
APPENDIX I-B (continued)

SCHEDULE OF EVALUATIONS FOR SITES OUTSIDE THE U.S.

11. Must be performed at DAIDS VQA-certified laboratory.
12. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at DAIDS IQA-certified laboratory.
13. Refer to Laboratory Processing Chart (LPC) for complete pharmacology collection and shipping instructions.
14. For subjects enrolled in Step II, Stage I only. Intensive PK sampling time points are pre-dose and 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Blood draws are 3 mL at pre-dose and 24 hours, and 2 mL at all other time points. Intensive PK will be repeated 14-20 days after any dose modifications.
15. For subjects enrolled in Step II, Stage I: Draw 3 mL at weeks 8 and 16 immediately pre-dose.
   For subjects enrolled in Step II, Stage II: Draw 3 mL at the following times:
   - Weeks 8 and 16: 2-5 hours post dose
   - Weeks 2, 24 and 48: 10-14 hours post dose
16. For subjects who meet criteria for virologic failure: Confirm 4 weeks after initial indication of virologic failure. Random PK sample should be collected at this visit, with time since last dose of drug recorded.
17. After Week 48, visits should continue to occur every 3 months for subjects who continue to receive study-provided VCV, and every 6 months for subjects who discontinue study-provided VCV, until 5 years after initiation of Step II.
18. For subjects who experience virologic failure and opt to discontinue VCV, if the enhanced version of the Trofile assay shows R5/X4 or X4 tropic virus, an enhanced version of the Trofile assay will be done every 3 months up to 12 months after VCV discontinuation, or until tropism reversal to R5, whichever comes first.
19. Subjects who prematurely discontinue study treatment (prior to week 48) will continue to be followed at scheduled study visits, but only the evaluations listed in this column are required.
20. The team is aware that the total blood volume may be excessive for younger children. Sites should comply with local IRB limitations. The NIH recommends a limit of 3mL/kg per single blood draw and a limit of 7 mL/kg in any 6 week period. Refer to the blood draw priority list below. Note that blood volumes indicate the range for subjects depending on age and Step assignment; not all subjects have all blood draws listed.

For insufficient blood draws, priorities are as follows:

(1) Hematology
(2) LFTs
(3) Pharmacology
(4) Virology
(5) Lymphocyte subsets
(6) Lipid profile
(7) Stored plasma and cells
APPENDIX II: Algorithm for Cohort Management in Step II, Stage I

General Guidelines:
Each Cohort is evaluated independently.
Cohorts I and II will open concurrently. Cohort III opening is dependent on data from Cohort II. Cohort IV opening is dependent on data from Cohort III.

Cohort: Enroll a mini-cohort (4 subjects) to assess PK and short term safety of vicriviroc.

Guidelines to accept VCV dose:
- **Safety**: Dose is safe and well tolerated (see safety criteria in section 8.5)
- **PK**: Median target \( C_{\text{min}} \) is \( \geq 130 \) ng/mL

Mini-cohort passes safety and PK evaluation

Accrue additional 8 subjects at this dose; Perform PK and safety evaluation on the full cohort (12 subjects).

Study team evaluation of dose using safety and PK guidelines (see above) for full cohort

Study Team dose recommendation for Stage II

DAIDS/IMPAACT SOC/Schering Plough review of recommended dose

DAIDS/IMPAACT SOC/Schering Plough review inconclusive

Sent to the Study Monitoring Committee.

Mini-cohort does not pass safety or PK evaluation

Adjust dose appropriately and enroll new mini-cohort (4 new subjects); complete PK and safety evaluations on the adjusted dose. Evaluate using safety and PK guidelines (see above)

Safety or PK guidelines not met

Stage II opens with Vicriviroc Cohort Selected Dose

Dose approved

Dose not approved

Stage II opens with Vicriviroc Cohort Modified Dose

INTRODUCTION

You are/your child is being asked to take part in this research study because you are/your child is infected with Human Immunodeficiency Virus (HIV), the virus that causes AIDS. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/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 about this information. You are free to ask questions about this study at any time. If you agree to/allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

This study is being done to study a new anti-HIV medication called vicriviroc (SCH-417690). Vicriviroc is a type of medicine called a CCR5 inhibitor. Vicriviroc works by preventing HIV from entering and infecting human cells.

This study will:
- Look at the safety of using vicriviroc in children and adolescents and if it causes any side effects.
- Help find the best amount or dose of vicriviroc for children and adolescents by looking at levels of vicriviroc in the blood.
- Help to find out how well vicriviroc works to limit the HIV virus in children and adolescents.
Vicriviroc has been tested before in animals and adults but not in children. At this time, vicriviroc has not been approved by the United States Food and Drug Administration.

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

If you decide/allow your child to enroll in this study, you will be asked to come to the clinic one time to be screened for Step I. If you are eligible and complete Step I, information from Step I will be used to see if you are eligible for Step II. If you are eligible for Step II, you will be asked to come to the clinic at least 9 times over 48 weeks. Depending on when you enter the study, you may be asked to complete Stage I or Stage II, which are described below. After completing the 48 weeks on study, you will be asked to come to the clinic for follow up visits until 5 years after you first started taking vicriviroc. These visits are described below.

Pre-Screening:
If you are interested in taking part/allowing your child to enroll in this study, we will see if you are/your child is eligible for the study:
- We will ask your/your child’s medical history including questions about your/your child’s health and what symptoms, medications, and illnesses you have/your child has had.
- We will do a physical exam including height, weight, and vital signs (temperature, blood pressure, pulse and respiratory rate).
- We will review the results of blood and urine tests done in the past few months to check the amount of HIV in the blood and other routine tests. You will be given the results of these tests. No blood will be drawn at this visit.
- This visit will take about 1 hour to complete.

On Study:

Step I:
If you are eligible, you will be asked to come to the clinic one time to complete Step I. The Step I visit must be within 30 days after the screening visit.

- We will ask more questions about your/your child’s medical history including questions about your /your child’s health and what symptoms, medications, and illnesses you have/your child has had.
- A physical examination will be done and we will ask you to provide a urine sample for routine tests.
- Girls and women of childbearing age will be asked to provide a urine or blood sample to test for pregnancy.
• We will draw about **6-7 teaspoons (29-34 mL)** of blood to see whether the type of HIV you are infected with will respond to vicriviroc, to check the amount of cholesterol and triglycerides (types of fat) in the blood, to see how well your immune system is working, and for other routine tests. Your doctor will give you the results, and will tell you whether you are eligible for Step II based on the results of these blood tests.

• One-two teaspoons (5-10 mL) of the blood that is drawn will be stored for future testing. This blood will be stored at a U.S.-based IMPAACT Laboratory.

• This visit will take about 1 hour to complete.

**Step II:**
Depending on how many children/adolescents have already enrolled, you may be asked to complete Stage I or Stage II. The study staff will tell you what stage you are eligible for.

**Stage I**

• If you are/your child is eligible for Step II of the study, you will be asked to come to the clinic at least 9 times over 48 weeks. The visits will be every two weeks at the beginning of the study (entry and weeks 2, 4, 6 and 8) and will spread out to every 4 weeks, and then to every 8 weeks (weeks 12, 16 and 24). After week 24, there will be one more visit at week 48.

• Most of these visits will take about 1-2 hours to complete.

• More visits will be needed if the amount of study drug in your blood is too low or too high and your dose needs to be adjusted.

• At each visit, a medical history will be taken and you/your child will have a physical exam. We will draw blood at each visit. You will be informed of results of routine blood tests.

• For 2 of the visits, you/your child will be asked to come to the clinic for a full day to have blood drawn 9 times over 24 hours. You may be asked to spend the night at the clinic. This is done to measure the amount of study drug in your/your child’s blood. If the first of these tests shows that the amount of study drug in your/your child’s blood is not enough or is too high, you/your child will be asked to take a different dose and return to the clinic for blood to be drawn again 9 times over 24 hours. A small plastic catheter (a needle that is placed in a vein for an extended period of time, so that blood can be drawn multiple times, without having to stick you with a needle each time) will be placed in your/your child’s arm to draw these blood samples. The needle will stay in place during the visit until all of the blood samples are drawn.

• At 3 visits, a blood sample will be drawn right before you take your dose of vicriviroc.

• The amount of blood drawn at the different study visits will vary from 1 teaspoon to **8 teaspoons (4 to 41 mL)**.
• One-two teaspoons (5-10 mL) of the blood that is drawn at most visits will be stored for future testing.
• If you and your doctor feel that continuing on vicriviroc will be good for you, you will continue to be given a supply of vicriviroc at these visits until it is available to you by prescription, and you will be asked to come to the clinic for routine tests to make sure you are continuing to do well. About 3-4 teaspoons (15-20 mL) will be drawn at these visits. These visits will be every 3 months until 5 years after you first started taking vicriviroc.
• If you do not continue to take study supplied vicriviroc, you will be asked to come to the clinic every 6 months until 5 years after you first started taking vicriviroc for routine tests to make sure you are continuing to do well. About 4-5 teaspoons (19-24 mL) will be drawn at these visits. These visits will be every 6 months until 5 years after you first started taking vicriviroc.

Stage II
• If you are/your child is eligible for this study, you/your child will come to the clinic a total of at least 9 times over 48 weeks.
• At each visit, a medical history will be taken and you/your child will have a physical exam. We will draw blood at each visit. You will be informed of results of routine blood tests.
• At 2 visits, a blood sample will be drawn between 2 and 5 hours after you take your dose of study drug. At 3 visits, a blood sample will be drawn between 10 and 14 hours after your dose of study drug.
• The amount of blood drawn at the different study visits will vary from 1 teaspoon to 8 teaspoons (4 to 41 mL).
• Most of these visits will take about 1-2 hours to complete.
• If you and your doctor feel that continuing on vicriviroc will be good for you, you will continue to be given a supply of vicriviroc at these visits until it is available to you by prescription, and you will be asked to come to the clinic for routine tests to make sure you are continuing to do well. About 3-4 teaspoons (15-20 mL) will be drawn at these visits. These visits will be every 3 months until 5 years after you first started taking vicriviroc.
• If you do not continue to take study supplied vicriviroc, you will be asked to come to the clinic every 6 months until 5 years after you first started taking vicriviroc for routine tests to make sure you are continuing to do well. About 4-5 teaspoons (19-24 mL) will be drawn at these visits. These visits will be every 6 months until 5 years after you first started taking vicriviroc.

When you start/your child starts taking the study drug, your/your child’s doctor will decide what other anti-HIV medicines are best to take with the study drug. Your doctor will prescribe at least 3 other anti-HIV medicines. Two of the other medicines must be a
protease inhibitor and ritonavir. You/your child must continue to take your/his/her anti-
HIV medications during the study as prescribed by your/your child’s HIV care provider.  If your/your child’s HIV care provider changes your/your child’s anti-HIV medications during the study, you/your child can still take the study drug. You/your child will be asked questions about taking your/his/her anti-HIV medications and the schedule you take/he/she takes them on and if you have/he/she has missed any medications.

FOR NICHD Sites:
Some of your blood specimens collected as part of this study will be stored for testing at a later date as part of this study. There is a separate consent form to explain this and get your/your child's consent.

For NIAID Sites:
Storage of Blood Samples
Some of your/your child’s blood will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-related research. At most study visits, about 1-2 teaspoons (5-10 mL) of blood (amount varies, depending on your/your child’s age) will be taken for this purpose.

Your/your child’s samples will be stored at a special laboratory facility. Only approved researchers will have access to them. People who work at the facility will also have access to your/your child’s samples to keep track of them. These people won’t have information that directly identifies you/your child. Your/your child’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your/your child’s samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your/your child’s samples will be stored.

The researchers do not plan to contact you or your/your child’s regular doctor with the results of studies done using your/your child’s stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your/your child’s medical care. If the researchers decide that the result of a certain study provides important information for your/your child’s medical care, your/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 address or phone number.

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

You may withdraw your consent for the storage and use of your/your child’s samples at any time. If you withdraw your consent, these stored samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.
I agree to allow my/my child’s blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes  __________ No  __________ Date

OTHER INFORMATION

The information collected in this study may be used for other IMPAACT-approved HIV-related research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 280 children and adolescents will take part in Step I of this study. About 140 of these children and adolescents will continue on and take part in Step II of this study.

HOW LONG WILL I/MY CHILD/BABY BE IN THIS STUDY?

If you/your child complete/completes Step I of this study, you/your child will be in this study for 1 day. If you/your child take/takes part in Step II, you/your child will be in this study for about 48 weeks, and then will be followed with clinic visits until 5 years after you started Step II. If you/your child continue(s) to receive study-provided vicriviroc, these visits will be every 3 months. If you/your child stop(s) taking vicriviroc provided by the study, these visits will be every 6 months.

After the study:
If you/your child can no longer come to the clinic for study visits before the end of the study, you will be asked to come to the clinic for a final study visit. This visit will include a medical history, physical exam, and blood tests to check the amount of HIV in your blood, to check the type of HIV in your blood, to see how well your immune system is working, and other routine tests.

WHY WOULD THE DOCTOR TAKE ME/MY CHILD OFF THIS STUDY EARLY?

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

- The study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the drug company supporting this study, the Office for Human Research Protections (OHRP), other national regulatory agencies, or the site’s Institutional Review Board (IRB) or Ethics Committee. An IRB is a committee that watches over the safety and rights of research subjects.
- You are/your child/baby is not able to attend the study visits as required by the study.
If you/your child must permanently stop taking study-provided vicriviroc before your study participation is over, the study staff will discuss other options that may be of benefit to you/your child. The study doctor will ask you/your child to continue to be part of the study and return for some study visits and procedures.

The study doctor may also need to take you/your child off the study drug without your permission if:

- Continuing the study drug may be harmful to you/your child
- You/your child need(s) a treatment that you/your child may not take while on the study
- You are/your child is not able to take the study drug as required by the study
- You become pregnant

After you have/your child has completed your/his/her study participation, vicriviroc will continue to be provided to you/your child if you and your/your child’s doctor feel that it has been helpful for you/your child. The study staff will discuss how you will be able to obtain it.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with 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

CCR5 Antagonist
Vicriviroc (VCV)  
Schering Plough Corporation

In studies of vicriviroc in animals, all species (rats, mice, dogs, and monkeys) had seizures at very high doses and death occurred in some animals. Researchers have found the dose and the blood level below which there were no seizures. The target blood levels of vicriviroc in this study are 10 times lower than the level that caused seizures in animals, and we do not expect seizures to occur in this study. A study in humans exposed to blood levels of vicriviroc several-fold higher than what researchers expect in this study showed no changes in brain wave tests (EEGs) that would suggest seizure activity.

Several cases of malignancies were identified in a study of vicriviroc in adults who have taken ARVs before. Based on the available information, independant experts concluded that they could not be sure that vicriviroc caused the cancers.

In animal studies, and at doses much higher than what you/your child will receive in this study, the study drug changed the normal electrical signals in the heart. This has not been seen in any clinical trials in human volunteers who have taken the drug.

Because of the way it works in the body, it is possible that vicriviroc might increase your risk of encephalitis if you/your child contracts West Nile virus or another arbovirus (arthropod-borne virus) while on vicriviroc. This is a possibility only; up to now, there have been no reports of encephalitis in studies of adults receiving vicriviroc.

There is the possibility that the HIV in your/your child’s body will change from CCR5 tropic to CXCR4 tropic HIV, which means the HIV can get into your T cells even while you are taking the study drug. In some cases, CXCR4 tropic HIV may be associated with faster progression of HIV disease.

Information from approximately 840 subjects who have received vicriviroc in earlier studies indicates that adverse (undesirable) events were generally mild to moderate in severity (most commonly fever (4%), nausea (3%), fatigue (2%), headache (2%), and shortness of breath (3%)), with no signs of seizure, or other central nervous system or cardiovascular effects. No pattern of significant changes has been observed in blood tests, vital signs or ECGs. Specifically, there has been no suggestion of liver damage from vicriviroc.

In studies in animals, no toxicity on the reproductive system or fetus have been found.

However, because this is an investigational drug that has been studied in only about 840 human subjects to date, there may be other unknown side effects.
Protease Inhibitors
The use of protease inhibitors may be associated with the following:

- Increases in the amount of triglycerides and/or cholesterol in the blood
- Development of diabetes or the worsening of high blood sugar

There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

Ritonavir (RTV, NORVIR®)
Abbott Laboratories

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

- Feeling weak and tired
- Stomach and bowel problems including abdominal pain, upset stomach, vomiting, abnormal stools, and loose or watery stools
- Loss of appetite
- Headache
- Dizziness
- Abnormal increases in triglycerides and cholesterol in blood
- Numbness and tingling in the arms, legs and around the mouth
- Rash
- Abnormal liver function blood tests which may be due to possible liver problems. Liver problems including cases of death have occurred in people taking ritonavir.
- Fever
- A change in the sense of taste
- 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.

Other Risks

There is the risk of serious and/or life threatening side effects when non-study medications are taken with study drugs. For your/your child’s safety, you must tell your/your child’s HIV care provider and the study doctor or nurse about all medications you take/your child takes before the start of this study and also before starting any new medications while you are/your child is on the study. In addition, you must tell the study doctor or nurse before you enroll/enrolling your child in any other clinical trials while on this study.
The use of potent antiretroviral drug combinations may also be associated with altered fat metabolism including elevated triglycerides (fatty acid in the blood) and/or elevated cholesterol.

Other side effects besides those listed and side effects from taking these drugs together may occur. If any unusual symptoms or changes happen, you should call your/your child’s doctor immediately. It is also important that while participating in the study, you do not/your child does not take any other prescription drugs or over-the-counter medications without first talking to your/your child’s doctor or study nurse.

If you join this study, some hospital staff and all study staff will know that you have HIV. These workers are very serious about your privacy. Study staff will make every possible effort to be sure that others do not learn your HIV status. However, sometimes if you receive special treatment or attend a special clinic, it may make others wonder if you have HIV.

Blood Drawing and Heparin Lock Risks:

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the drug or drug combinations in this study harm fetuses. Tests in animals showed no permanent or long-term effects on growth, development or reproductive capability of infant animals whose mothers were treated with vicriviroc before and after birth (during breastfeeding). If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a female pregnant.

Because of the risk involved, you and your partner must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until three months after stopping study drug. You may choose two of the birth control methods listed below:

- Birth control drugs that prevent pregnancy given by pills, shots, placed on the skin (e.g. Patch) or placed under the skin
- Male or female condoms with or without a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD)
All birth control methods listed above except condoms do not reduce the risk of giving HIV to someone else. HIV-infected individuals should use a birth control method that includes condoms to keep from giving HIV to someone else.

If you/your child can become pregnant, you/she must have a pregnancy test before entering this study. If you/your child are/is pregnant, you/she can not be in the study. If you think you/your child may be pregnant at any time during the study, tell the study staff right away. The study staff will talk to you about your/your child’s choices. You/your child will be tested again during the study if it is possible that you/she may be pregnant. If you/your child are/is pregnant, you/she will not be allowed to continue on the study drug.

Breastfeeding
If you are a breastfeeding mother, you can not enroll in this study. It is unknown whether the study drug or study drug combinations pass through the breastmilk and may cause harm to your infant. Infants enrolling in this study may be breastfed.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you/your child take(s) part in this study, the amount of HIV in your/your child’s body may go down and your/your child’s immune system may become stronger, but no guarantee can be made. You/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I/DOES MY CHILD/BABY HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- treatment with prescription drugs available to you/your child
- treatment with experimental drugs, if you/your child qualify(ies)
- participation in another clinical trial, if you/your child qualify(ies)
- no treatment

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

WHAT ABOUT CONFIDENTIALITY?

U.S. sites:
To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal,
state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your records include the U.S. Food and Drug Administration, the site IRB (insert name of site IRB), the National Institutes of Health, study staff, study monitors, drug companies supporting the study, and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

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

Your/your child’s records may be reviewed by the U.S. Food and Drug Administration (FDA), (insert name of site) IRB or Ethics Committee, National Institutes of Health (NIH), study staff, study monitors, and drug companies supporting this study.

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you/your child/baby are/is taking part in a research study.

The study will not provide or pay for any drugs, other than vicriviroc, that you are taking.

If your/your child’s doctor thinks it would be helpful for you/your child, the study will continue to provide vicriviroc to you/your child after the 48 weeks are complete, at no cost to you, until it is available by prescription.

WHAT HAPPENS IF I AM/MY CHILD IS INJURED?
If you/your child are/is injured as a result of being in this study, you/your child will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

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

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

We will tell you about new information from this or other studies that may affect your/your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE 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/your child’s rights as a research subject, contact:
  • name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
  • 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 take part in or allow your child to take part in this study, please sign your name below.

_____________________                              ____________________________________
Participant’s Name (print)   Participant’s Signature and Date

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

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

________________________                        ____________________________________
Witness’ Name (print)              Witness’s Signature and Date
(As appropriate)
APPENDIX IV
INFORMATION SHEET

TITLE: IMPAACT P1071, Phase I/II Open-Label Study to Evaluate the Pharmacokinetic, Safety, Tolerability and Antiviral Activity of Vicriviroc (SCH-417690) a novel CCR5 Antagonist in combination regimens in HIV-Infected Antiretroviral Therapy Experienced Children and Adolescents

This information sheet is to tell you about a change that has been made in how the special laboratory called a specimen repository will be managed.

As part of IMPAACT P1071 you agreed to have some of your blood or your child’s blood stored in the repository of the National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH).

NICHD has a repository because although researchers can learn a lot from a study, as time goes by sometimes the tests that they use get improved or brand new tests are developed, and more can be learned with these better tests. When study volunteers consent, like you did, to put specimens in the repository, and also consent to have the researchers do new tests on the specimens – at some time in the future after their time in the study is ended - researchers might learn new information by being able to use the stored specimens.

We are very grateful for your trust and willingness to help researchers keep learning more from the time you gave to the study.

The change we are making is in the group of people who oversee your stored specimens to make sure that your rights and privacy are protected in any future studies.

Before, the Institutional Review Board (IRB) at Westat, a data and operations center, was responsible for reviewing each future study.

Now we have a new procedure, approved by the NICHD IRB, which will have NICHD program staff review each future study. These NICHD staff members are very knowledgeable of the rules and procedures for oversight of specimen repositories, and they will be responsible for ensuring that your rights and privacy are protected.

If you have any questions about this change, you may contact:

[Add site research staff contact information here.]

NICHD program staff and everyone working on this study thank you for all you have done to make it successful.
When your child joins this NICHD sponsored Study, you will be asked to give permission for having some specimens that the doctor or nurse will take from your child’s body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during a study are kept. Your child’s name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your child’s name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or brand new tests are developed, and more can be learned with these better or new tests. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens at some time in the future after their time in the study is ended, researchers can learn new information by being able to use the specimens. Your child’s rights and privacy will be protected in any of these new studies.

How will my child’s privacy be protected?

The only record that your child participated in this NICHD sponsored study is at the clinic where it is kept separate from your child’s health records and locked away.

Your child’s specimens in the repository will not have your child’s name on them. The specimens will have a special study code. It will be the same code that is on your child’s information in the NICHD sponsored Study from your child’s interviews and examinations. Again, none of this information will have your child’s name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD sponsored repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

Why wouldn’t I find out the results of the research using my child’s specimens?
APPENDIX IV

You will not receive the results of research done with your child’s specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your child’s specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your child’s care right now, but they may be helpful to people like your child in the future. Your child’s specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my child’s specimens?

All of the studies to be done in the future on your child’s specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from your child and others from this NICHD Study has to be reviewed to make sure that what is planned is the same kind of study that you agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my permission to testing my child’s specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from your child in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your child’s name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my child’s specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (insert title), your child is being asked to have some (insert specimen source- blood, urine, tissue, genital fluid, saliva, etc.) taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your child’s time in this NICHD sponsored Study.
APPENDIX IV
You do not have to agree to store your child’s specimens for future tests for your child to take part in this study. Your child will not lose any benefits to which your child is entitled if you decide against storing your child’s specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from your child and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.

TEMPLATE CONSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your child’s DNA).

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test.
What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your child’s DNA) either protects them or puts them at greater risk. It may be that researchers use some of your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your child’s genetic makeup.
I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (special HIV-related tests).

<table>
<thead>
<tr>
<th>Parent or Legal Guardian Signature</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

<table>
<thead>
<tr>
<th>Participant Signature</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your child’s samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your child’s rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected from my child stored in the repository.

<table>
<thead>
<tr>
<th>Parent or Legal Guardian Signature</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
</table>
FACT SHEET and TEMPLATE CONSENT FORM for
Specimen Storage at the Repository of the National Institute of Child Health and Human Development (NICHD)
YOUTH FACT SHEET (Version 2.0- 29 November 2005)

When you join this NICHD sponsored Study, you will be asked to consent to having some specimens that the doctor or nurse will take from your body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during the study are kept. Your name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or brand new tests are developed, and more can be learned with these better or new tests. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens at some time in the future after their time in the study is ended, researchers can learn new information by being able to use the specimens. Your rights and your privacy will be protected in any of these new studies.

How will my privacy be protected?

The only record that you participated in this NICHD sponsored Study is at your clinic where it is kept separate from your health records and locked away.

Your specimens in the repository will not have your name on them, only a special study code. It will be the same code that is on your information in the NICHD sponsored Study from your interviews and examinations. Again, none of this information will have your name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

Why wouldn’t I find out the results of the research using my specimens?
APPENDIX V

You will not receive the results of research done with your specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your care right now, but they may be helpful to people like you in the future. Your specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my specimens?

All of the studies to be done in the future on your specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from you and others from this NICHD Study has to be reviewed to make sure that what is planned is the same kind of study that you agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my consent to testing my specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from you in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests or drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (insert title), you are being asked to have some (insert specimen source- blood, urine, tissue, genital fluid, saliva, etc.) taken from you. These specimens
APPENDIX V

will go into the NICHD repository for research to be done at some time in the future so that more information can come from your time in this NICHD sponsored Study.

You do not have to agree to store your specimens for future tests to take part in this study. You will not lose any benefits to which you are entitled if you decide against storing your specimens.

TEMPLATE CONSENT/ASSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your DNA).

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test.

I consent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

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What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your DNA) either protects them or puts them at greater risk. It may be that researchers use some of your blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your DNA for tests to be done in the future. This kind of information
APPENDIX V

will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your genetic makeup.

I consent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

___________________________ ___________________________   _________
Participant Signature   Witness Signature   Date

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your samples, contact (Study personnel) at (phone).
If you have questions about giving consent or your rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected for storage in the repository.

___________________________ ___________________________   _________
Participant Signature   Witness Signature   Date