CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	NDA 20-628/SDN-034 NDA 21-785/SDN-011
Priority or Standard	P
Submit Date(s)	July 29, 2010
Received Date(s)	July 29, 2010
PDUFA Goal Date	January 30, 2011
Division / Office	DAVP/OAP
Reviewer Name(s)	Tafadzwa Vargas-Kasambira, M.D., M.P.H.
Review Completion Date	December 26, 2010
Established Name	Saquinavir mesylate
(Proposed) Trade Name	INVIRASE®
Therapeutic Class	Antiretroviral drug
Applicant	Hoffmann La-Roche, Inc.
Formulation(s)	Hard capsules (200 mg) Film coated tablets (500 mg)
Dosing Regimen	Invirase (b) (4) twice a day boosted with ritonavir
Indication(s)	Treatment of HIV-1 infection
Intended Population(s)	HIV-infected pediatric patients from 4 months to 16 years of age.

Template Version: March 6, 2009

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The element of the Amended Written Request (WR) for Pediatric Studies (Amendment #6) to evaluate INVIRASE® for treatment of human immunodeficiency virus-1 (HIV-1) infection in pediatric patients < 16 years of age has been fulfilled. The completion of the Post Marketing Requirement (PMR) to complete pediatric studies under the Pediatric Research Equity Act (PREA), with the completion of Studies PACTG 397, HIVNAT 017 (ML19540), and NV20911, has not been fulfilled as the studies are currently considered inadequate. In addition, Pediatric Exclusivity was sought and granted by the Food and Drug Administration (FDA) on October 20, 2010. The studies provided data on safety, tolerability, bioavailability, and activity of saquinavir (SQV) alone and in combination with ritonavir (RTV) or lopinavir/ritonavir (Lpr/RTV) in children ranging in age from 4 months to 16 years, for up to 96 weeks of therapy. The study site inspections conducted by the Division of Scientific Investigations (DSI) indicated deficiencies with the bioanalytical method validation at the Netherlands site (where NV20911 was conducted), rendering the study data obtained unreliable, and necessitating revalidation of the method of analysis. Weaknesses were also noted for the pharmacokinetic (PK) bioanalyses for study HIVNAT 017. As a result, the pediatric PK data on which to bridge adult efficacy trials is lacking, and the Agency is unable to approve this sNDA submission at this time, nor complete the process of product labeling.

(b) (4)

The extrapolation of efficacy for antiretroviral drugs like SQV is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric patients (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)1. The Division of Antiviral Products (DAVP) agrees that HIV disease in pediatric

[1] TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT — IN GENERAL —If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other

patients is similar but not identical to adult HIV disease (Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468), although the route of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult patients, in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric patients. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in adults.

In pediatric and adult patients, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and HIV RNA load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been shown to lower HIV RNA, improve CD4 count (or percentage) and improve general clinical outcome in all ages, and treatment recommendations are very similar across all ages (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

For this supplement, consideration of approval is based on extrapolation of efficacy from adequate and well-controlled trials in HIV-infected adults, and supportive pharmacokinetic and safety data from Studies HIVNAT 017 and NV20911.

(b) (4)

The pharmacokinetic data for the youngest patients in the study cohorts displayed significant intra-subject variability, rendering a conclusion on appropriate dosing difficult. SQV soft gel capsules (FORTOVASE®), which were taken off the market in 2006, were used in study PACTG 397 alone initially, then in combination with RTV or nelfinavir (NFV) in pediatric subjects aged 3 years to 16 years for duration of 48 weeks. Cohort 1 was designed to assess safety, tolerability, bioavailability, and efficacy of FORTOVASE alone or in combination with NFV. Preliminary analysis of the PK parameters indicated inadequate blood concentrations of unboosted SQV in both treatment arms, so the trial was revised (Cohort 1A) to allow subjects on the SQV alone

information obtained in pediatric patients, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

arm to switch to combination therapy with RTV, and the subjects on the SQV + NFV combination to raise the maximum dose of SQV. Fourteen subjects were dosed with SQV 50 mg/kg twice daily and RTV 100 mg/m^2 twice daily with one or two nucleoside reverse transcriptase inhibitors (NRTIs) as background therapy.

Both treatments in study PACTG 397 were well-tolerated. New Grade 3 toxicities were experienced by 2 of the 14 (14%) subjects in the SQV + RTV arm, and Grade 4 toxicities were experienced by 2 of 8 (25%) of the subjects on the SQV + NFV arm. Comparing PK parameters across Cohorts 1 and 1A, SQV AUC and troughs were significantly higher when the drug was combined with RTV than when combined with the Cohort 1A dose of NFV. After 48 weeks of therapy, 7 subjects had HIV-1 RNA < 400 copies/mL, 9 were > 400 copies/mL, 4 were off study treatment, and 2 had incomplete Week 48 data. There were no significant changes noted in CD4 or CD8 counts or percentages after 16 or 48 weeks of treatment.

Study HIVNAT 017 was an open-label, single arm study conducted at two centers in Thailand that evaluated the safety, PK, and activity of LPV/RTV with SQV twice daily (given as 200 mg hard gel capsule) in 50 HIV-1 infected pediatric subjects aged 4 years to 15 years for 96 weeks. The pediatric subjects were protease inhibitor (PI)-naïve and had been previously exposed to NRTI- and NNRTI-containing antiretroviral (ARV) regimens. The trial was divided into two recruitment phases. The first 20 children enrolled underwent intensive PK sampling for 12 weeks at steady state for plasma levels of LPV, RTV, and SQV (phase 1), then continued directly into Phase 2 (96 weeks of treatment). An additional 30 subjects were enrolled directly into Phase 2 of the study schedule, which included the collection of limited PK samples to permit dose adjustment.

In terms of virologic response in study HIVNAT 017, the HIV RNA level decreased over the course of the study, measured in terms of percentage of subjects with HIV RNA < 400 and < 50 copies/mL at Week 96 compared with baseline values. The percentage of subjects who achieved an HIV RNA decrease of > 1 $\log_{10}$ from screening to Week 96 was 82%. The percentage of subjects who experienced virologic failure (defined as two consecutive viral load measurements ≥400 copies/mL [missing visits were assumed to be above 400 copies/mL]) by Week 96 was 20% for all subjects and 24% for subjects with HIV RNA > 10,000 copies/mL at screening. No subjects with HIV RNA ≤ 10,000 copies/mL at screening experienced virologic failure at Week 96. The mean absolute CD4 cell count increased from 224 cells/mm^3 at screening to 800 cells/mm^3 at Week 96. The CD4 cell percentage (though limited to only 20 subjects) increased and the CD8 cell percentage decreased from screening to Week 96. Eight subjects experienced at least one HIV-related event up to Week 96. The majority of subjects experienced either none (n=19) or minor (n-18) changes in lipodystrophy parameters measured every 12 weeks up to Week 96, while 10 subjects experienced major changes in either decreased facial fat or increased fat in one or more parameters measured. Adverse events were reported in 45 subjects, the majority of which were of mild or moderate

intensity, and included nasopharyngitis, cough, pyrexia, and diarrhea. Twenty-four serious AEs were reported in 12 subjects; infections and infestations and gastrointestinal disorders were the most commonly reported. Two subjects discontinued treatment prematurely due to AEs. Three subjects died during the 96 week treatment period or within 28 days of discontinuing treatment. The reasons for the deaths (bacterial sepsis, bacterial meningitis, and chronic gastroenteritis) were not considered by the investigator to be related to trial treatment.

Study NV20911 was an open-label, multicenter study conducted in Argentina, Spain and Thailand that evaluated safety, PK, and activity of SQV and RTV oral solution plus ≥ 2 background ARVs, in 18 children aged 7 months to less than 6 years. The pediatric subjects were stratified into two groups: Low Age group (infants 4 months to < 2 years) and High Age group (age 2 years to < 6 years). Drug administration was for 48 weeks.

The mean HIV viral load decreased from a baseline value of 3.50 log10 copies/mL to 2.0 log10 copies/mL. Only 4 percent of subjects had an HIV viral load at baseline that was < 400 copies/mL, and 96 percent of subjects had HIV viral load that was not BLQ. Fifty percent of subjects (8/16) in the combined all subject population with a baseline and Week 48 HIV RNA assessment experienced a > 1 log decrease from baseline in their HIV RNA. Mean CD4 lymphocyte count was maintained above the baseline value through Week 48, with a small increase in CD4 cell count expressed as a percentage of the total lymphocyte count. With regard to the SQV PK, the exposure parameters exhibited a large inter-subject variability in both age groups, while the half-life was comparable across subjects. Dose normalized SQV exposure appeared to be higher in the High Age group compared with the Low Age group.

The safety results of study NV20911 showed that 78% (14/18) of subjects reported at least one AE during the trial. All reported AEs were mild or moderate in intensity, with the most commonly reported individual events being bronchitis, dental caries, diarrhea, constipation and vomiting. There were no subjects who died in this trial, and no adverse events led to premature withdrawal from the trial. Three subjects experienced an SAE during the treatment period; these events were pneumonia (2 subjects) and bronchitis (1 subject).

1.2 Risk Benefit Assessment

INVIRASE® hard gel capsules (200 mg) were approved for use in the United States on December 6, 1995 and INVIRASE® film-coated tablets (500 mg) were approved for marketing on December 17, 2004. Post marketing events have been reported, and these are similar to adverse events observed in clinical trials with INVIRASE and soft gel capsules alone or in combination with ritonavir in adults.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) will not be required for this application.

1.4 Recommendations for Postmarket Requirements and Commitments

(b) (4) The applicant has, however, responded adequately to the WR, through the completion of the three trials under review – PACTG 397, HIVNAT 017, and NV20911. There are no new PMCs or PMRs the applicant is required to complete.

2 Introduction and Regulatory Background

2.1 Product Information

INVIRASE® (saquinavir mesylate) is an HIV-1 protease inhibitor (PI) that is indicated for the treatment of HIV-1 infection in adults (over the age of 16 years) in combination with ritonavir (RTV) and other antiretroviral agents. The drug received initial approval for marketing in the United States in 1995 (200 mg hard capsules) and 2004 (500 mg film-coated tablets).

Description: Saquinavir mesylate is a white to off-white, very fine powder with an aqueous solubility of 2.22 mg/mL at 25°C. INVIRASE is available as light brown and green, opaque hard gelatin capsules for oral administration in a 200mg strength (as saquinavir free base). INVIRASE is also available as a light orange to grayish- or brownish-orange, oval cylindrical, biconvex film-coated tablet for oral administration in a 500-mg strength (as saquinavir free base).

Chemical Class: N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide methanesulfonate.

Molecular Formula: $C_{38}H_{50}N_6O_5 \cdot CH_4O_3S$

Pharmacological Class: Inhibitor of the HIV-1 protease.

(b) (4)

The proposed dosing schedule is as follows:

(b) (4)

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

(b) (4)

As of October 2010, a total of 18 drugs had been approved for this indication in the United States.2. The currently approved drugs for this indication are described specifically in Table 1:

Table 1. Currently Available Treatments for Treatment of HIV-1 Infection in Children

Copy Right Material

2 Marón G, Gaur AH, Flynn PM. Antiretroviral therapy in HIV-infected infants and children. Pediatr Infect Dis J 2010;29:360-363

Adapted from Table 1, page 361, Marón, PIDJ 2010
Table is based on formulations available in the United States.
S indicates oral solution or suspension; ST, Scored tablet; P, Powder for oral solution; C, Capsule; T, Tablet; I, Injectable

2.3 Availability of Proposed Active Ingredient in the United States

Saquinavir mesylate, the active ingredient in INVIRASE, is available in the United States by prescription only.

2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Throughout the applicant's drug development program for saquinavir, the focus has remained on development of an age-appropriate delivery of saquinavir, and definition of the studies to be conducted (via a Written Request for Pediatric Studies).

The chronological sequence of FDA-Roche interactions is noted below, with a focus on the major interactions that occurred:

1997: Draft protocol (NV15545) for pediatric drug development program submitted to the Agency . The protocol explored the use of "unboosted" saquinavir soft-gel capsules (FORTOVASE®) and an experimental pediatric formulation, to the current use of "boosted" Invirase capsules, either as provided or opened and mixed with a vehicle.

January 20, 1999 and June 30, 2004: The pediatric drug development program for SQV was discussed at face-to-face meetings between the applicant and the Agency.

April 9, 1999: The first Written Request for Pediatric Studies was issued by the Agency on this date. Amendments to the WR were made on December 20, 2001, November 10, 2004, March 1, 2007, January 31, 2008, and December 23, 2009. The Written Request in effect is Amendment #6, issued on December 23, 2009.

Written Requests
Revisions to the Written Request have reflected: the recognition that adequate exposures could not be achieved with unboosted saquinavir and that ritonavir would be needed; increasing specificity in the drafting of Written Request letters over time (e.g. numbers of children in different age groups); and changes to allow the use of data from both hard-gel (saquinavir mesylate) and soft-gel (saquinavir) capsules to meet the requirements.

The current Written Request, issued by the Agency on December 23, 2009, asked for the following:

- Multiple-dose PK, safety and activity study(ies) of saquinavir or saquinavir mesylate boosted with low-dose ritonavir in combination with other antiretroviral agents; and
- Multiple-dose PK, safety and activity study(ies) of saquinavir or saquinavir mesylate boosted with lopinavir/ritonavir in combination with other antiretroviral agents, with the OBJECTIVE to
- Propose an appropriate dose of INVIRASE for use in HIV infected pediatric patients.

- The target PK sample size for pediatric age groups is;

    - 4 months to <2 years: 5
    - 2 years to <6 years: 12
    - 6 years to <12 years: 8
    - 12 years to <18 years: 6

- Studies must be submitted on or before August 1, 2010.

June 2004: Critical meeting was held between applicant and the Agency to discuss the attempts at developing an age-appropriate formulation. Early efforts to develop a

pediatric formulation (solution or suspension) were hampered by problems with solubility and the extremely bitter taste of saquinavir, as well as by manufacturing scalability. At the June 2004 meeting, the formulation attempts to date were discussed and it was agreed between the applicant and the Agency that: (1) while unsuccessful, a good-faith and reasonable effort had been made to develop a pediatric formulation; and, and (2) the Sponsor would explore the feasibility of emptying Invirase capsules as a viable method of dosing pediatric patients.

July 29, 2010: The applicant Hoffmann-La Roche Inc. (Roche) submitted a Supplemental New Drug Application (sNDA) to NDA 20-628 and NDA 21-785 for INVIRASE®.

The pediatric sNDA comprises data from three separate studies: PACTG 397, HIVNAT 017 (ML19540), and NV20911. The applicant claims that the data demonstrate safety, PK, and tolerability of INVIRASE in 82 pediatric patients aged 4 months to 16 years. The pediatric data submitted in the sNDA were aimed at fulfilling the following:

- The amended Written Request (WR) for Pediatric Studies (Amendment #6, dated 12/23/2009). The original pediatric WR for saquinavir (SQV) was issued 4/9/1999 to IND 41,099, and amendments were made on 12/20/2001, 11/10/2004, 3/01/2007, 1/31/2008, and 12/23/2009;
- Completion of the post-marketing commitment (PMC) to complete pediatric studies under PREA; and
- Determination of pediatric exclusivity extension. Pediatric exclusivity was granted to the applicant on 10/19/2010.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate.

3.2 Compliance with Good Clinical Practices

According to the applicant, the three studies were conducted in accordance with the principles of the Declaration of Helsinki and its amendments, or with the laws of the country in which the research was conducted, whichever afforded greater protection to

the individual. The studies were also said to have adhered fully to the principles outlined in *"Guidance for Good Clinical Practice"* International Conference on harmonization Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the subject. The applicant also states that investigators ensured adherence to the EU Clinical Trial Directive (2001/20/EC) and to the basic principles of Good Clinical Practice as outlines in the current version of 21CFR, subchapter D, part 312, *"Responsibilities of Sponsors and Investigators"*, part 50, *"Protection of Human Subjects"*, and part 56, *"Institutional Review Boards"* (IRB).

3.3 Financial Disclosures

The sponsor submitted financial information pertinent to the application. The statement specified that the sponsor had not entered into any financial arrangement with particular clinical investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Several sub-investigators disclosed significant interests (b) (6) The remainder of investigators did not disclose any interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Invirase is an FDA-approved drug, and CMC did not, therefore, review this sNDA submission.

4.2 Clinical Microbiology

Please refer to the Microbiology/Virology review for this sNDA.

4.3 Preclinical Pharmacology/Toxicology

Invirase is an FDA-approved drug, and Pharmacology/Toxicology did not, therefore, review this submission.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Saquinavir mesylate binds to the site of the HIV-1 protease and inhibits cleavage of viral Gag-Pol polyprotein precursors into individual functional proteins required for infectious HIV. This results in the formation of immature, noninfectious viral particles.

4.4.2 Pharmacodynamics

Absorption of the drug is poor (bioavailability ~ 4%), and is increased with a high fat meal. Volume of distribution (Vd) is approximately 700 L, and the drug does not distribute into the cerebrospinal fluid (CSF). SQV is highly protein bound in plasma (~98%), and metabolism is exclusively hepatic via CYP3A4, with extensive first-pass effect. Excretion occurs in the feces (81% to 88%) and urine (1% to 3%) within five days.

4.4.3 Pharmacokinetics

SQV is a major substrate of CYP3A4, and of CYP2D6 and P-glycoprotein. It inhibits CYP2C9, CYP2C19, CYP2D6, CYP3A4 (moderately), and P-glycoprotein. SQV has many drug-drug interactions with other agents, particularly when boosted with RTV.

In study HIVNAT 017, the first 20 subjects who were enrolled underwent a PK assessment between 10 days and 4 weeks after starting trial medication for those not using an NNRTI in the previous regimen, and after week 4 for those switched from an NNRTI-containing regimen at baseline. Nineteen of the 20 subjects had evaluable data. In study NV20911, PK data were available from 18 subjects.

In general, PK exposure parameters were generally independent of age and of body weight, particularly when body weight was greater than 10 kg. There was large inter-subject variability in dose-normalized (to 50 mg/kg) PK exposure parameters such as C_{trough}, C_{max} and $AUC_{0\text{-}12h}$.

Medical Officer's comments: DSI audited the bioanalytic sites for the pediatric PK data at the study sites for HIVNAT 017 and NV20911, and provided the preliminary findings of this audit to the Division on January 18, 2011. Overall, DSI advised that most, if not all, of the bioanalytical method validation at the Netherlands site needed to be repeated, with successful outcomes on all sections, for the study data to be usable. In addition, most of the bioanalysis for study HIVNAT 017 possessed significant weaknesses, and data from at least two subjects were unusable.

For the Bangkok Analytical Site, there were no records of validation experiments maintained, with the exception of within and between runs precision and accuracy. Other inaccurate information was contained in the bioanalytical report as well. There was a failure to identify the interference of RTV or SQV peaks by a LPV metabolite in plasma samples of children who received LPV/RTV dose. The CSs and QCs for SQV, LPV, and RTV were prepared from reference standard material with unknown purity (SQV) and expiration dates (SQV, LPV, and RTV). In addition, several aspects of the study were not disclosed e.g. no source records for the preparation of CSs and QCs used in the analytical runs.

With regard to study NV20911, freshly-prepared calibrators were not used in the validations of SQV and RTV assays, and failing validations for stability of SQV and RTV stock solutions were not addressed, among other deficiencies.

For the Thailand site in Khon Kaen (HIVNAT 017), one subject was taking Rifampicin, a prohibited concomitant medication; and another subject experienced two AEs (vomiting three days after initiation of ARVs, and rash seven days after starting ARVs) that were not documented on the case report forms. There were no records to support the assertion that concomitant drugs (e.g. prednisolone, azithromycin, co-trimoxazole, AZT, d4T, ddI, 3TC, etc) received by children in study HIVNAT 017 did not interfere with analysis of SQV, RTV, and Lpr.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The data were submitted to the Agency in the form of clinical study reports that provided an analysis of the information obtained, and clinical datasets. The report for study PACTG 397 was originally submitted to the IND on May 6, 2005, and that for study HIVNAT 017 (ML 19540) was submitted on September 29, 2006. The final report for study NV20911 was submitted on July 29, 2010, as were copies of the two study reports previously submitted, as just noted. Clinical datasets were submitted in SDISC format.

5.2 Review Strategy

The clinical information provided by the applicant for the three studies were reviewed. Case Report Forms (CRFs) for all patients who died or withdrew from the studies due to related or unrelated adverse events were included. In addition, for study HIVNAT 017, narratives were provided for all subjects who experienced deaths, SAEs (drug-related and non drug-related), and all drug-related AEs leading to withdrawal; there were no deaths in the other two studies, and narratives for SAEs and withdrawals for these two

studies were not provided. A single high level Clinical Overview was provided, as agreed with the Agency, that assesses the submitted pediatric data in the context of the historical development program. The Clinical Overview was submitted in lieu of Clinical Safety and Clinical Efficacy Summaries.

5.3 Discussion of Individual Studies/Clinical Trials

The submission contains clinical summaries of three separate studies: PACTG 397, HIVNAT 017, and NV20911. Studies HIVNAT 017 and NV20911 will be discussed in detail in this clinical review.

Study PACTG 397 will be described briefly, and will not be addressed in greater detail elsewhere in this review because this study is least supportive of the dosing regimen due to the fact that a different formulation was studied (FORTOVASE), and the initial cohorts in the study did not use RTV boosting.

Summary of Study PACTG 397

Background
This study was a randomized trial designed to assess the safety, tolerability, bioavailability, and activity of SQV soft gel capsules (FORTOVASE) alone and in combination with RTV or NFV in children aged 3 years to 16 years. The original Invirase formulation had such poor bioavailability that the sponsor, in agreement with the Agency, developed a second, more bioavailable FORTOVASE formulation. The antiretroviral activity of the two formulations was equivalent, but their PK profile was not. The sponsor was not able to achieve adequate drug levels with SQV alone (i.e. Fortovase unboosted with ritonavir) due to rapid clearance of the drug and poor bioavailability of the formulation. In the RTV-boosted regimens, SQV exposure resulting from either formulation is similar and the side effect profile acceptable, with fewer reported gastrointestinal AEs from Invirase/RTV compared with Fortovase/RTV.

Subjects in the original study were rolled over into Cohort 1A, which was designed to study PI-boosted regimens SQV + RTV and SQV + NFV. Because the study was not powered for efficacy, it produced mainly data on safety and dose-ranging.

Objectives
The primary objective of Cohort 1A was to assess the tolerance, safety, and steady-state PK of the Cohort 1A regimens. The secondary objectives included: evaluation of the regimens with respect to short and long term changes from baseline in plasma HIV-1 RNA, CD4 and CD8 counts and percentages, and exploration of the relationships between SQV and NFV, or RTV exposure and antiviral activity.

Methods

Two regimens were compared initially in HIV-infected children: SQV soft gelatin capsules (50 mg/kg PO TID to a maximum of 1200 mg PO TID) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), and SQV (50 mg/kg PO BID to a maximum of 1200 mg PO BID) in combination with NFV (55 mg/kg PO BID to a maximum of 1500 mg PO BID) and one or two NRTIs. The study was to enroll 50 children aged 3 years to 16 years, randomized to the treatment arms and followed for 48 weeks.

The study was revised in light of the inadequate blood concentrations of SQV in both arms. Participants still on treatment were given the option of enrolling in Cohort 1A. Those originally assigned to the SQV arm would be switched to SQV (same dose) plus RTV 100 mg/m^2 PO BID), plus one or two NRTIs. Subjects originally in the SQV + NFV arm would continue this therapy, but the maximum dose of SQV would be increased from 1200 mg to 1600 mg.

Twenty-two subjects rolled over from Cohort 1 to Cohort 1A: 14 going on to the SQV + RTV combination and 8 continuing on the SQV + NFV arm. Subjects were monitored for safety and efficacy through 48 weeks of follow up, Intensive PK assessments were performed on all subjects after 14 days on study treatment. Random trough levels were collected throughout the study treatment period.

Results
Both treatment regimens were well tolerated. Four subjects experienced toxicities ≥ 3 in grade. Two of the 14 (14%) subjects on the SQV + RTV arm experienced new grade 3 toxicities (one with creatinine phosphokinase [CPK] and glucose abnormalities), and 2 of the 8 (25%) subjects on SQV + NFV arm experienced new grade 4 toxicities (CPK and aspartate aminotransferase [AST] abnormalities), but no events were judged to be related to study treatment. Four subjects came off study treatment prematurely, two on each study arm.

PK parameters were compared across Cohorts 1 and 1A. SQV AUC was significantly higher when combined with RTV than with the Cohort 1 dose of NFV. SQV trough levels were significantly higher in the SQV + RTV arm than the SQV alone arm. Focusing on the Cohort 1A treatments, median trough levels of SQV, NFV and RTV were all higher in subjects with HIV-1 RNA < 400 copies/ml at week 16 compared to those with uncontrolled viral load. These differences were statistically significant for SQV and NFV.

Eight of the 22 subjects (36%) had HIV-1 RNA levels < 400 copies/ml at the start of Cohort 1A. Overall, after 48 weeks of treatment in this cohort, 7 had HIV-1 RNA < 400 copies/ml, 9 were > 400 copies/ml, 4 were off study treatment and 2 had incomplete week 48 data. There were no statistically significant changes in CD4 or CD8 counts or percents after 16 or 48 weeks of treatment.

Conclusions

SQV soft gel capsules, given in combination with NFV or RTV and one or two NRTIs, showed acceptable tolerability. SQV AUC was significantly higher when SQV was given in combination with RTV compared with the Cohort 1 combination of SQV + NFV. SQV trough levels were significantly higher when given in combination with RTV compared with SQV alone. SQV and NFV trough levels were significantly higher in subjects with short term (16 week) HIV-1 RNA levels < 400 copies/ml compared with subjects with less well controlled viral load.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

(b) (4)

6.1.1 Methods

The Methods used for each of the two trials under evaluation are summarized below:

HIVNAT 017
This is an open-label, single-arm study designed to evaluate the safety, activity, and PK of LPV/RTV with SQV for 96 weeks in PI-naïve HIV-infected children who had previously been exposed to NRTI- and/or NNRTI-containing ARV regimens. The study was to enroll 50 children in Thailand aged between 4 and 15 years. Stratification was into two groups: Low Age Group: ≥3 years, < 12 years, and the High Age Group: ≥12 years, ≤16 years. The first 20 children enrolled underwent intensive PK sampling at steady state for plasma levels of LPV, RTV, and SQV.

NV29011
This study was an open-label, multicenter study that was designed to evaluate the safety, activity, and PK of SQV and RTV oral solution in 18 children aged 4 months to less than 6 years. Subjects were deemed by the investigator to perhaps benefit from study therapy. Infants and young children were stratified into two groups: Group A “Low Age Group” (4 months to less than 2 years), and Group B “High Age Group” (2 years to less than 6 years).

6.1.2 Demographics

HIVNAT 017

The main demographics characteristics of the study population are shown in the table below:

Table 2. Baseline Demographics for Study HIVNAT 017

	Low Age Group	**High Age Group**	**All Patients**
N of Population	40	10	50
Age (years)			
Mean	7.98	12.5	8.9
SD	1.91	0.97	2.53
Median	8	12	9.0
Range	4 - 11	12 - 15	4 - 15
Gender (%)			
Male	17 (42.5%)	5 (50%)	22 (44%)
Female	23 (57.5%)	5 (50%)	28 (56%)
Weight (kg)			
Mean	20.1	31.63	22.4
SD	5.27	10.18	7.93
Median	19.4	29.5	20
Range	10.7 – 40.0	18.0 – 55.0	10.7 – 55.0
Height (cm)			
Mean	115.76	137.03	120
SD	10.97	13.1	14.19
Median	116	136.65	119
Range	92 - 147	120 - 159	92 - 159
Body Surface Area (m^2)			
Mean	0.80	1.1	0.86
SD	0.14	0.21	0.19
Median	0.79	1.09	0.81
Range	0.57 – 1.28	0.77 – 1.52	0.57 0 1.52

Low Age Group: ≥3 years, < 12 years
High Age Group: ≥12 years, ≤16 years
Race/ethnicity: Study conducted in Thailand; all 50 subjects (100%) were Asian

Medical Officer's comments: The majority of subjects in study HIVNAT 017 were in the Low Age group (N=40). There was a slightly higher number of females who were enrolled (56% females, 44% males).

The majority of subjects in study HIVNAT 017 were moderately symptomatic (CDC HIV Classification B) at screening (70%), and those severely symptomatic (Classification C) were next most frequent (14%).

In terms of previous diseases and conditions, 56% of subjects (28 of 50) had experienced at least one HIV-related illness prior to the study (22 of 40 in the Low Age group, and 6/10 in the High Age group). The most common illnesses reported were infections and infestations, and oral candidiasis was the most frequently reported of these (total 26% of subjects). A total of 20% (8 of 40) in the Low Age group experienced diarrhea prior to the initiation of the study.

Previous significant illnesses not related to HIV disease were experienced by 33% (13 of 40) of subjects in the Low Age group, and 20% (2 of 10) of those in the High Age group. The most common of these was otitis media, being reported in 8% (3 of 40) of subjects in the Low Age group.

Ongoing HIV-related illnesses at screening were experienced by 38% (19 of 50) subjects (35% or 14 of 40 subjects in the Low Age group, and 60% or 6 of 10 subjects in the High Age group). The most common illnesses were infections and infestations, with the following being reported in more than one subject each: pulmonary TB (6%, or 3 of 50 subjects); herpes simplex (4%, or 2 of 50 subjects); and pneumonia (4%, or 2 of 50 subjects). Other conditions reported included lymphadenopathy (4%, or 2 of 50 subjects), and dermatitis (4%, or 2 of 50 subjects).

Of the 28% (10 of 50 subjects) of subjects in each Age group who reported having at least one ongoing significant illness at screening not related to HIV disease, chronic otitis media was the most common, being reported in 10% (4 of 40 subjects) in the Low Age group.

Medical Officer's comments: The trends for otitis media were as expected; younger subjects reported these more than older subjects. The prevalence of oral candidiasis being the most commonly reported HIV-related illness is not surprising given the fact that the majority of subjects were moderately symptomatic from their HIV disease.

NV20911

The main demographic characteristics of the study population are shown in the table below:

Table 3. Baseline Demographics in Study NV20911

	Low Age Group	High Age Group	All Patients
N of Population	5	13	18
Age (years):			
Mean	0.8	4	3.11
SD	0.45	1.08	1.75
Median	1	4	4
Range§	4 mo - < 2	2 - 5	4 mo - 5
Gender (%)			
Male	2 (40%)	5 (38.4%)	7 (39%)
Female	3 (60%)	8 (61.6%)	11 (61%)
Race			
Caucasian	3 (60%)	5 (38.5%)	8 (44%)
Asian	2 (40%)	8 (61.5%)	10 (56%)
Weight (kg)			
Mean	9.36	15.23	13.6
SD	2.30	3.05	3.89
Median	9	15.2	14
Range	6.3 – 12.3	10.5 - 20	6.3 - 20
Height (cm)			
Mean	76.6	97.69	91.83
SD	8.88	9.55	13.32
Median	78	100	91
Range	62 - 86	81 - 116	62 - 116

Low Age Group: ≥4 months, < 2 years
High Age Group: ≥2years, < 6 years
§ The youngest subject enrolled was 7 months of age

Medical Officer's comments: The majority of subjects in Study NV20911 were female (61%). Most subjects were classified as "Oriental" by the sponsor (55.6%), and the remainder were Caucasian. It should be remembered that most of the centers involved in the study were located in Thailand (4 centers), followed by Argentina (3 centers) and Spain (1 center). The classification of "Caucasian," therefore, is most likely closer to Hispanic.

Baseline Diseases Characteristics

The majority of subjects were either severely symptomatic (CDC HIV Classification C) or not symptomatic at baseline (6 subjects, or 33% each). Four subjects (22%) were moderately symptomatic (B), and two (11%) were mildly symptomatic (A). All subjects had been infected with HIV vertically.

In terms of family history, 16 of the 18 subjects (89%) had no family history of cardiovascular disease, and 14 of 18 subjects (78%) had no history of lipid disorders.

6.1.3 Subject Disposition

HIVNAT 017

A total of 20 subjects were enrolled in Phase 1 of this trial, and underwent intensive PK assessments before continuing into Phase 2. A total of 30 additional subjects were enrolled directly into Phase 2, making a total of 50 subjects who completed up to 96 weeks of treatment. Three subjects withdrew prematurely from the trial, leaving 47 subjects to complete the entire trial.

Table 4 shows the previous and concomitant disease conditions in the subjects enrolled in study HIVNAT 017.

Table 4. Previous and Concomitant Disease Conditions in Study HIVNAT 017

Diagnosis Type	
HIV-related illnesses	56
Other significant illnesses	14
Past medical history	15
Diagnosis SOC	
Blood and lymphatic system disorders	4
Gastrointestinal disorders*	12
General disorders and administration site conditions	10
Infections and infestations	51
Injury, poisoning and procedural complications	1
Metabolism and nutrition disorders**	1
Respiratory, thoracic and mediastinal disorders	1
Skin and subcutaneous tissue disorders	4

Surgical and medical procedures	1

NV20911

A total of 18 subjects were enrolled, with 5 in the Low Age group and 13 in the High Age group. All 18 subjects completed at least 12 weeks in the trial, while 4 in the Low Age group completed 48 weeks (1 withdrew prematurely) and all 13 in the High Age group completed 48 weeks.

6.1.4 Analysis of Primary Endpoint(s)

Given the fact that the designs of the three studies were quite different, as were the patient populations enrolled and the underlying antiretroviral treatment regimens employed, pooling of information from the studies is impractical.

The sponsor provided a Clinical Overview document in which the Efficacy Results from studies HIVNAT 017 and NV20911 were presented on an individual study basis.

This review will present the results in categories that are appropriate for comprehending the findings as a whole.

Of note, evaluation of the antiviral activity was based on summary statistics for five parameters, namely HIV-1 RNA viral load, CD4+ T-cell count, CD4 percentage, CD8+ T-cell count and CD8 percentage. The summary statistics for HIV-1 RNA viral load included, per DAVP recommendations, percentage of patient with HIV-1 RNA viral load <400 copies/mL, <50 copies/mL, mean change from baseline in HIV-1 RNA viral load, and percentage of patients with at least 1 $\log_{10}$ drop from baseline. The applicant used a 'missing-failure' analysis, while results were reanalyzed by the DAVP Statistics team using a 'Snapshot approach (see Statistics Review by Dr. Susan Zhou.) The time windows used by the applicant were found not to be completed in an acceptable manner, so these were recoded according to the standard definition of time window used by the Agency.

<u>HIV-1 RNA Viral Load</u>

HIVNAT 017

Table 5 Table 5reveals the percentage of subjects with HIV RNA viral load < 400 copies/mL, comparing the applicant's results with those obtained by the DAVP Statistics review team.

Forty-seven of the 50 subjects (94%) in this study had evaluable HIV RNA results at baseline. The mean HIV RNA viral load at baseline was 4.7 $\log_{10}$ copies/mL (SD 0.75), and this value decreased over the course of the study, to 1.85 $\log_{10}$ copies/mL at week 96. This trend was noted in both Low Age and High Age treatment groups, though the HIV RNA values in the latter group began and remained higher than those of the Low Age group.

Table 5. Percentage of Subjects with HIV RNA Viral Load < 400 copies/mL in Study HIVNAT 017

		Reviewer's[1]		Applicant's[2]	
Week	N	n<LOQ	%	n<LOQ	%
HIVNAT017					
Screening	47	2	4	2	4
12	27	19	38	20	40
24	48	35	72	35	70
36	45	39	78	37	74
48	45	36	72	37	74
60	47	36	72	40	80
72	47	42	84	41	82
84	47	41	82	40	80
96	45	39	78	28	56

1. Source: Statistics Reviewer's analysis: "Missing as Failure" approach.
2. Applicant's results (Table 6 for HIVNAT017) from Clinical Overview

Table 6. Percentage of Subjects with HIV RNA Viral Load < 50 copies/mL in Study HIVNAT 017

		Reviewer's[1]		Applicant's[2]	
Week	N	n<LOQ	%	n<LOQ	%
HIVNAT017 (LOQ=50 copies/mL)					
Screening	47	0	0	0	0
12	27	9	18	10	20
24	48	27	54	27	54
36	45	27	54	26	52
48	45	31	62	31	62
60	47	29	58	33	66
72	47	34	68	31	62
84	47	33	66	32	64
96	45	33	66	26	52

Source: Statistics Reviewer's analysis: "Missing as Failure" approach

Medical Officer's comments: For HIV RNA viral load < 50 copies/mL, the percentage of subjects calculated at Week 96 (66%) was significantly greater than that calculated by the applicant (52%.) For HIV RNA viral load < 400 copies/mL, the percentage of subjects at Week 96 was 78% (Division's calculations) vs. 56% (applicant's calculations).

HIV RNA change from baseline to Week 96: The overall decreases from baseline to Weeks 48 and 96 were 2.66 and 2.73, respectively. The older age group (12 to 16 years) had slightly greater HIV RNA viral load at screening compared with the younger age group (3 to < 12 years). The viral load for the higher age group was maintained at a higher level throughout the study period.

Subjects with HIV RNA decrease of > 1 log_{10} copies/mL from baseline: The percentages of subjects with HIV RNA decreases of > 1 log_{10} copies/mL from baseline at Weeks 24, 48, and 96 were 82%, 80%, and 82%, respectively, based upon the Statistics reviewer's calculations (Table 7).

Table 7. Subjects with at least 1 log_{10} Decrease from Baseline in HIV-1 RNA Viral Load in Study HIVNAT 017

Week	n	r	%	n	r	%
HIVNAT017 (n=50)						
		Reviewer's			Applicant's[1]	
12	27	24	48	26	22	44
24	48	41	82	40	33	66
36	45	41	82			
48	45	40	80	36	32	64
60	47	40	80			
72	47	43	86	37	35	70
84	47	43	86			
96	45	41	82	24	22	44

[1]Applicant's Table 6 from Clinical Overview

Medical Officer's comments: The assessment of HIV RNA viral load decrease of > 1 log_{10} copies/mL from baseline yielded apparently more encouraging results than those presented by the applicant. The percentages calculated were significantly higher than those provided by the applicant.

The SQV + LPV/RTV treatment appeared to have efficacy over the course of the study, as shown in the decrease in HIV RNA value. The HIV viral load was higher in the younger subjects throughout, and this is an expected finding. Younger HIV-infected children generally have higher viral loads than older children.

The mean change in the HIV RNA from baseline was not significantly different over time, though it did increase slightly. The percentage of subjects with HIV viral load < 400 copies/mL increased slowly over time, demonstrating the activity of the drug treatment regimen. A similar trend was seen for HIV RNA < 50 copies/mL. It should be noted, however, that a percentage of subjects on treatment still did not have HIV viral loads < 400 copies/mL and < 50 copies/mL at Week 96 (22% and 34%, respectively), and this is somewhat concerning, considering that these subjects were all PI-naïve. Resistance testing for PIs was not conducted.

NV20911

Table 8 and Table 9 display the percentage of subjects in study NV20911 with HIV RNA viral load < 400 copies/mL and < 50 copies/mL, respectively, comparing the results obtained by the Division with those presented by the applicant.

All 18 subjects in the study have evaluable HIV-1 RNA assessments at baseline.

Table 8. Percentage of Subjects with HIV RNA Viral Load < 400 copies/mL in Study NV20911

		Reviewer's[1]		Applicant's[2]	
Week	N	n<LOQ	%	n<LOQ	%
NV20911					
Screening	18	6	33	6	33
12	17	15	83	15	83
24	17	16	89	15*	83
36	16	13	72	12	67
48	16	13	72	13	72

[1]Source: Statistics Reviewer's analysis: "Missing as Failure" approach.
[2]Applicant's results: Table 7 from Clinical Overview.
* PT (4101) had Week 24 HIV-1 RNA VL=50 copies/mL. Sponsor assigned missing.
Four subjects with screening viral load < 50, two subjects with 50 < VL < 400 copies/mL

Table 9. Percentage of Subjects with HIV RNA Viral Load < 50 copies/mL in Study NV20911

		Reviewer's[1]		Applicant's[2]	
Week	N	n<LOQ	%	n<LOQ	%
NV20911 (LOQ=50 copies/mL)					
Screening	18	4	22	4	22
12	17	7	39	7	39
24	17	14	78	13[3]	72

36	16	10	56	10	56
48	16	11	61	11	61

The results obtained by the applicant were similar to those obtained by the Division for both HIV RNA viral load parameters.

The mean viral load for the complete subject population was 3.5 log10 copies/mL at baseline. The overall mean HIV viral load decreased over the course of the study to 2.10 log10 copies/mL at Week 48. The change was similar in both the Low and High Age groups

Changes from baseline in HIV RNA: The mean change in HIV RNA from baseline was 1.36 copies/mL.

Subjects with > 1 log_{10} decrease from baseline in HIV RNA: Based upon the "missing=failure" principle, 44% percent of subjects in the study population had a > 1 log_{10} decrease in their HIV RNA viral load from baseline to Week 48 (Table 10.)

Table 10. Subjects with at Least 1 log_{10} Decrease from Baseline in HIV-1 RNA VL in Study NV20911

Week	n	r	%	n	r	%
NV20911 (n=18)						
		Reviewer's			Applicant's[1]	
8	16	8	44			
12	17	9	50	17	9	50
24	16	9	50	16	9	50
36	15	7	39	15	7	39
48	16	8	44	16	8	44

[1]Applicant's Table 7 from Clinical Overview

Table 11. Subjects with at Least 1 log_{10} Decrease from Baseline in HIV-1 RNA VL in Study NV20911

Week	n	r	%	n	r	%
NV20911 (n=18)						
		Reviewer's			Applicant's[1]	
8	16	8	44			
12	17	9	50	17	9	50
24	16	9	50	16	9	50
36	15	7	39	15	7	39
48	16	8	44	16	8	44

[1]Applicant's Table 7 from Clinical Overview

Medical Officer's comments: The percentages of subjects with HIV RNA < 400 copies/mL decreased over time, suggesting that activity lessened over the course of the study, although with such small subject numbers, it is difficult to make this conclusion definitively. The numbers of subjects who experienced a > 1 log_{10} decrease in their viral load fell slightly over the course of the study.

CD4 T-Lymphocyte count, Percentage, and Change from Baseline

All three studies obtained results for changes in CD4 count. HIVNAT 017 also looked at CD4 percentage.

HIVNAT 017

There were 44 evaluable absolute CD4 cell counts at screening out of 50 enrolled subjects, and there were decreasing numbers of available values for analysis over the course of the study. There was a general increase in the mean absolute CD4 cell count over the course of the 96 weeks of the study that was seen in both the Low and High Age groups (Table 12); the mean CD4 cell count increased from 210 cells/mm^3 at baseline to 231 at Week 24, 273 at Week 48, and 313 cells/mm^3 at Week 96 (Table 12.) Of note, the Low Age group had higher absolute CD4 cell counts from screening to week 96.

Table 12. CD4 T-cell Counts (cells/mm^3) in Study HIVNAT 017

	Reviewer's						Applicant's[1]		
Week	N	med	Min	Max	Mean	Std	n	Mean	Std
HIVNAT017 (n=50)									
Screening	49	160	6	939	210	207			
12	28	397	98	1102	452	252	28	196	192
24	48	396	71	1221	439	231	42	211	191
36	46	526	36	1104	546	231			
48	47	571	61	1177	612	273	46	375	242
60	47	631	26	1580	721	335			
72	47	662	36	1522	760	331	39	521	313
84	47	718	39	1427	756	294			
96	46	691	233	1452	781	313	27	536	404
HIVNAT017: Age (3-<12)									
Screening	40	150	6	939	221	221			
12	21	421	98	1102	482	273			
24	38	415	71	1221	472	243			
36	36	556	36	1104	577	231			
48	37	606	263	1116	647	257			

	Reviewer's					Applicant's[1]		
Week	N	med	Min	Max	Mean	Std	n	Mean	Std
60	37	716	364	1580	782	319			
72	37	721	400	1522	835	314			
84	37	799	364	1427	811	283			
96	37	702	233	1452	807	318			
HIVNAT017: Age (12-16)									
Screening	9	167	6	411	159	121			
12	7	330	180	623	362	158			
24	10	355	103	464	314	123			
36	10	500	48	644	435	201			
48	10	457	61	1177	484	308			
60	10	514	26	995	492	301			
72	10	495	36	763	483	240			
84	10	554	39	902	555	254			
96	9	575	366	1193	672	281			

[1]Statistics reviewer analysis for study NV20911

There was an increase in CD4 percentage between screening and Week 96 in both age groups, although, as noted with the CD4 counts, the CD4 cell percentages were slightly higher in the Low Age group throughout (Table 13). The mean increases in CD4 cell percentages were 11% and 14% at Weeks 48 and 96, respectively.

Table 13. CD4 percentages in Study HIVNAT 017

	Reviewer's						Applicant's[1]		
Week	N	median	Min.	Max.	mean	Std	N	Mean	Std
HIVNAT017 (n=50)[2]									
Screening	49	7.0	0.0	23.0	7.5	5.6			
12	28	12.0	5.0	30.0	12.6	6.5	28		
24	48	13.0	3.0	28.0	13.8	5.6	42		
36	46	16.5	3.0	35.0	16.2	6.6			
48	47	16.0	1.0	47.0	18.2	8.1	46		
60	47	21.0	2.0	39.0	20.4	6.8			
72	47	22.0	2.0	38.0	21.3	6.1	39		
84	47	22.0	2.0	33.0	21.5	5.8			
96	46	22.0	11.0	33.0	22.1	5.1	27		
NV20911 (n=18)[2]									
Screening	18	30.4	14.5	51.5	29.7	10.9			
8	17	29.8	13.0	54.8	30.0	11.1			
12	17	30.0	15.0	49.7	30.1	9.1	16		
24	16	33.0	12.0	45.4	31.2	9.3	15		
36	16	31.0	17.9	47.0	32.0	8.6	15		

		Reviewer's					Applicant's[1]	
48	16	30.0	17.0	77.0	33.8	14.3	15	

[1]Applicant's Table 8 from Clinical Overview
[2]Statistics reviewer analysis for revised data

The mean increases in CD4+ T-cell count (cells/mm^3) from baseline were 228 at Week 24, 282 at Week 48, and 566 at Week 96.

Medical Officer's comments: The general trend in CD4 count and percentage in study HIVNAT 017 was an increase in both categories. This trend was also noted with the change from baseline in CD4+ T-cell count.

NV20911

Seventeen of 18 subjects who were enrolled in study NV20911 had valid CD4 cell count assessments performed at baseline. The mean CD4 T-cell count at Weeks 24 and 48 were 1212 cells/mm^3 and 1381 cells/mm^3, respectively (Table 14.)

Table 14. CD4+ T-Cell Count (cells/mm3) for Study NV20911

		Reviewer's					Applicant's[1]		
Week	N	med	Min	Max	Mean	Std	n	Mean	Std
NV20911 (n=18) [2]									
8	17	957.0	454.1	2575.0	1257.4	646.7			
12	17	1080.8	429.3	2921.3	1217.6	606.9	17	1217	607
24	16	864.9	518.9	3647.8	1211.8	807.0	16	1212	807
36	16	984.3	328.1	3560.8	1307.8	934.6	16	1308	935
48	16	1288.1	539.1	2679.2	1380.9	639.1	16	1381	639

[1]Applicant's Table 9 from Clinical Overview
[2]Statistics Reviewer's analysis for revised NV20911 data

There was an increase in the mean CD4 percentage by Week 48 of 5% from baseline (Table 15.)

Table 15. CD4 Percentages for Study NV20911

		Reviewer's					Applicant's[1]		
Week	N	median	Min.	Max.	mean	Std	N	Mean	Std
NV20911 (n=18)[2]									
Screening	18	30.4	14.5	51.5	29.7	10.9			
8	17	29.8	13.0	54.8	30.0	11.1			

12	17	30.0	15.0	49.7	30.1	9.1	16
24	16	33.0	12.0	45.4	31.2	9.3	15
36	16	31.0	17.9	47.0	32.0	8.6	15
48	16	30.0	17.0	77.0	33.8	14.3	15

[1]Applicant's Table 9 for NV20911 from Clinical Overview
[2]Statistics reviewer's analysis for revised NV20911 data

The mean increases in CD4+ T-cell count (cells/mm^3) from baseline were -4 at Week 24, and 165 at Week 48.

Medical Officer's comments: The trend seen for CD4 cell count and percentage was as expected, with a general increase noted over the duration of the study. It is interesting to note that the mean change from baseline was negative in the Low Age group, unlike that in the High Age group and overall. This change is consistent with the observed decrease in the absolute CD4+ T-cell count that occurs in HIV-infected children from infancy to around age 5 years.

CD8 Cell Count

HIVNAT 017

The CD8+ T-cell count and CD8 percentage information in this study was limited to the first 20 subjects who were enrolled for PK assessments (Group 1.) Seventeen of these 20 subjects had evaluable CD8 cell counts at screening. According to the applicant, the mean absolute CD8 cell count overall was 1296 cells/mm^3 at screening, 1494 at Week 24, 1427 at Week 48, and 1224 at Week 96.

The overall decreases in CD8+ T-cell count from screening were 366, 204, and 49 cells/mm^3, at Weeks 24, 48, and 96, respectively. The subjects experienced a mean decrease in CD8 percentage of 11% at Week 48 and 16% at Week 96.

NV20911

Seventeen of the 18 subjects enrolled in this study had valid baseline CD8 cell counts for assessment. The overall decreases in CD8+ T-cell count from screening were 366, 204, and 49 cells/mm^3, at Weeks 24, 48, and 96, respectively (Table 16.) The subjects experienced a mean decrease in CD8 percentage of 11% at Week 48 and 16% at Week 96.

Table 16. Change from Baseline in CD8+ T-Cell Count (cells/mm3)

Week	n	med	Min	Max	mean	Std

NV20911 (n=18)[1]						
8	17	-116	-1754	1816	-3	1034
12	17	3	-1443	909	-60	615
24	16	-40	-1837	1570	-47	685
36	16	-132	-1063	930	-149	540
48	16	-17	-1269	1174	32	581

[1]Statistics reviewer's analysis for revised NV20911 data

Medical Officer's comments: The trend for CD8+ T-cell count and percentage was as expected, as was the trend for the change from baseline in absolute CD8+ cell count, except for a mean increase of 91 cells/mm^3 from baseline to Week 48.

Virologic Failure

The percentages of subjects who experienced virological failure, namely HIV RNA ≥ 400 copies/mL on two consecutive occasions, was similar in both studies.

HIVNAT 017

According to the applicant, virologic failure was experienced in this study by 24%, 16%, and 20% of subjects at Weeks 24, 48, and 96, respectively. Only subjects with HIV RNA > 10,000 copies/mL at baseline experienced virologic failure, and these numbered 27%, 19%, and 24% at Weeks 24, 48, and 96, respectively.

NV20911

At Weeks 24 and 48, 2 of 18 (11%) subjects and 4 of 18 (22%) subjects, respectively, were deemed virologic failures, per the applicant. A total of 9 subjects had HIV RNA > 10,000 copies/mL at baseline, and of these 2 were deemed virologic failures at Week 48 (one in the Low Age group, one in the High Age group.) Of the 9 subjects with HIV RNA ≤ 10,000 copies/mL at baseline, 2 were deemed virologic failures at Week 48 (both in the Low Age group).

Medical Officer's comments: The applicant notes that the subject in study NV20911, High Age group who experienced virologic failure (subject 118172/1204) underwent genotyping at screening and at Week 48. The results showed a major protease-resistant mutation L90M, as well as an additional PI mutation G48V at Week 48.

HIV-Related Illness

HIVNAT 017

At least one event that was considered to be related to the underlying HIV disease was experienced by a total of 8 subjects in this study (6 in the Low Age group, 2 in the High Age group). These events are displayed in Table 17:

Table 17. Summary of HIV-Related Events in Study HIVNAT 017

Body System/ Adverse event	**Low Age Group N = 40**	**High Age Group N = 10**	**All Subjects N = 50**
ALL BODY SYSTEMS			
Total Subj w/at least on AE	6 (15%)	2 (20%)	8 (16%)
Total number AEs	7	2	9
INFECTIONS AND INFESTATIONS			
Total Subj w/at least one AE	6 (15%)	1 (10%)	7 (14%)
Herpes zoster infection	0	1 (10%)	1 (2%)
Infection	1 (3%)	0	1 (2%)
Mycobacterial infection	1 (3%)	0	1 (2%)
Oropharyngeal candidiasis	3 (8%)	0	3 (6%)
Tuberculosis	2 (5%)	0	2 (4%)
TOTAL number of AEs	7	1	8
RENAL AND URINARY DISORDERS			
Total Subj w/at least one AE	0	1 (10%)	1 (2%)
Nephropathy	0	1 (10%)	1 (2%)
TOTAL number of AEs	0	1	1

Eight subjects (6 in the Low Age group, 2 in the High Age group) experienced at least one event considered to be related to underlying HIV disease. All except one event (nephropathy) were reported as an infection or infestation.

NV20911

The applicant reported no CDC category B or C HIV-related illnesses during the study.

Height and Weight: z-scores

HIVNAT 017

According to the applicant, the mean height z-score increased for all subjects from -2.14 at screening to -1.60 at Week 96. The mean weight z-score for all subjects increased from -1.67 at screening to -1.32 at Week 96.

NV20911

z-scores for height and weight were not reported for this study.

Lipodystrophy

HIVNAT 017

The parameters for lipodystrophy included habitus changes in the following areas: face; front or side of neck; back or base of neck; arms; legs; abdomen; and buttocks. Investigators were asked to rank changes on a scale from 1 to 7 for each parameter, 1 being much thinner, 4 being no change, and 7 being much fatter. A cumulated score was then calculated, and displayed graphically to show changes in lipodystrophy over time.

Answers were to reflect comparisons of the subjects' status at each visit with the previous visit (e.g. Week 24 compared with Week 24), but some investigators interpreted the instructions to reflect comparisons of subjects' status at each visit with the baseline visit. This therefore limited the description of basic trends and degrees of changes seen.

Data on lipodystrophy were available for 47 of 50 subjects. No changes were reported in 19 subjects; minor changes were reported in 18 subjects (mostly increased fat in one or more parameters); and major changes in 10 subjects (mostly increased fat in one or more parameters, and decreased facial fat). Site number 20000 (Bankok Kaen Center) reported all of the major changes noted.

Medical Officer's comments: The assessment of lipodystrophy was subjective, and the measurements cannot therefore be considered conclusive. Another more reliable method of measurement (though still subjective) would have been patient reported outcome (PRO) with respect to lipodystrophic changes.

NV20911

Lipodystrophic changes were not assessed in this trial.

6.1.5 Analysis of Secondary Endpoints(s)

HIVNAT 017

This study had no secondary endpoints.

NV20911

The secondary endpoints in this study were as follows:

1. To characterize PK of RTV when given as booster in combination with SQV in HIV-infected pediatric patients
2. To evaluate antiviral activity of SQV when boosted with RTV against HIV-1 infection

Pharmacokinetics: The exposure parameters of SQV PK showed a great deal of inter-subject variability in both age groups. Dose normalized SQV exposure appeared to be higher in the older age group (age 2 years to < 6 years) compared to the younger group (age 4 months to < 2 years). Mean SQV trough concentrations in the younger age group through mean 8 through week 24 were lower in the younger subjects.

In terms of RTV PK, dose normalized exposures appeared to be higher in the older age group compared with the younger age group.

Medical Officer's comment: Please see Clinical Pharmacology review of this sNDA by Dr. Shirley Seo. The antiviral activity results for study NV20911 are discussed in section 6.1.4. (Analysis of Primary Endpoints).

6.1.6 Other Endpoints

There were no other endpoints studied in HIVNAT 017 or NV20911.

6.1.7 Subpopulations

There were no subpopulations studied in HIVNAT 017 or NV20911.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Invirase is an approved drug for adults, but not for pediatric patients. Exploration of dosing was an endpoint for study PACTG 397, as was the confirmation of PK of the

dose identified in the study, In addition, the studies were conducted to obtain long-term clinical data.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance was not assessed in this study.

6.1.10 Additional Efficacy Issues/Analyses

From the results of both studies HIVNAT 017 and NV20911, it appears that the applicant achieved their goal of demonstration of activity of the study drug Invirase. It is difficult, however, to assess the contribution of SQV to the effective treatment regimen because the drug was only used in combination with other antiretroviral drugs.

HIVNAT 017 demonstrated that treatment with SQV 50 mg/kg twice daily with LPV/RTV 230/57.5 mg/m^2 led to benefits in virologic, immunologic and clinical parameters over a 96 week study period, although the latter included lipodystrophy, which was assessed subjectively to an extent. NV20911 demonstrated that treatment with SQV 50 mg/kg boosted with RTV also resulted in virologic, immunologic, and clinical benefit, over a 48 week study period. The number of subjects in the Low Age group was only 5, and as such, there were insufficient data to allow for a recommendation of SQV dose for pediatric subjects < 2 years of age.

7 Review of Safety

Safety Summary

7.1 Methods

Safety data for this NDA supplement were provided by the applicant in the form of electronic datasets that contained tables of clinical adverse events. As previously agreed with the Division, the applicant did not provide a Clinical Safety Summary due to the divergent nature of the three studies submitted (in terms of time windows, age groups, and dosing regimens studied), but rather submitted a Clinical Overview that assessed the submitted pediatric data and set it in the context of the historical development program.

Narrative summaries and case report forms were provided for all subjects who died and who experienced serious adverse events (those deemed to be at least possibly related to study drug exposure) in studied PACTG 397, HIVNAT 017, and NV20911. Narratives were provided for all subjects in study HIVNAT 017 who had one or more of the following: Deaths; all SAEs; and discontinuations for safety reasons. Tabulations of AEs, SAEs, and study drug interruptions or discontinuations were compiled using the JMP Statistical Discovery Software (SAS Institute, Inc.).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation was conducted using the data generated from the three trials under review, PACTG 397, HIVNAT 017, and NV20911.

7.1.2 Categorization of Adverse Events

Subjects in the Safety Population were assigned to treatment groups as treated with at least one dose of study drug, for the purposes of analysis.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data from across the three trials was not done, given the disparate nature of said data. The data varied in terms of time windows in which the studies were conducted, the age groups studied, and the dosing regimens employed.

7.2 Adequacy of Safety Assessments

The monitoring of clinical and laboratory safety parameters in the three trials was considered adequate in light of the fact that Invirase is an approved drug for which a significant amount of safety data are available from previously-reviewed treatment protocols in adults.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

HIVNAT 017

“Trial treatment” was defined as having received all three drug components (SQV, LPV, and RTV simultaneously. Phase 1 subjects were on trial treatment for approximately 12 weeks longer than for those directly enrolled into this phase. This is because a PK assessment was conducted at steady-state before entering the 96-week treatment period.

Study exposure duration for phase 1 subjects was a mean of 729 days overall (range, 200 to 748 days); this mean was 729 days for the Low Age group, and 722 days for the High Age group (Table 18.) The duration of trial drug exposure for phase 2 subjects was 673 days overall (range, 6 to 700 days), with a mean of 673 days for the Low Age group, and 671 for the High Age group.

Table 18. Summary of Trial Treatment Exposure in Study HIVNAT 017

	Age Group		**All Subjects**
	Low	**High**	
Phase 1 (N=20) N of Population	**17**	**3**	**20**
Duration of trial treatment (days)			
n	17	3	20
Mean (SD)	733 (8.1)	550 (303.4)	706 (119.3)
Median	729	722	729
Range	723 - 748	200 – 729	200 - 748
Phase 2 (N=30) N of Population	**23**	**7**	**30**
Duration of trial treatment (days)			
n	23	7	30
Mean (SD)	602 (202.8)	625 (134.7)	607 (187.2)
Median	673	671	673
Range	6 – 700	320 – 687	6 - 700
All Subjects (N=50) N of Population	**40**	**10**	**50**
Duration of trial treatment (days)			
n	40	10	50
Mean (SD)	658 (166)	603 (184)	647 (169.3)
Median	689	675	686
Range	6 – 748	200 – 729	6 - 748

NV20911

“Trial treatment” was defined as having received both drug components (SQV and RTV) simultaneously. The median duration of SQV treatment was 337 days (range, 75 to 384 days), as shown in Table 19.

Subjects who received RTV in the form of LPV/RTV (Kaletra) did not need to receive additional boosting doses of RTV in combination with SQV. The sponsor states that four subjects (subject 118169/4203 in the Low Age group, and subjects 118169/4201, 118169/4202 and 142299/4401 in the High Age group) received concomitant LPV/RTV at baseline, and were not documented to have received SQV without RTV during the trial.

Table 19. Summary of Extent of Exposure to Trial Medication in Study NV20911

	Age Group		All Subjects N=18
	Low N=5	High N=13	
Duration of trial treatment (days)			
n	4	10	14
Mean (SD)	212 (151.7)	344 (20.9)	306 (97.2)
Median	211.5	337	337
Range	75 – 349	309 – 384	75 - 384

Medical Officer's comments: In study HIVNAT 017, the maximum number of days of drug exposure a subject could theoretically receive is 756 days (96 weeks x 7 days), and none reached this threshold.

In study NV20911, the maximum number of days of drug exposure a subject could theoretically receive was 336 days (48 weeks x 7 days). The mean duration of trial treatment in the High Age group (306 days) was less than this theoretical maximum, although the range extended to 384 days. It appears that two subjects in study NV20911 had drug durations of < 336 days, and the remaining 16 subjects took study drug for longer than this time period.

7.2.2 Explorations for Dose Response

There were no explorations made for dose response in studies HIVNAT 017 or NV20911.

7.2.3 Special Animal and/or In Vitro Testing

Invirase is an approved medication for treatment of HIV infection in adults, and no additional animal or in vitro testing was therefore conducted for this supplement.

7.2.4 Routine Clinical Testing

Routine safety monitoring was conducted in both studies HIVNAT 017 and NV20911, including chemistries, hematology, urinalysis, etc.

7.2.5 Metabolic, Clearance, and Interaction Workup

Pharmacokinetic evaluations wee conducted in both studies HIVNAT 017 and NV20911.

The PK analysis was conducted in the first 20 subjects who were enrolled (Phase 1). The general findings from the two trials were that PK parameters were basically independent of age and of body weight (particularly when body weight was > 10 kg). Also, there was great inter-subject variability in dose-normalized (to 50 mg/kg) PK exposure parameters.

Medical Officer's comment: Please see Clinical Pharmacology review by Dr. Shirley Seo for further details of the PK analysis.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There were no evaluations for potential adverse events for similar drugs in the same drug class as SQV (protease inhibitors).

7.3 Major Safety Results

7.3.1 Deaths

HIVNAT 017

Three patients died during treatment period (96 weeks) or within the 28 day follow-up after their last dose of trial treatment. None of these deaths were considered by the investigator to be related to therapy.

The line listing for these patients is noted below:

Table 20. Death Listing in Study HIVNAT 017[1]

Trial	Center	Subject ID	Age at time of death (years)	Sex	Last Treatment Day[2]	Day of Death[3]	Study Drug	Source[4]	Description
HIVNAT 017	20000	0211	9	M	67	87	SQV, LPR/RTV	Primary	HIV-infected, anemia, bacterial sepsis, generalized seizure
HIVNAT 017	10000	0127	11	F	No information	9	SQV, LPR/RTV	Primary	HIV-infected, bacterial meningitis
HIVNAT 017	10000	0120	10	F	218	307	SQV, LPR/RTV	Primary	HIV-infected, pulmonary TB, abdominal pain, diarrhea, chronic gastroenteritis

[1]Includes all deaths that occurred during the period of drug exposure and following discontinuation from study drug.
[2]Number of days on study drug before discontinuation.
[3]Number of days off drug at time of death.
[4]Source is clinical study report.

The narratives of the three deaths in study HIVNAT 017 are summarized below:

Subject 20000/0211
This 10 year old congenitally HIV infected male with a history of hemoglobin E alpha thalassemia, was started on SQV and LPR/RTV. He was found to have anemia at baseline, and on Day 36, was found to have a persistently low hemoglobin level, and was mildly icteric with pallor and hepatosplenomegaly. He was admitted to the hospital on Days 43 and 63 for a red blood cell transfusion. All study medications were stopped on Day 67 due to high blood levels of SQV, and these were not restarted. After being admitted again to hospital on Day 71 with severe cachexia, fever and fatigue, he was found to have *Escherichia coli* urosepsis. Antimicrobial treatment was administered. A urine culture on Day 79 grew *Enterococcus* spp, and the subject received appropriate antimicrobial therapy. He experienced a generalized seizure on Day 83, and was taken home by his mother soon afterwards against medical advice. The subject died at home on Day 87.

The investigator determined that the patient's anemia was related to his pre-existing thalassemia rather than the study medication. The patient's bacterial sepsis was determined to be related to the pre-existing HIV infection rather than to study medication.

Subject 10000/0127
This 11 year old HIV-infected female with a history significant for chronic diarrhea, oral candidiasis, and lymphatic tuberculosis was started on SQV and LPR/RTV. She developed persistent fever, nausea and vomiting on Day 5 of treatment, and deteriorated rapidly, becoming comatose by Day 8. There is no note of when study treatment was stopped. The subject was admitted to the hospital on Day 8, and was provisionally diagnosed with meningitis; this was confirmed later by suggestive CSF indices and a positive CSF culture that grew *Streptococcus pneumoniae*. She was treated appropriately, but her condition continued to worsen, and she was taken home against medical advice on Day 9, where she died the same day.

The investigator determined that the subject's death was caused by the meningitis, which was a result of her pre-existing HIV infection.

Subject 10000/0120
This 10 year old HIV-infected female with a history significant for oral candidiasis, pruritic papular eruption, and chronic otitis media, who was started on SQV and LPR/RTV. She developed hemoptysis and was admitted to hospital on Day 217. A chest X-ray showed bilateral hilar adenopathy, bilateral reticulo-nodular infiltration, areas of atelectasis in the right upper and left lower lobes, as well as a left pleural effusion. With the provisional diagnosis of pulmonary TB, sputum smears were performed, and found to be negative for acid-fast bacilli. The subject was transfused with red blood cells for anemia.

Antiretroviral therapy was stopped on Day 218, while anti-tuberculosis therapy was initiated on the same day. The subject was hospitalized with diarrhea on Day 232, after a 3-day history of fever and abdominal pain, She was pale, had epigastric pain, and was found to have hepatomegaly. Serum transaminases were elevated. Antimicrobial therapy was started, but abdominal pain continued. After remaining in the hospital until Day 240, her fever and GI symptoms had resolved.

The subject was again hospitalized on Day 301, with a 2-week history of fever, headache, abdominal pain and diarrhea. Physical examination showed pallor, hepatomegaly, course pulmonary rhonchi, and a herpetic vesicle on the upper lip. The subject was anemic, and stool examination revealed no acid-fast bacilli. Admission diagnosis was chronic gastroenteritis. The subject left the hospital against medical advice on Day 306, and died at home the next day.

The investigator determined that the pulmonary TB was related to the pre-existing HIV infection, and not to study medication. The abdominal pain and diarrhea was also attributed to the subject's underlying disease. The investigator determined that the chronic gastroenteritis was also due to the pre-existing HIV disease.

Medical Officer's comments: The cause of death for all three subjects was deemed to be related to the underlying illness, and the likelihood of an association with study drug is low. Subject 20000/0211 developed bacterial sepsis, subject 10000/0127 meningitis, and subject 10000/0120 developed pulmonary TB (presumptive diagnosis) and chronic gastroenteritis. None of these conditions were believed to be related to the deaths of the subjects.

NV20911

There were no deaths that occurred in this study.

7.3.2 Nonfatal Serious Adverse Events

HIVNAT 017

A total of 24 serious adverse events (SAEs) occurred in this study during the treatment period, as noted by the applicant and corroborated by the reviewer using the submitted datasets. These SAEs occurred in 12 subjects. A summary of these SAEs by SOC, and a listing of the most common SAEs by Preferred Terms, is shown in Table 21.

Table 21. Safety Data Analysis for SAEs in Study HIVNAT 017: Applicant versus Review Team

	DAVP Reviewer	Applicant

	DAVP Reviewer				Applicant
	DAVP-on study[1]		On study or <2 weeks[2]		
	#Patients	#SAEs	#Patients	#SAEs	#SAEs
AE Term (Super Class Term)					
Infections/infestations	8	13	9	14	13
Gastrointestinal	3	5	3	6	6
Blood and Lymphatic	2	4	2	4	2
General Disorders and Administration Site	1	1	1	1	2
Nervous System	1	1	1	1	1
Total	12	24	12	26	24
Most Common SAEs (AE Preferred Term)					#Subjects
Diarrhea	3	4	3	4	4
Anemia	2	4	2	4	2
Bacterial Sepsis	1	2	2	2	2

1. On-study: SAEs occurred during the treatment period.
2. SAE occurred during or within two weeks from the treatment period.

The most common SAEs were diarrhea, anemia and bacterial sepsis, occurring in 4, 4, and 2 subjects, respectively.

Medical Officer's comments: The majority of SAEs were classified as gastrointestinal disorders and infections and infestations. The most common infections and infestations were bacterial sepsis and pneumonia, and the most common gastrointestinal disorder was diarrhea. The safety profile for these pediatric subjects is similar to that seen for adults using Invirase.

An analysis of SAEs that occurred outside the treatment period was conducted by the reviewer (results not shown), and it was discovered that subjects experienced a total of 19 SAEs off study treatment. For the total of 43 SAEs (including both on and off treatment), 18 of these (36%) were categorized under SOC Infections and Infestations, while 12 (24%) were categorized under SOC Gastrointestinal Disorders.

The deaths noted in the dataset are classified under the general disorders and administration site conditions SOC for reasons that are unclear. All three deaths occurred as a result of infections (bacterial sepsis, meningitis, and pulmonary TB and gastroenteritis).

NV20911

A total of 3 subjects experienced 3 SAEs in this study, with 1 in the Low Age group, and 2 in the High Age group. All SAEs were categorized as infections and infestations. There was one case of pneumonia in each age group, and one case of bronchitis in the High Age group.

Table 22. Serious Adverse Events in Study NV20911

Adverse Event	**Low Age Group N = 5**	**High Age Group N = 13**	**All Subjects N = 18**
Infections and Infestations	1 (20%)	2 (15%)	3 (17%)
Bronchitis	0	1 (8%)	1 (6%)
Pneumonia	1 (20%)	1 (8%)	2 (11%)

*Percentages calculated as % in each age group

Medical Officer's comments: There was a low number of subjects who experienced SAEs in study NV20911 compared with study HIVNAT 017. The subjects in study NV20911 were exposed to SQV and RTV, and for a maximum of 48 weeks, while subjects in study HIVNAT 017 were exposed to SQV and LPV/RTV for a maximum of either 96 weeks or 108 weeks (i.e. those in phase 1 received 12 additional weeks of study drug). This longer duration of exposure and addition of LPV may have contributed to the higher number of SAEs seen in study NV20911. In addition, the subjects in study HIVNAT 017 were older and may have been more advanced in their HIV disease status, with less access to previous medical care.

7.3.3 Dropouts and/or Discontinuations

Two subjects in study HIVNAT 017 were withdrawn prematurely from the study due to AEs. Subject 10000/0127 had bacterial meningitis (SAE) and the other subject (10000/0120) had pulmonary TB, which was also considered to be an SAE. There were no subjects who were prematurely discontinued due to laboratory abnormalities.

There were no reported adverse events that led to premature discontinuation of any subject in study NV20911.

7.3.4 Significant Adverse Events

There were no other significant AEs noted in either study HIVNAT 017 or study NV20911.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

None.

7.4.1 Common Adverse Events

HIVNAT 017

A summary of AEs reported during the treatment period of the study by SOC is shown in Table 23. The most commonly reported AEs were infections and infestations (43% of all AEs reported), followed by gastrointestinal disorders (110 subjects, or 47%), gastrointestinal disorders (33 subjects, or 14%), and respiratory, thoracic and mediastinal disorders (29 subjects, or 12%.)

Table 23. HIVNAT 017: Safety Data Analysis for AEs[1]

Adverse Event: Super Class Term (CDMS)	**# Patients**	**#AEs[2]**
# of Patients With AEs[3]	45	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4	6
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1	1
EAR AND LABYRINTH DISORDERS	2	2
ENDOCRINE DISORDERS	3	3
EYE DISORDERS	4	4
GASTROINTESTINAL DISORDERS	17	33
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14	18
HEPATOBILIARY DISORDERS	5	7
INFECTIONS AND INFESTATIONS	39	110
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	1

Adverse Event: Super Class Term (CDMS)	# Patients	#AEs[2]
INVESTIGATIONS	3	4
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	1
NERVOUS SYSTEM DISORDERS	2	2
RENAL AND URINARY DISORDERS	2	2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	23	29
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	10	11
MISSING CODES	2	2
Total	133	236

1. Source: reviewer's analysis.
2. AE occurred during the treatment period.
3. Patients with AE during the treatment period (n=45): 36 in Age 4-<12, 9 in Age >=12.

The majority of AEs that occurred were of moderate/Grade 2 severity (70%). The remainder were mild/Grade 1 (37%), severe/Grade 3 (18%) or life-threatening/Grade 4 (3%); the remainder (13%) were missing from the dataset.

The most frequent AEs were nasopharyngitis (23 AEs), cough (20), pyrexia (13), and diarrhea (8), as shown in Table 24. AEs that occurred at a rate of ≥2% are shown in Table 25.

Table 24. Study HIVNAT 017: Most Frequent AEs[1]

	AE Preferred Term (CDMS)	# Subjects	#AEs
1	NASOPHARYNGITIS	44	23
2	COUGH	21	20
3	PYREXIA	17	13
4	DIARRHOEA	13	8
5	OTITIS MEDIA	10	7
6	IMPETIGO	9	7
7	BRONCHITIS	8	5
8	RHINORRHOEA	6	5
9	HEPATOMEGALY	5	4
10	DENTAL CARIES	5	5
11	VOMITING	5	5
12	ANAEMIA	4	2
13	PNEUMONIA	4	2
14	RASH	4	3
15	BLOOD TRIGLYCERIDES INCREASED	3	2
16	MOUTH ULCERATION	3	2
17	ADDISON'S DISEASE	3	3

	AE Preferred Term (CDMS)	# Subjects	#AEs
18	OROPHARYNGEAL CANDIDIASIS	3	3
19	PHARYNGOTONSILLITIS	3	3
20	TUBERCULOSIS	3	3

1. Source: reviewer's analysis for AEs (>2) during the treatment period.

Table 25. Study HIVNAT 017: AEs During Treatment Period that Occurred at Frequency ≥2%[1]

Adverse Event: Super Class Term (CDMS)	# Subjects	#AEs[2]	%
# of Subjects With AEs	45		
BRONCHITIS	5	8	3%
COUGH	20	21	9%
DENTAL CARIES	5	5	2%
DIARRHOEA	8	13	6%
HEPATOMEGALY	4	5	2%
IMPETIGO	7	9	4%
NASOPHARYNGITIS	23	44	19%
OTITIS MEDIA	7	10	4%
PYREXIA	13	17	7%
RHINORRHOEA	5	6	3%
VOMITING	5	5	2%
Total	187	236	

[1]Source: reviewer's analysis for AEs (>2) during the treatment period.
[2]AEs occurred during the treatment period.

The majority of AEs that occurred were of mild severity (46). The remainder were of moderate severity (13). There were no severe or life-threatening AEs reported.

Medical Officer's comments: The frequency of AEs noted by the applicant, and the nature of these AEs, was corroborated by this reviewer's analysis of the submitted data. There were slight differences between the two analyses, but these were not greatly significant. The safety profile of the SQV combined with RTV in this pediatric population appears to be consistent with that noted in adults. There were fewer AEs noted in the Low Age group compared with the

High Age group of subjects, mostly due to a higher number of AEs in the High Age group classified as gastrointestinal disorders. This finding is consistent with the expected experience of subjects who are using protease inhibitors.

7.4.2 Laboratory Findings

HIVNAT 017

Standard laboratory test parameters were assessed (mean and median values) from screening until Week 12, and every subsequent 12 weeks through Week 96. The applicant notes that there were no significant changes noted in the combined population, or in either of the age groups.

The mean hematocrit fraction (0.34, reference range 0.37 to 0.49) and mean hemoglobin concentration (116 g/L, reference range 130 to 180 g/L) were outside the reference range at baseline. Both parameters normalized by Week 96 in the High Age group, as did the mean hematocrit in the Low Age group; the mean hemoglobin remained below the reference range at Week 96 in the High Age group.

At Week 12, the mean triglyceride levels for all subjects increased to above the upper limit of the reference range and ULN through Week 96.

There were no other clinically significant changes noted in other laboratory test parameter.

NV20911

Laboratory test parameters were assessed by examining the mean changes from baseline to Weeks 8, 12, 24, 36, and 48. It is noted by the applicant that there were few marked changes from baseline in either of the age groups, or in the combined population.

The laboratory test parameters that were outside the reference ranges included: mean hematocrit fraction (0.36, reference range 0.37 to 0.49); mean hemoglobin (119 g/L, reference range 130 to 180 g/L); mean platelets (354 cells/µL, reference range 150 to 350 cells/µL); lymphocytes (5.6 cells/µL, reference range 1.0 to 4.8 cells/µL); alkaline phosphatase (121 U/L, reference range 0 to 115 U/L); and phosphate (1.73 mmol/L, reference range 0.84 to 1.45 mmol/L).

There were no other clinically significant changes noted in other laboratory test parameter.

7.4.3 Vital Signs

HIVNAT 017

The applicant reported no vital sign abnormalities for study HIVNAT 017.

NV20911

In study NV20911, five subjects developed tachycardia that was not sustained when reported.

Abnormally high temperature was experienced by two subjects in the High Age group, and low temperature was experienced by one subject in the High Age group, on at least one occasion.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not obtained as a routine part of the assessments carried out in the two studies.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

No special immunogenicity studies were conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This aspect was not assessed.

7.5.2 Time Dependency for Adverse Events

Adverse events were assessed throughout the treatment periods for both trials. No specific time-dependency was identified

7.5.3 Drug-Demographic Interactions

In study HIVNAT, a total of 100% of males and 96% of females developed at least one AE. In study NV20911, a total of 71% of males and 82% of females developed at least one AE.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not evaluated in either of the two studies. All subjects had underlying HIV infection, and the three deaths appeared to have occurred as a result of opportunistic infections (bacterial meningitis, pulmonary TB, and chronic diarrhea).

7.5.5 Drug-Drug Interactions

All subjects were on more than one drug during each of the studies; in HIVNAT 017, subjects were administered SQV and RTV or LPV/RTV (in addition to one or two additional antiretroviral drugs), while in NV20911 subjects were given SQV and RTV. No formal assessment was made of the drug interactions between SQV and these other drugs.

7.6 Additional Safety Evaluations

Invirase is an approved drug, and this submission did not, therefore, contain any pre-clinical data or analysis. Section 7.6 is therefore not applicable.

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

The baseline z-scores for weight and height in study HIVNAT 017 indicate that the children were fairly small in stature. This may be a function of their nutritional status or genetics (ethnicity, family history, etc). The trend for both weight and height z-scores was in the direction of improvement while on antiretroviral therapy.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

There are no additional submissions that have been received from the applicant. There are no further safety issues other than those that have been previously discussed.

In conclusion, the use of Invirase in the settings of both studies HIVNAT 017 and NV20911 was found to be safe, while tolerability was acceptable. The safety profile was acceptable in younger subjects aged 4 months to < 6 years (study NV20911), and in older subjects aged 4 years to 16 years (study NV20911).

The safety results of the two studies under review appear to be fairly consistent with the known safety profile of Invirase combined with RTV. No update in the safety information of the label is warranted.

8 Postmarket Experience

DAVP and OSE are continuously monitoring post-marketing AEs and reviewing specific events as needed.

9 Appendices

9.1 Literature Review/References

Marón G, Gaur AH, Flynn PM. Antiretroviral therapy in HIV-infected infants and children. Pediatr Infect Dis J 2010;29:360-363

9.2 Labeling Recommendations

None. The applicant will be issued a Complete Response for this sNDA.

9.3 Advisory Committee Meeting

There will be no Advisory Committee meeting convened for this sNDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAFADZWA S VARGAS-KASAMBIRA
01/28/2011

LINDA L LEWIS
01/28/2011