OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	Capsule: 20-628 SE-34 (SDN 252) Tablet: 21-785 SE-11 (SDN 118)
Submission Date	July 29, 2010
Brand Name	Invirase®
Generic Name	Saquinavir Mesylate
OCP Reviewer	Shirley K. Seo, Ph.D.
OCP Team Leader	Sarah M. Robertson, Pharm.D.
Pharmacometrics Reviewer	Jeffry A. Florian, Ph.D.
Pharmacometrics Team Leader	Jogarao V. Gobburu, Ph.D.
OCP Division	DCP IV
OND Division	DAVP
Sponsor	Roche
Relevant IND(s)	41,099
Submission Type	Efficacy supplement (pediatric)
Formulation; Strength(s)	Eq. 200 mg base capsule; Eq. 500 mg base tablet
Dosing regimen (Approved in Adults)	1000 mg twice daily in combination with 100 mg ritonavir twice daily
Sponsor's proposed dosing regimen	(b) (4)
Indication	Treatment of HIV-1 infection in combination with ritonavir and other antiretroviral agents

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1 Executive Summary

Saquinavir mesylate (SQV, Invirase®) is a protease inhibitor indicated for the treatment of HIV-1 infection in combination with ritonavir and other antiretroviral agents. The current recommended dose for Invirase in the treatment of HIV-1 in adults (16 years of age and over) is 1000 mg in combination with 100 mg ritonavir (RTV) twice daily. The sponsor is proposing to add a pediatric dosing regimen for children 2 to <16 years of age using the approved Invirase capsule formulation. No new pediatric formulation is being proposed for marketing. The submission is supported by two pivotal PK and safety studies (HIVNAT017 and NV20911) conducted in children using the approved Invirase capsule at the proposed dose and one supportive PK and safety study (PACTG 397) using a previously marketed soft-gel capsule (Fortovase)®. HIVNAT017 enrolled pediatric subjects ≥3 to ≤16 years of age and NV20911 enrolled pediatric subjects 4 months to <6 years of age. A dose of Invirase was not proposed for patients <2 years of age based on the scarcity of data and wide variability in PK observed in subjects <2 years of age in NV20911.

The Division of Scientific Investigations (DSI) discovered significant deficiencies at the bioanalytical sites of both pivotal studies. The PK data generated by the bioanalytical site for study HIVNAT017 were deemed unusable and irreparable. Therefore, the PK data from this trial, which included data from subjects 3 to <16 years of age, will not be used in determining dosing recommendations for pediatric patients. The PK data generated by the bioanalytical site for NV20911 can be used if a bridging method re-validation experiment is performed. (b) (4) In addition, this data could be used along with PK data from adults (≥16 years) to interpolate PK data for pediatric patients 6 to <16 years of age. These simulated PK results can then be used to support a dosing recommendation for patients 6 to <16 years of age, if the clinical reviewers deem the efficacy and safety data from NV20911 to be sufficient supportive information. However, in the absence of the additional re-validation, no dosing recommendations can be made for pediatric patients in any age range at this time.

1.1 Recommendations

(b) (4) No dosing recommendations for any age range can be provided at this time. (b) (4) (b) (4)

(b) (4)

(b) (4)

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

SQV is currently approved in adults ages 16 years and older for the treatment of HIV-1 infection. (b) (4) (b) (4)

(b) (4)

(b) (4)

Roche has pursued pediatric development of SQV since 1992. Several early pediatric studies indicated that SQV alone would not provide adequate exposures in the pediatric population. Thus, PACTG 397 was initiated with administration of SQV (as Fortovase®) in combination with either nelfinavir (NFV) or ritonavir (RTV) in pediatric patients ages 5 to 16 years old. PACTG 397 showed that SQV dosing without RTV did not

provide adequate exposures in children and led to less well-controlled viral load. Subsequently, at week 16, all subjects were given the option to roll over into another cohort that would study dosing with SQV 50 mg/kg and RTV 100 mg/m^2. Trough SQV concentrations in the subgroup of patients who had <400 copies HIV-1 RNA/mL at week 16 were significantly higher than patients who had >400 copies/mL (1683.85 ng/mL vs. 739.45 ng/mL). The studied dose of SQV/RTV was well-tolerated in this study.

The proposed dose of SQV 50 mg/kg BID selected for evaluation in HIVNAT107 was based on two concepts. First, a previous adult dose for SQV (soft-gel capsule) was 400 mg BID when given in combination with RTV 400 mg BID. (This dose provided AUCτ exposures that are similar to the current recommended Invirase/RTV 1000/100 mg dose.) When the dose was changed to incorporate the low-dose option of RTV (100 mg BID), the SQV dose became 1000 mg BID, which is 2.5-fold higher than the original 400-mg dose. Similarly, because SQV doses of between 15-30 mg/kg boosted with high doses of RTV had been used in small numbers of children with success in matching adult exposures, the same 2.5X factor was applied to this SQV dose in order to pair it with a low dose of RTV. The result is a dose between 37.5 and 75 mg/kg. Additionally, a dose of 50 mg/kg in combination with RTV 100 mg/m^2 in combination with 2 NRTI's was shown to be well-tolerated in study PACTG 397. Thus, the SQV 50 mg/kg dose (in combination with low-dose RTV) was chosen as the dose to be studied.

The goal of study HIVNAT017 was to achieve exposures equal to or exceeding the exposures resulting from the approved adult dose of SQV/RTV 1000/100 mg. A total of 50 pediatric subjects ages 3 to 16 years were included in the safety and efficacy analysis for this study. However, due to DSI's negative inspection results from the HIVNAT017 bioanalytical site, there are essentially no usable PK data to support dosing in this age group. Since the results of this study formed the basis for dose selection in the second pivotal study (NV20911), a substantive review of study HIVNAT017 is included in the appendix.

Based on the results of HIVNAT017, the SQV 50 mg/kg dose and a corresponding RTV dose (Kaletra equivalent) was chosen for further evaluation in NV20911. A total of 18 subjects were included in the safety and efficacy analysis for this study. Subjects who could not swallow intact capsules were allowed to open the Invirase capsules into one of the following vehicles: sugar syrup, sorbitol syrup (for children who could not tolerate glucose or had type I diabetes), baby formula, or jelly jam. The results of NV20911 show that in children ages 2 to <6 years (n=13), SQV 50 mg/kg BID in combination with RTV (3 mg/kg BID for children weighing 5 to <15 kg and 2.5 mg/kg BID for children weighing 15 to 40 kg) provides mean systemic SQV exposures that are approximately 37-200% higher in $AUC_{0\text{-}12h}$ and 42-190% higher in Cmax values than mean adult values (using range of historical means as comparison). However, the means are lower than the highest individual exposures previously observed in adults and still considered to be safe (historical studies). The subject number was too low and the PK data too variable in the 4 months to <2 years of age group to derive appropriate dosing recommendations. The proportion of subjects who attained HIV-1 RNA <50 copies/mL at week 48 (68.8%) was similar to the proportion of adults who attained HIV-1 RNA <400 copies/mL at week 48 (61%; historical results in Invirase label). Adverse events were similar between pediatric subjects and adults with no new or unexpected events occurring during this study.

When the data from HIVNAT017 are excluded, there are PK data for a total of 5 patients in the 4 mos. to <2 yrs. age range and 13 patients in the 2 to <6 yrs. age range

from study NV20911 (Table A). For comparison purposes, a review of literature and information from the Invirase label yielded historical adult PK data in Table B.

Table A Summary of Pediatric SQV PK Parameters from Study NV20911*

Age	**AUC_{0-12h}** (µg*hr/mL) (Range)	**Cmax** (µg/mL) (Range)	**Cmin** (µg/mL) (Range)	**Source of Data**
4 mos. to <2 yrs. (n=5)	**17.3** (2.1-43.8)	**2.7** (0.3-6.9)	**0.77** (0.03-1.09)	NV20911 (n=5)
2 to <6 yrs. (n=15)	**37.3** (10.6-65.3)	**6.1** (1.6-10.3)	**1.8** (0.47-3.4)	NV20911 (n=13)

*Data from this study have been audited at the clinical and bioanalytical sites. The PK data can be valid for determining a dosing recommendation with additional bridging bioanalytical validation experiments.

Table B Historical Adult Mean SQV PK Parameters in HIV-1 Infected Patients

Dosing Regimen	**AUC_{0-12h}** (µg*hr/mL) (Range)	**Cmax** (µg/mL) (Range)	**Cmin** (µg/mL) (Range)
Invirase 1000 mg BID + ritonavir 100 mg BID (geometric mean and 95% CI)*	**14.61** (10.22-20.88)	Not provided	**0.371** (0.25-0.56)
Saquinavir SGC (Fortovase®) 1000 mg BID + ritonavir 100 mg BID (geometric mean and 95% CI)*	**19.09** (13.94-26.12)	Not provided	**0.433** (0.30-0.62)
Invirase 1000 mg BID + ritonavir 100 mg BID (Range of means across studies)**	**12.67-27.67**	**1.92-3.91**	**0.31-0.78**

* From Invirase label

**Mean values are derived from literature references provided by the sponsor and do not represent the highest or lowest observed individual PK parameter. The lowest and highest reported historical AUC_{0-12h} values in adults are 10.2 and 56.6 µg*h/mL.

Overall, the subject number was too low and the PK data too variable for pediatric subjects <2 years of age to provide sufficient dosing recommendations for this age group. Although SQV exposures for pediatric patients ages 2 to <6 years exceeded adult effective exposures, both safety and efficacy data were collected for study NV20911 and support the use of the proposed SQV and RTV doses. When the safety and efficacy data are taken either from study NV20911 or pooled across studies (HIVNAT017, NV20911, PACTG 397), the 50 mg/kg dose of SQV administered with a 3 mg/kg (for body weight from 10 to <15 kg) or 2.5 mg/kg (for body weight from 15 to 40 kg) dose of RTV resulted in similar antiviral efficacy as adults and did not result in any new or unexpected adverse events (see clinical review by Dr. Linda Lewis). If the outcome of the additional bioanalytical re-validation results is positive, then a bridging of PK data can be performed between the 2 to <6 year age range and adult data to support dosing for patients between 6 and <16 years of age. The successful use of this interpolation method would be contingent upon the development of an appropriate population PK model to accurately describe both adult and pediatric PK data as well as acceptable efficacy and safety data to support dosing in the entire age range (2 years to <16 years).

2 Question Based Review (QBR)

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

The formulation and physical-chemical properties of the drug product are the same as that for Invirase® capsules. Saquinavir mesylate has a molecular weight of 766.96. The molecular weight of the free base is 670.86. The composition of Invirase® capsules is given in the table below.

Components [1]	Quality	Function	Actual Weight (mg/ capsule)	Actual weight % (w/w)
Capsule fill mass				
Saquinavir mesylate corresp. to 200.0 mg saquinavir	In house monograph	Drug substance	228.7	(b) (4)
Lactose, (b) (4)	Ph. Eur., NF	(b) (4)		
Cellulose, microcrystalline	Ph. Eur., NF			
Povidone K 30	Ph. Eur., USP			
(b) (4) Sodium starch glycolate	Ph. Eur., NF			
Talc	Ph. Eur., USP			
Magnesium stearate	Ph. Eur., NF			
Total capsule fill weight			*408.0*	(b) (4)
Capsule shell		(b) (4)		
Body:				
Iron oxide black (b) (4)	(b) (4)			
Iron oxide red (b) (4)				
Iron oxide yellow (b) (4)				
Titanium dioxide (b) (4)	Ph. Eur., USP			
(b) (4) (b) (4) Gelatine	Ph. Eur., NF			
Cap:				
Iron oxide black (b) (4) (b) (4)	(b) (4)	(b) (4)		
Iron oxide yellow (b) (4)				
(b) (4) FD & C blue 2 (b) (4)				
Titanium dioxide (b) (4)	Ph. Eur., USP			
(b) (4) Gelatine (b) (4)	Ph. Eur., NF			
Capsule shell weight			97.0	
		Total capsule weight	**505.0**	

(b) (4)

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2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Saquinavir is an inhibitor of HIV-1 protease. In combination with ritonavir and other antiretroviral agents, saquinavir is currently indicated for the treatment of HIV-1 infection in (16 years of age and older).

2.1.3. What are the proposed dosage(s) and route(s) of administration?

(b) (4)

Ritonavir should be taken at the same time as Invirase, and within 2 hours after a meal. If Invirase is to be taken with Kaletra (LPV/RTV), then no additional ritonavir is needed.

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Two pivotal studies were used in support of the dosing recommendations for pediatric subjects: HIVNAT017 and NV20911. An additional bioavailability study, supportive pediatric study, and palatability study were also included in the submission. These studies were not pivotal in the determination of an appropriate pediatric dose; however, because they provide supportive information, a brief review of each of those studies is provided in the appendix of this review.

HIVNAT017 was a single-arm, non-randomized, open label clinical trial that included 50 PI-naïve HIV-1 infected children ages 4 to ≤16 years old who were previously failing NRTI- and/or NNRTI-containing ARV regimens. The study assessed 96 weeks of treatment with LPV/RTV 230/57.5 mg/m^2 and SQV 50 mg/kg BID in all patients. Whole 500 mg tablets or 200 mg capsules were administered (no opening of capsules). Intensive PK sampling at steady-state was conducted in a subset of 20 subjects at week 12 of the study. The primary objectives of the study were to assess the PK parameters, treatment response, safety, and tolerability of SQV 50 mg/kg BID in

pediatric subjects. Because the antiviral activity of SQV can be extrapolated from the adult population, regulatory approval of the pediatric indication would be dependent on matching or exceeding adult SQV exposures at the approved dose.

NV20911 was a non-randomized, open label, 48-week study in pediatric subjects ages 4 months to <6 years old. The study evaluated the previously studied 50 mg/kg BID dose of SQV (in HIVNAT017) along with a RTV dose of 3 mg/kg BID for children weighing 5 to <15 kg, 2.5 mg/kg BID for children weighing from 15 to 40 kg, and 100 mg BID for children weighing >40 kg. The doses of RTV roughly correlated with the RTV portion of Kaletra that was previously used in HIVNAT017. If the children in this study were not able to swallow Invirase capsules, the capsules were opened and mixed with one of the following vehicles (previously studied in a bioavailability study): sugar syrup (sorbitol syrup could be used for children with Type I diabetes or glucose intolerance), jam or baby formula. The primary objectives of the study were to assess the PK parameters, treatment response, safety, and tolerability of SQV/RTV at the specified doses in pediatric subjects. Again, because the antiviral activity of SQV can be extrapolated from the adult population, regulatory approval of the pediatric indication would be dependent on matching or exceeding adult SQV exposures at the approved dose

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The clinical endpoints for SQV used for the basis of the original NDA approval are reduction in viral load (measured as copies/mL of HIV-1 RNA) and increase in CD4 cell counts. However, because antiviral response to protease inhibitor therapy is not expected to be different between the adult population and pediatrics for a given level of exposure, efficacy can be extrapolated from the adult population to the pediatric population in the treatment of HIV-1 infection. Thus, if the adult exposures resulting from the approved dose are matched or exceeded in the pediatric population at the proposed dose (and is accompanied by acceptable safety data), then this data is sufficient to support a dosing regimen in pediatric patients. This approach is the basis of the current submission.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, plasma SQV concentrations were appropriately measured. No formal exposure-response analysis was conducted in any of the pivotal or supportive studies submitted.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Prior to NDA approval of Invirase (1996), the sponsor conducted an informal PK/PD analysis in one of their exploratory phase I/II studies in

patients to evaluate an exposure-response relationship between SQV AUC and decrease in viral load and change in CD4 count. The SQV doses studied at that time were 600 mg q4h and 1200 mg q4h (without RTV). A significant correlation was observed between SQV AUC and decrease in HIV-1 RNA. Those data were limited; however, a preliminary relationship was established between higher SQV concentrations and greater antiviral activity.

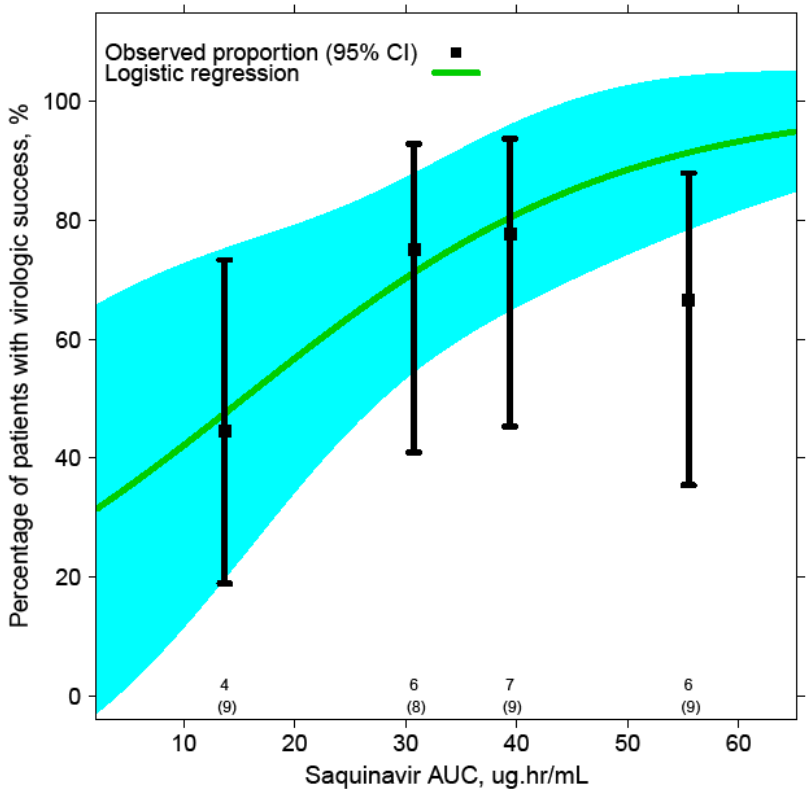
Subsequently, later formulations of SQV had increased bioavailability and lowered the pill burden for patients as well as reduced the frequency of dosing. Over time, the doses of Invirase evolved such that mean SQV AUCτ and Cmin increased nearly 17-fold and 5-fold, respectively, and included RTV in the dosing regimen. An exposure-response relationship has not been established for adults at the currently approved higher SQV exposure. However, a trough range of 100-250 ng/mL has been recommended as a target for therapeutic drug monitoring (TDM) of SQV in adults with wild-type virus (DHHS Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents, December 2009).

2.2.4.2 Is there evidence of an exposure-response relationship for efficacy in pediatrics administered SQV/RTV?

Exposure-Response: Combined Pivotal Pediatric Trial Analysis

A significant exposure response relationship was identified between SQV exposure ($AUC_{0\text{-}12h}$) and percent of patients achieving virologic success (HIV-1 RNA <50 copies/mL at Week 48) from NV20911 and HIVNAT017. A logistic regression was performed using outcome data from both pivotal pediatric trials (NV20911: n=18; HIVNAT017: n=17) versus SQV $AUC_{0\text{-}12h}$ (Figure 1). The two patients with the $AUC_{0\text{-}12h}$ 116 and 203 µg·hr/mL from HIVNAT017 were removed from the analysis as these values exceeded highest reported adult SQV $AUC_{0\text{-}12h}$ from the SQV label (56.6 µg·hr/mL). A significant exposure-response relationship was identified (p-value = 0.016) between percent of patients achieving virologic success and SQV $AUC_{0\text{-}12h}$ with a mean (95% CI) odds ratio (OR) of 1.28 (1.15; 1.44) for a 4.2 µg·hr/mL change in exposure. The upper quartile had a slightly lower response rate than the middle two quartiles and may indicate that the percent of patients achieving virological success saturates above 30 µg·hr/mL.

Figure 1: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus Saquinavir AUC from NV20911 and HIVNAT017.

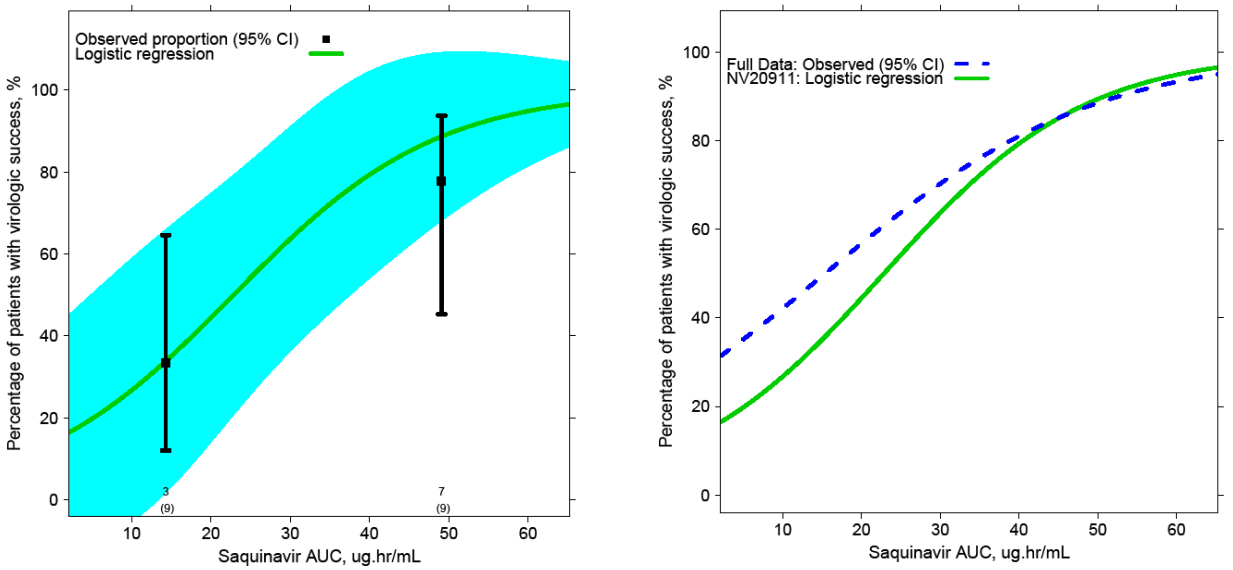


Exposure-Response: Analysis of NV20911

A significant exposure-response relationship was identified between SQV exposure ($AUC_{0\text{-}12h}$) and percent of patients achieving virologic success (HIV-1 RNA <50 copies/mL at Week 48) using only data from NV20911 (n=18).

Similar to the previous exposure-response analysis, a logistic regression was performed using outcome data from NV20911 (n=18) versus SQV $AUC_{0\text{-}12h}$ (Figure , left). There analysis was motivated by two concerns: i) the efficacy data from HIVNAT017 was reliable but SQV $AUC_{0\text{-}12h}$ from the same study was not obtained using validated bioanalytical methods; and ii) HIVNAT017 also included lopinavir as part of the active regimen. In contrast, only 8 of the pediatrics 2 through 5 were on lopinavir in NV20911. A significant exposure-response relationship was identified (p-value = 0.011) between percent of patients achieving virologic success and SQV $AUC_{0\text{-}12h}$ with a mean (95% CI) odds ratio (OR) of 1.39 (1.19; 1.63) for a 4.2 µg·hr/mL change in exposure. The exposure-response relationship identified using only NV20911 data was steeper likely due to response driven solely by SQV exposure instead of a combination of SQV with lopinavor. Indeed, if the logistic regression results from the two analyses are plotted on top of each other (Figure , right), similar profiles are observed with the exception of lower SQV $AUC_{0\text{-}12h}$. It is possible that lopinavir is driving the increased response in this region and that the overall response rate is saturating at higher exposures where the two analyses converge.

Figure 2: Percentage of Patients Achieving Virologic Success (<50 Copies/mL) Versus Saquinavir AUC from NV20911 (left). Overlayed Mean Logistic Regression Results from the Full Data Set and NV20911 Versus Saquinavir AUC (right).



2.2.4.3. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

No clear exposure-response relationship with respect to safety has been identified. The main adverse events that arose out of the pediatric studies were diarrhea and vomiting. These events are similar to the adverse events previously reported in adults taking Invirase/RTV 1000 mg/100 mg BID (Invirase label).

Invirase/RTV has been shown to cause PR prolongation and also dose-dependent QT prolongation. Torsades de pointes has been reported rarely during the post-marketing period. The Cmax achieved in the thorough QTc prolongation study on day 3 (at the time of maximal CYP3A4 inhibition by RTV) at the therapeutic dose, is approximately 75% higher than the mean steady-state Cmax achieved in HIVNAT017. At the supratherapeutic dose (1500/100 mg), the Cmax achieved in the tQTc study was ~148% higher.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the proposed dosing regimen is supported by well-established PK and efficacy data in adults (see 2.2.1 and 2.2.2 above).

2.2.5. What are the PK characteristics of saquinavir?

SQV is 98% protein bound and has a volume of distribution of 700 L. Following an intravenous radioactive dose of SQV, 81% and 3% of the radioactivity was recovered in feces and urine, respectively. A high-fat meal increases SQV AUC and Cmax 2-fold as compared with a low-fat meal. SQV is primarily metabolized by hepatic CYP3A4 and undergoes extensive first-pass metabolism.

Similar bioavailability was demonstrated when Invirase 500 mg film-coated tablets (2 x 500 mg) and 200 mg capsules (5 x 200 mg) were administered with low-dose ritonavir (100 mg) under fed conditions. The ratio of mean exposures (90% confidence intervals) of tablets vs capsules was 1.10 (1.04-1.16) for AUC_{inf} and 1.19 (1.14-1.25) for Cmax. Steady-state SQV AUC, Cmax, and Cmin in healthy subjects are approximately 50% higher than that observed in HIV-1-infected patients. Representative steady-state PK parameters for SQV when administered as Invirase/RTV 1000 mg/100 mg in HIV-1 infected patients are as follows:

Dosing Regimen	**N**	**AUC_{τ} (ng·h/mL)**	**AUC_{24h} (ng·h/mL)**	**C_{min} (ng/mL)**
INVIRASE 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	14607 (10218-20882)	29214	371 (245-561)

2.2.6 Do the studied pediatric saquinavir/ritonavir doses result in similar saquinavir exposure to that observed in adults?

The studied pediatric doses in pediatrics 2 through 5 years (NV20911) and 6 through 16 years (HIVNAT017) resulted in a 160% and 240% increase in AUC_{0-12h}, respectively, compared to historical data in adults. The additional increase in pediatrics 6 through 16 years was driven by two patients with AUC_{0-12h} 116 and 203 µg·hr/mL. Excluding those two patients, the mean increase in AUC_{0-12h} was 150% compared to historical data in adults.

2.2.7 Can the pediatric SQV exposures be predicted from modeling and simulation based on the adult data?

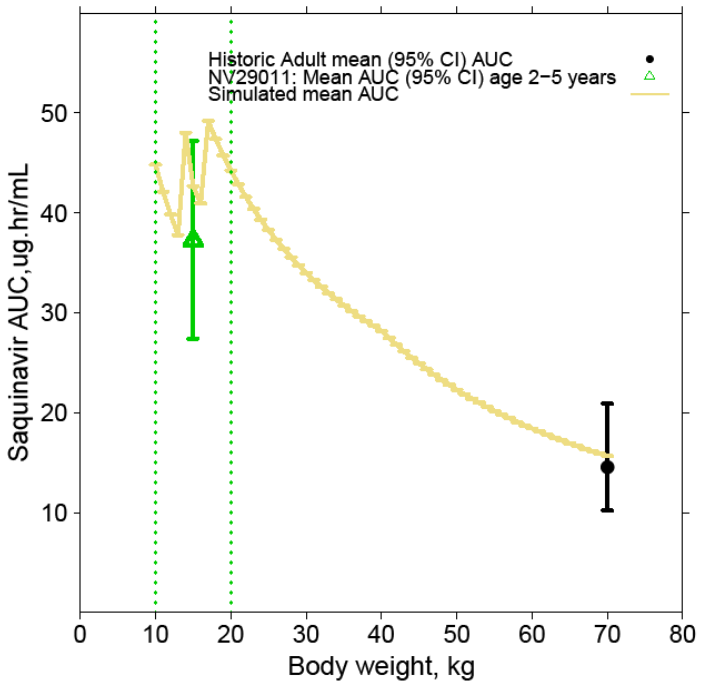
SQV exposures for pediatrics 2 through 6 are accurately predicted based on adult SQV exposures from the label.

- Observed mean SQV exposures for pediatrics 2 through 5 years treated with the sponsor's proposed doses (b) (4) at either 3 mg/kg q12h for children weighing 5 to <15 kg or 2.5 mg/kg q12h for children weighing 15 to 40 kg) are accurately predicted using SQV and RTV exposure relationships from the literature (observed AUC: 37.3 µg·hr/mL; predicted AUC: 37.8–49.2 µg·hr/mL).
- The doses proposed by the sponsor have maximum SQV exposure in pediatrics 10 through 20 kg (42.9 µg·hr/mL; 200% increase over adult mean), and decrease to the adult mean value with increasing body weight. Simulations for pediatrics 6 through 16 years predict mean SQV AUC_{0-12} ranging between 42.9 µg·hr/mL for a 21 kg pediatric subject and 18.4 µg·hr/mL for a 60 kg pediatric subject.

For a 70-kg adult administered 1000/100 mg SQV/RTV q12h, the predicted adult AUC_{0-12h} is 15.7 µg·hr/mL, which is in good agreement with the mean SQV AUC_{0-12h} for the same dose and formulation from the SQV label (mean (95% CI): 14.6 (10.2; 20.9)

μg·hr/mL). Likewise, mean $AUC_{0\text{-}12h}$ for pediatrics 2 through 5 years are predicted to range between 37.8–49.2 μg·hr/mL compared to observed mean exposures of 37.3 μg·hr/mL observed in study NV20911. Mean SQV predictions for pediatrics 10–70 kg treated according to the sponsor's dosing recommendations, mean ± 95% CI SQV exposures from NV20911, and historic mean ± 95% CI exposures from 1000/100 mg SQV/RTV q12h are shown in Figure 3 below.

Figure 3: Simulated mean SQV exposures for the proposed sponsor's pediatric dosing versus body weight. Observed mean and 95% CI SQV exposures from NV20911 (pediatrics, green triangle) and the SQV label (adults, black circle) are shown for a 15 kg and 70 kg subject, respectively. SQV dosing in NV20911 was 600, 800, and 1000 mg q12h for pediatrics ≥10 through <14 kg, ≥14 through <17 kg, and ≥17 through <20 kg, respectively.



2.3 Analytical Section

2.3.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In study HIVNAT017, quantitative determination of SQV and RTV in human plasma was performed using an HPLC method. In study NV20911, SQV and RTV and the internal standards were isolated from heparin plasma by liquid-liquid extraction and plasma SQV and RTV concentrations were determined by HPLC with tandem mass spectrometric detection (LC-MS/MS).

2.3.2. Which metabolites have been selected for analysis and why?

No SQV metabolites were measured for this study. Based on in vitro studies, saquinavir is rapidly metabolized to a range of inactive mono- and di-hydroxylated compounds.

2.3.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Since SQV is highly protein bound the most likely moiety measured is total, which is mostly comprised of bound SQV.

2.3.4 What bioanalytical methods are used to assess concentrations?

The analytes and the internal standards were isolated from heparin plasma by liquid-liquid extraction and SQV concentrations were determined by HPLC with tandem mass spectrometric detection.

2.3.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The ranges of the standard curves for SQV and RTV in study HIVNAT017 were 0.04-26.5 µg/mL and 0.048 to 32.3 µg/mL, respectively. The ranges of the standard curves for both SQV and RTV in study NV20911 were 1.0-100 ng/mL (low range assay) and 10 to 10,000 ng/mL (high range assay). These standard curve ranges were appropriately wide and adequate for the concentrations obtained in this study without necessitating dilution of any samples. An un-weighted linear regression of the logarithm of the analyte concentration and the logarithm of the mean peak height ratio was used to obtain the calibration curves for study HIVNAT017 while a weight of $1/x^2$ was used in the fitting of the calibration curve for study NV20911.

2.3.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ and ULOQ for SQV in study HIVNAT017 were 0.04 and 26.5 µg/mL, respectively. The LLOQ and ULOQ for RTV were 0.048 and 32.3 µg/mL, respectively. The LLOQ and ULOQ for both SQV and RTV in study NV20911 were 1.0 and 10,000 ng/mL, respectively.

2.3.4.3 What are the accuracy and precision at these limits?

Study HIVNAT017

Analyte (concentrations)	**LLOQ**	**ULOQ**
SQV (0.04, 26.5 µg/mL)	Accur: 99.42% Prec: 1.31%	Accur: 102.46% Prec: 2.11%
RTV (0.048, 32.3 µg/mL)	Accur: 106.85% Prec: 4.49%	Accur: 103.22% Prec: 2.35%

Study NV20911

Analyte	LLOQ	ULOQ
SQV (1.0, 10,000 ng/mL)	Accur: 101.9% Prec: 9.4%	Accur: 102.7% Prec: 5.5%
RTV (1.0, 10,000 ng/mL)	Accur: 102.0% Prec: 7.8%	Accur: 104.4% Prec: 5.5%

Note: Although these are the bioanalytical data presented in the submission, DSI was not able to locate any records of the validation at the bioanalytical site for study HIVNAT017. (Please see 1-20-2011 review by Dr. Michael Skelly and Dr. Martin Yau for full details.)

2.3.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

For study HIVNAT017, no source data were locatable for any of the validation experiments performed for the bioanalytical method. Thus, DSI was not able to audit these data. DSI recommends that the validation and study records are insufficient to demonstrate the reliability of the bioanalytical method. (Please see 1-20-2011 review by Dr. Michael Skelly and Dr. Martin Yau for full details.)

For study NV20911, SQV in plasma was stable at -20^{o} C for 356 days, stable for 5 freeze-thaw cycles, stable at room temperature (22^{o} C) for 24 hours, and stable in eluent at room temperature for 95 hours. RTV in plasma was also stable at -20^{o} C for 356 days, stable for 5 freeze-thaw cycles, stable at room temperature (22^{o} C) for 24 hours, and stable in eluent at room temperature for 95 hours. DSI found that the bioanalytical site failed to use freshly prepared calibrators in the validations of the saquinavir and ritonavir assays. Additionally, they failed to evaluate potential interferences from concomitant medications. (Please see 1-20-2011 review by Dr. Michael Skelly and Dr. Martin Yau for full details.)

2.3.4.5 What is the QC sample plan?

For study HIVNAT017, the following QC concentrations for SQV were assessed in each run: 0.133 µg/mL, 1.3 µg/mL, and 6.63 µg/mL. For RTV, the following QC concentrations were assessed in each run: 0.162 µg/mL, 1.62 µg/mL, and 8.08 µg/mL. For study NV20911, the following QC concentrations for both SQV and RTV were assessed in each run: 3.0 ng/mL, 20 ng/mL, and 80 µg/mL (low range assay) and 30 ng/mL, 500 ng/,L, and 80,000 ng/mL.

3 Labeling Recommendations (Major Changes Pertaining to Clinical Pharmacology)

The sponsor has proposed the following dosing recommendations for pediatric subjects:

(b) (4)

(b) (4)

Because DSI has determined that the bioanalytical results and thus the PK data are invalid for studies HIVNAT017 and NV20911, no pediatric dosing recommendations can be made at this time. The bioanalytical results may be re-validated for NV20911, but the same cannot be done for HIVNAT017. (Refer to the *Executive Summary* (1) and *Introduction* (1.1) sections for further details.) The proposed wording for the label is pending the sponsor's re-validation results and possible PK interpolation.

4 Appendix

4.1 Individual Study Review—Pivotal Study (HIVNAT017)

Title (Study HIVNAT017, Protocol ML19540)

"Lopinavir/r with saquinavir in HIV-infected children: Pharmacokinetics and 2-year treatment follow-up"

Objectives

To evaluate the following in PI-naïve, HIV-1 infected children (3 to ≤16 years of age) previously exposed to NRTI- and/or NNRTI-containing ARV regimens administered 230/57.5 mg/m^2 of LPV/RTV with 50 mg/kg of SQV (Invirase) q12h:

- Pharmacokinetic parameters
- Treatment response (clinical, virological, immunological responses), safety and tolerability

Study Dates and Location(s):

November 14, 2003 – June 12, 2007

The clinical portion of the trial was conducted at two different sites: 1.) the HIV NAT center in Bangkok, Thailand and 2.) Khon Kaen University in Khon Kaen, Thailand.

Study Doses Used

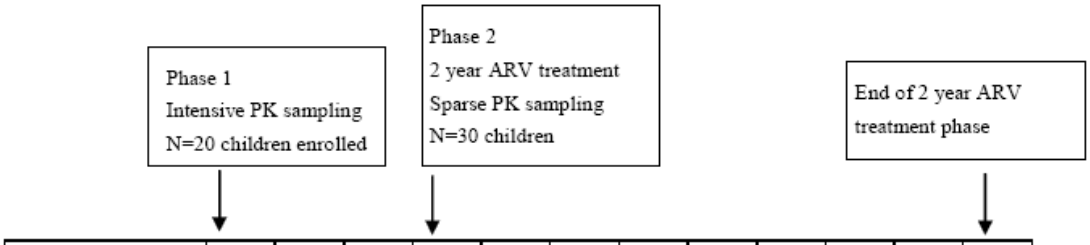
LPV/RTV: 230/57.5 mg/m^2 q12h

SQV: 50 mg/kg q12h

Study Design

This study was a single-arm, non-randomized, open-label clinical trial in PI-naïve, HIV-infected children (3 to ≤16 years of age) who were previously exposed to and were failing an NRTI- and/or NNRTI-containing ARV regimens (see Figure 1 below for study design). A total of 50 subjects were enrolled. The study assessed 96 weeks of treatment with LPV/RTV 230/57.5 mg/m^2 and SQV 50 mg/kg in all patients with intensive PK in a subset of 20 subjects. These 20 subjects were enrolled in phase 1 of the study to undergo intensive PK sampling at steady-state (12 weeks) and then continued directly into phase 2 (96 weeks of treatment). An additional 30 patients were enrolled directly into phase 2 of the study schedule, which included the collection of sparse PK samples for dose adjustment, if needed.

Figure 1 Study Design Schematic



Study Week				0	12	24	36	48	60	72	84	96
Time on ARV (weeks) for first group of 20 children	0	4	8	12	24	36	48	60	72	84	96	108
Time on ARV (weeks) for second group of 30 children				0	12	24	26	48	60	72	84	96

Two key protocol amendments were made after the start of the study:

1. After the initial results of the PK subset revealed that most children had a LPV and SQV Cmin value several fold above the IC_{50} of each compound, the sponsor proposed to extend the study to an additional 30 children and introduce an analysis at week 24 in order to determine the appropriateness of the current dosing of LPV/RTV + SQV.
2. The sponsor proposed to revise the study procedures and laboratory studies to include a second group of 30 children who would be enrolled into the 2-year treatment and follow-up phase.

Subjects were instructed to take their medications with food in the morning and evening at regular 12-hour time intervals. On the PK sampling day, drug administration was directly observed and was ingested with a standard breakfast in the morning.

Formulation(s) Used

LPV/RTV was administered as soft capsules of 133/33 mg LPV/RTV each, or oral solution containing 80/20 mg LPV/RTV per mL. SQV was administered as hard-gel capsules of 200 mg or film-coated tablets of 500 mg SQV each. These trial medications could also be combined with 1 or 2 nucleoside analogues chosen based upon genotypic resistance profile of the virus and ARV history (at the discretion of the investigator).

Dose Rationale

The rationale for the SQV dose was based on two concepts. First, a previous adult dose for SQV (soft-gel capsule) was 400 mg BID when given in combination with RTV 400 mg BID. This dose provided AUCτ exposures that are similar to the current recommended Invirase/RTV 1000/100 mg dose (Buss, N., 2001). When the dose was changed to incorporate the low-dose option of RTV (100 mg BID), the SQV dose became 1000 mg BID, which is 2.5 times the original 400-mg dose. Similarly, because SQV doses of between 15-30 mg/kg boosted with high doses of RTV have been used in small numbers of children with success in matching adult exposures, the same 2.5X factor was applied to this SQV dose in order to pair it with a low dose of RTV. The result is a dose between 37.5 and 75 mg/kg. Additionally, a dose of 50 mg/kg in combination with RTV 100 mg/m^2 in combination with 2 NRTI's was shown to be well-tolerated (in study PACTG 397). Thus, the SQV 50 mg/kg dose (in combination with low-dose RTV) was chosen as the dose to be studied.

Key Inclusion Criteria:

-Confirmed HIV-1 infection by HIV-DNA or HIV RNA PCR at any age or by HIV ELISA if ≥18 months old
-Subject was ≤16 years of age at the day of the first dosing.
-Subject was failing a current NRTI and/or NNRTI containing regimen and was naïve to protease inhibitor containing therapy.
-Results of biochemistry and hematology testing were to be within pre-specified ranges.
-Subject is able to swallow capsules

Key Exclusion Criteria:

-History of sensitivity/idiosyncrasy to lopinavir, ritonavir, saquinavir or chemically related compounds or excipients which could have been employed in the trial.
-Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.

-Use of any concomitant medication, including the drugs listed below, that may interfere with the pharmacokinetics of LPV/r or SQV.

– NNRTIs
– Rifampicin
– Rifabutin
– Phenobarbital
– Phenytoin
– Carbamazepine
– Dexamethasone
– Ketoconazole
– Clarithromycin

-Subjects who were pregnant

Blood Sampling for PK

Intensive PK sampling for Group 1 took place during week 12 at 0, 2, 4, 6, 8, 10, and 12 hours post-dose. Additional samples for evaluation of Cmin were also taken at 24, 36, 48, 60, 72, 84, 96 weeks. Sparse sampling for subjects in Group 2 took place at Cmin (~12 hours post-dose) during weeks 4, 12, 24, 36, 48, 60, 72, 84, and 96. Sparse sampling for C_{4hr} took place at weeks 4, 12, and 24.

Bioanalytical Validation

Quantitative determination of LPV, RTV, and SQV in human plasma was performed using an HPLC method. Plasma samples were collected between December 18, 2003 and April 4, 2004. Samples were kept frozen in a -20° C freezer at the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) Research Laboratory until analyzed. Samples were analyzed from February 3, 2004 to April 27, 2004.

LPV

The accuracy and precision of the calibration standards for the determination of LPV plasma concentrations are presented in the table below.

Analyte	Run Number	STD 1 -	STD 2 0.108 mg/L	STD 3 0.308 mg/L	STD 4 1.076 mg/L	STD 5 3.075 mg/L	STD 6 10.763 mg/L	STD 7 30.75 mg/L
Lopinavir	PI # 62	-	0.110	0.303	1.063	3.005	11.334	30.133
	PI # 70	-	0.110	0.304	1.081	3.017	10.795	31.040
	PI # 76	-	0.111	0.304	1.057	3.026	10.790	31.268
	PI # 77	-	0.116	0.293	1.039	2.969	10.939	31.728
	Mean	-	0.112	0.301	1.060	3.004	10.965	31.042
	% Rel Err	-	3.47	-2.27	-1.48	-2.30	1.87	0.95
	% CV	-	2.70	1.82	1.64	0.83	2.33	2.16

All precision and accuracy values are within acceptable limits (<15% deviation for all concentrations). The LLOQ for LPV was 0.108 µg/mL. The inter-assay precision and accuracy for the QC samples ranged from 1.27-4.78% and 96.25-99.59%, respectively. Long-term stability for LPV was demonstrated at -20^{o} C for 4 months (99.8% of nominal concentrations at two different concentrations).

RTV

The accuracy and precision of the calibration standards for the determination of RTV plasma concentrations are presented in the table below.

Analyte	Run Number	STD 1 0.048 mg/L	STD 2 0.113 mg/L	STD 3 0.323 mg/L	STD 4 1.131 mg/L	STD 5 3.23 mg/L	STD 6 11.305 mg/L	STD 7 32.3 mg/L
Ritonavir	PI # 62	0.051	0.112	0.307	1.090	3.149	12.039	32.235
	PI # 70	0.053	0.110	0.303	1.101	3.133	11.545	33.557
	PI # 76	0.053	0.113	0.297	1.059	3.154	11.565	34.078
	PI # 77	0.048	0.124	0.303	1.082	3.101	11.559	33.491
	Mean	0.051	0.114	0.302	1.083	3.134	11.677	33.340
	% Rel Err	6.85	1.13	-6.35	-4.26	-2.96	3.29	3.22
	% CV	4.49	5.50	1.41	1.65	0.77	2.07	2.35

All precision and accuracy values are within acceptable limits (<15% deviation for all concentrations). The LLOQ for RTV was 0.04 µg/mL. The inter-assay precision and accuracy for the QC samples ranged from 1.07-4.96% and 92.6-101.54%, respectively. Long-term stability for RTV was demonstrated at -20° C for 1 year (92-97% of nominal concentrations at 3 different concentrations).

SQV

The accuracy and precision of the calibration standards for the determination of SQV plasma concentrations are presented in the table below.

Analyte	Run Number	STD 1 0.04 mg/L	STD 2 0.093 mg/L	STD 3 0.265 mg/L	STD 4 0.928 mg/L	STD 5 2.65 mg/L	STD 6 9.275 mg/L	STD 7 26.5 mg/L
Saquinavir	PI # 62	0.042	0.092	0.255	0.894	2.578	9.919	26.296
	PI # 70	0.043	0.091	0.252	0.908	2.578	9.420	27.376
	PI # 76	0.042	0.095	0.252	0.884	2.591	9.418	27.523
	PI # 77	0.043	0.092	0.249	0.890	2.562	9.585	27.410
	Mean	0.043	0.092	0.252	0.894	2.577	9.586	27.151
	% Rel Err	-0.58	-4.97	-4.97	-3.63	-2.75	3.35	2.46
	% CV	1.31	1.68	1.05	1.12	0.47	2.46	2.11

All precision and accuracy values are within acceptable limits (<15% deviation for all concentrations). The LLOQ for SQV was 0.048 µg/mL. The inter-assay precision and accuracy for the QC samples ranged from 1.41-5.33% and 96.25-99.59%, respectively. Long-term stability for SQV was demonstrated at -20° C for 1 year (90-96% of nominal concentrations at 3 different concentrations).

Reviewer's Comments:
-The longest a potential study sample could have been stored at -20° C before being analyzed is 4 months and 1 week (based on dates of assay). The long-term storage stability testing for LPV demonstrated stability for 4 months while RTV and SQV were both stable for 1 year. Although the LPV stability testing is off by 1 week, the results show that the concentration after 4 months was 99.8% of the nominal concentration at 2 different concentrations tested. Therefore, it is unlikely that 1 additional week would make a significant difference in the stability of LPV in plasma. The within-study bioanalytical validation results are acceptable.
-After DSI's inspection of the bioanalytical site for this study, it was determined that the results from the analysis are not usable due to several significant deficiencies that could not be repaired. (Please see 1-20-2011 review by Dr. Michael Skelly and Dr. Martin Yau for full details.)

Results

Demographics

Patient groups are identified as:

Group 1 - the group of children enrolled during Part 1 of the study and then continued into Part 2 (N=20).

Group 2 - the group of children enrolled during Part 2 of the study (N=30).

Age groupings are designated as:

Low - the group of children ≥3 years to <12 years of age

High - the group of children ≥12 years to ≤16 years of age

Below is a table detailing the demographics of all subjects in both groups.

Table 1 Combined Demographics (N=50)

	AGE GROUP		ALL PATIENTS
	LOW	HIGH	
N of Population	40	10	50
Age (years)			
n	40	10	50
Mean	8.0	12.5	8.9
SD	1.9	1.0	2.5
Median	8.0	12.0	9.0
Min-Max	4.0 - 11.0	12.0 - 15.0	4.0 - 15.0
Sex			
n	40	10	50
Male	17 (42.5%)	5 (50.0%)	22 (44.0%)
Female	23 (57.5%)	5 (50.0%)	28 (56.0%)
Height (cm)			
n	40	10	50
Mean	115.8	137.0	120.0
SD	11.0	13.1	14.2
Median	116.0	136.7	119.0
Min-Max	92.0 - 147.0	120.0 - 159.0	92.0 - 159.0
Weight (kg)			
n	40	10	50
Mean	20.1	31.6	22.4
SD	5.3	10.2	7.9
Median	19.4	29.5	20.0
Min-Max	10.7 - 40.0	18.0 - 55.0	10.7 - 55.0
Body Surface Area (1)			
n	40	10	50
Mean	0.8	1.1	0.9
SD	0.1	0.2	0.2
Median	0.8	1.1	0.8
Min-Max	0.6 - 1.3	0.8 - 1.5	0.6 - 1.5

n represents number of Patients contributing to summary statistics
Percentages are based on n (number of valid values).
(1) calculated according to: body surface area = sqrt[height(cm) * body weight(Kg)/3600]

Concomitant Antiretroviral Treatments

The majority of subjects in the study were receiving concomitant ART's at baseline (93%, 37/40 in the low age group and 70%, 7/10 in the high age group). NRTI's were the most commonly used ART's at baseline with lamivudine (48%), stavudine (44%) and zidovudine (44%) being the most commonly used agents. Nevirapine and efavirenz were taken by 24% (n=12) and 12% (n=6), respectively. (The table below shows a summary of all concomitant ART's used by age group.)

Concomitant ARVs

Class/ Other Treatment or Procedure	LOW N = 40 No. (%)	HIGH N = 10 No. (%)	ALL PATIENTS N = 50 No. (%)
ALL CLASSES			
Total Pts with at Least one Treatment	37 (93)	7 (70)	44 (88)
Total Number of Treatments	89	19	108
NUCLEOSIDE/NUCLEOTIDE ANALOGUES			
Total Pts With at Least one Treatment	36 (90)	7 (70)	43 (86)
LAMIVUDINE	19 (48)	5 (50)	24 (48)
STAVUDINE	19 (48)	3 (30)	22 (44)
ZIDOVUDINE	18 (45)	4 (40)	22 (44)
DIDANOSINE	14 (35)	1 (10)	15 (30)
ZALCITABINE	1 (3)	-	1 (2)
Total Number of Treatments	71	13	84
NON-NUCLEOSIDE REV. TRANSCRIPTASE INHIB.			
Total Pts With at Least one Treatment	15 (38)	2 (20)	17 (34)
NEVIRAPINE	11 (28)	1 (10)	12 (24)
EFAVIRENZ	4 (10)	2 (20)	6 (12)
Total Number of Treatments	15	3	18
ANTIVIRAL AGENTS			
Total Pts With at Least one Treatment	2 (5)	2 (20)	4 (8)
ACICLOVIR	2 (5)	2 (20)	4 (8)
Total Number of Treatments	2	2	4
ANTIRETROVIRALS			
Total Pts With at Least one Treatment	1 (3)	1 (10)	2 (4)
LAMIVUDINE/NEVIRAPINE/STAVUDINE	1 (3)	1 (10)	2 (4)
Total Number of Treatments	1	1	2

Reviewer's Comments:
-There were a total of 7 subjects included in the PK subset who were taking nevirapine at the time of PK assessment (none were taking efavirenz). Nevirapine is a known CYP3A4 inducer and has been shown to decrease SQV exposures (by ~25%) when SQV is administered without RTV. No studies have been conducted investigating the effect of nevirapine on SQV exposures when co-administered with RTV. However, when nevirapine's effects on fosamprenavir was compared with and without co-administration of RTV, there was a less pronounced effect of nevirapine when RTV was on board as compared to unboosted fosamprenavir (25-33% decrease in fosamprenavir exposures without RTV boosting and no change when fosamprenavir was boosted with RTV). Thus, although it is unknown what the effect of nevirapine on SQV exposures is when SQV is boosted with RTV, it is unlikely to cause a significant decrease in SQV exposures and is unlikely to be a greater change than ~25%.

Efficacy

Mean viral load at baseline for the combined all-patient study population was 4.7 $\log_{10}$ copies/mL (4.64 $\log_{10}$ copies/mL in the low age group category and 4.97 $\log_{10}$ copies/mL in the high age group category). During the first 24 weeks of the study, mean HIV viral load in the combined all-patient population decreased from 4.7 $\log_{10}$ copies/mL to 2.33 $\log_{10}$ copies/mL. The decrease in mean viral load was slighter greater in the low age group category (mean change from baseline of -2.47 log10 copies/mL) than the high age group category (mean change from baseline of -1.96 log10 copies/mL).

At weeks 24, 48, and 96, the percentages of patients with HIV RNA <400 copies/mL were 70%, 74%, and 56%, respectively, when using an analysis that considered missing values as failure. When considering only those patients who were on treatment, the percentages of patients with HIV RNA <400 copies/mL were 72.9%, 84.1%, and 93.3% at weeks 24, 48, and 96, respectively. The percentages of patients with HIV RNA <50 copies/mL were 54%, 62%, and 52%, respectively, using a missing = failure analysis. Using an on-treatment analysis, the

percentage of patients with HIV RNA <50 copies/mL were 56.3%, 70.5%, and 86.7% at weeks 24, 48, and 96, respectively. Please refer to the medical officer's review for further details.

Safety

Overall, 90% of all subjects reported at least one adverse event (AE) during the study, and was similar in both high age subjects and low age subjects. Severe AE's were more common in high age subjects (50%) compared with low age subjects (20%). Life-threatening AE's were rare (4%) and only occurred in low age subjects (5%). The most common categories of adverse events reported were those considered infections and infestations, gastrointestinal, respiratory, and general disorders. The most frequently reported AE's, nasopharyngitis (46%) and cough (40%) were reported in a greater percentage of low age subjects (53% and 43%) compared with high age subjects (20% and 30%), respectively. Please refer to the medical officer's review for further details.

Pharmacokinetics

LPV exposures were approximately 50-70% higher than previously reported for pediatric subjects. The mean steady-state AUCτ, Cmax, and Cmin reported for this study were 123 ± 51 µg*h/mL, 13.8 ± 5.76 µg/mL, and 5.79 ± 3.07 µg/mL, respectively (Table 2). In the Kaletra® label, the mean values for AUCτ, Cmax, and Cmin were 72.6 ± 31.1 µg*h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 µg/mL, respectively.

The mean (range) dose of ritonavir administered in this study was 2.3 mg/kg (1.6-3.1 mg/kg). Pediatric RTV exposures in this study were similar to previously reported steady-state adult RTV exposures resulting from a SQV/RTV 1000/100 mg dose (Autar, R.S., 2004). However, RTV AUCτ, Cmax, and Cmin values were approximately 88%, 50%, and 74% higher, respectively, than previously reported for RTV exposures when administered in combination with LPV and efavirenz in HIV-infected pediatric patients in a similar age range (King, J.R., 2009). The inter-individual variability was high for this study, particularly for the high age group (n=3) where a maximum AUC reached 88.7 µg*h/mL and the minimum for the group was 5.33 µg*h/mL.

SQV PK parameters are shown in Table 2 below. Mean SQV AUCτ, Cmax, and Cmin values are approximately 126%, 71%, and 113% higher, respectively, than previously reported in HIV-infected adults (Boffito, M., 2004). The mean SQV AUCτ for HIV-infected adults reported in the Invirase® label is 14.61 µg*h/mL; however, according to the sponsor, a 2001 study report from the EPIMED protocol reported individual SQV AUCτ values as high as 56.6 µg*h/mL following a 1000/100 mg dose. Mean Cmax values reported in literature range from 1.9 to 3.91 µg/mL in adults receiving SQV/RTV 1000/100 mg. Again, the inter-individual variability was relatively high for all SQV PK parameters.

Table 2 PK Summary Table for All Three Analytes for All Ages

Mean ± SD (range) N=19	**AUCτ (µg*h/mL)**	**Cmax (µg/mL)**	**Cmin (µg/mL)**	**T1/2 (hr)**
LPV	**123** ± 51 (51.1-231)	**13.8** ± 5.8 (6.11-25.2)	**5.8** ± 3.1 (0.61-14.1)	**6.8** ± 3.8 (1.78-17.32)
RTV	**12.4** ± 19.1 (3.2-88.7)	**1.5** ± 1.8 (0.32-8.46)	**0.52** ± 1.0 (0.01-4.69)	**5.2** ± 4.1 (0.90-16.53)
SQV	**49.5** ± 43.2 (8.58-203)	**6.4** ± 4.6 (1.16-20.8)	**1.8** ± 2.2 (0.16-9.79)	**3.4** ± 1.1 (1.92-5.47)

SQV PK Parameters Broken Down by Age

Mean ± SD (range)	AUCτ (µg*h/mL)	Cmax (µg/mL)	Cmin (µg/mL)	T1/2 (hr)
SQV ages 5 to <10 yrs (n=14)	**35.7** ± 14.3 (8.6-55.6)	**4.9** ± 2.2 (1.2-9.2)	**1.1** ± 0.7 (0.2-2.3)	**3.2** ± 0.9 (1.9-5.0)
SQV age ≥10 yrs (n=5)	**88.3** ± 72.2 (30.8-203)	**10.4** ± 7.2 (4.0-20.8)	**3.6** ± 3.7 (0.5-9.8)	**4.0** ± 1.3 (2.3-5.5)

Reviewer's Comments:
- When SQV PK parameters were broken down by age, the high age group had a significantly higher mean AUC, Cmax, and Cmin than the low age group. This is mostly driven by 2/5 subjects with unusually high exposures. These two subjects were the only ones with SQV Cmax values that exceeded the level obtained in the tQT study at day 3 Cmax using the therapeutic dose in healthy subjects (11.2 ng/mL). However, the safety data from these two subjects did not differ significantly from the rest of the age group over the 96-week dosing period.
-The study in the Kaletra label (study 940) was conducted in pediatric patients as young as 6 months old. The current study was conducted in patients ages 3 years and older. The age differences may partially have accounted for the difference in LPV PK between the two studies.
-Although the SQV exposures in pediatric subjects in this study were considerably higher than historical adult values, the higher AUC, Cmax, and Cmin values were driven by 2 subjects in the high age group who had individual exposures between 3- and 6-fold higher than the mean for the rest of the group. The subject with 6-fold higher SQV exposures (#101) also had an unusually high RTV AUC value (~10-fold higher than the mean for the group), suggesting a dosing error.
-The RTV dose administered in this study (as part of the Kaletra formulation) corresponded well with the proposed pediatric RTV dose.
*-Of note, since the clinical portion of this study was conducted entirely in Thailand, the subjects were all of Thai descent. The sponsor postulates that ethnic differences may account for the differences in SQV exposures. A study comparing 3 different SQV/RTV dosing regimens in HIV-infected Thai adults demonstrated that mean SQV AUCτ values were approximately 27.7 µg*h/mL, which is ~90% higher than the mean in Caucasians presented in the Invirase label. Although CYP3A4 is not generally considered to be a polymorphic enzyme, it is possible that differences in weight between Caucasian and Thai populations or dietary differences could have partially accounted for the difference in SQV exposure.*

Conclusion

Efficacy results from this study show a similar proportion of patients who achieved HIV RNA <50 copies/mL at week 24 as a previous study in which children received a combination of SQV+NFV and 2 NRTIs. In addition, efficacy results are similar to what has been reported for adults taking the SQV/RTV 1000/100 mg regimen (historical results in Invirase label). The studied dose of SQV (50 mg/kg) in combination with RTV (at a standard dose of 57.5 mg/m^2 in combination with LPV) was well-tolerated with no new or unexpected adverse events. Although the totality of the PK, efficacy, and safety data would support the use of SQV/RTV at the studied doses in children ages 3 to <16 years, as a result of the DSI audit, none of the PK data are valid. The PK data from this study will not be used in determining a dosing recommendation for this age group. However, the efficacy and safety data can still be used to support a dosing recommendation in case PK interpolation is used to provide "bridging" PK data for pediatric patients 3 to <16 years of age.

4.2 Individual Study Review—Pivotal Study (NV20911)

Title (Study NV20911)

"A phase I/II study of Invirase® boosted with Ritonavir in HIV infected infants and children 4 months to less than 6 years old"

Objectives

- To evaluate the pharmacokinetics of saquinavir that, when boosted with ritonavir, provides a systemic exposure in HIV-infected infants and children 4 months to <6 years similar to that which has been shown to be safe and effective in older children and adults.
- To determine the safety and tolerability of saquinavir when boosted with ritonavir in HIV-infected infants and children 4 months to <6 years of age.
- To characterize the pharmacokinetics of ritonavir when given as a booster in combination with saquinavir in HIV-infected infants and children 4 months to <6 years.
- To evaluate the antiviral activity of saquinavir when boosted with ritonavir against HIV infection in infants and children 4 months to <6 years.

Study Dates and Location(s):

May 20, 2008 – March 11, 2010

The clinical portion of the trial was conducted at 8 total sites in Argentina (3 centers), Spain (1 center), and Thailand (4 centers).

Study Doses Used

SQV: 50 mg/kg q12h

RTV: 3 mg/kg q12h for children weighing 5 to <15 kg; 2.5 mg/kg q12h for children weighing 15 to 40 kg.

Study Design

This study was a phase I/II multi-center, open label, 48-week, non-randomized study conducted in pediatric subjects ages 4 months to <6 years. Children were grouped by age as follows:

- Group A: children aged 4 months to <2 years
- Group B: children aged 2 years to <6 years

Subjects started treatment with saquinavir at a dose of 50 mg/kg BID (up to the adult dose of 1000 mg BID) and ritonavir at a dose of 3 mg/kg BID for children weighing from 5 to <15 kg, 2.5 mg/kg BID for children weighing from 15 to 40 kg, and 100 mg BID for children weighing >40 kg. In addition, 2 or more background ARVs were prescribed. Background ARVs included NRTIs and could also include LPV/RTV as deemed appropriate by the investigator. If LPV/RTV was used, the total dose of RTV was to be as specified above.

After 14 days of treatment (or Day 28 for patients switching from an NNRTI-containing regimen), $AUC_{0\text{-}12h}$ and Ctrough were compared to the range of exposures seen in older children in HIVNAT017. The reference ranges were: $AUC_{0\text{-}12h}$ between 30.7 and 51.6 µg*hr/mL and Ctrough between 70 and 2,000 ng/mL. If exposures were found outside or at the extremes of that range, and/or were considered to be associated with toxicities, dose adjustments were made within the age group or for individual patients as deemed appropriate. For children unable to swallow Invirase capsules, the capsules were opened and the powder mixed with a vehicle before the dose was administered. Opened capsules were taken with either sugar syrup

(sorbitol syrup could be used for children with Type I diabetes or glucose intolerance), jam or baby formula.

Formulation(s) Used

SQV was administered as hard-gel capsules of 200 mg or film-coated tablets of 500 mg SQV each. For children unable to swallow Invirase capsules, the capsules were opened and the powder mixed with sugar syrup, jam or baby formula before the dose was administered. RTV was administered as the 80 mg/mL oral solution. These trial medications were also combined with 2 or more background ARVs.

Dose Rationale

A SQV dose of 50 mg/kg BID was chosen for use in this study. The 24-week interim analysis results of HIVNAT017 suggested that a dose of 50 mg/kg BID in combination with the established pediatric doses of LPV/RTV were appropriate in the age group studied in that study (2 to 16 y.o.a.). The 57.5 mg/m^2 BID ritonavir dose (established for Kaletra) is approximately equivalent to a RTV dose of 3 mg/kg for body weight from 5 to <15 kg, 2.5 mg/kg for body weight from 15 to 40 kg and a maximum dose of 100 mg for body weight >40 kg.

From the investigator's brochure for Invirase, a target Ctrough of 100 ng/mL was recommended to achieve minimal SQV activity based on an EC_{50} of 50 ng/mL from exposure-response modeling in PI-naive patients. From HIVNAT017, where activity and safety was demonstrated in older children receiving SQV 50 mg/kg BID and LPV/RTV 230/57.5 mg/m^2 BID, SQV exposures ($AUC_{0\text{-}12h}$) ranged from 30.7 to 51.6 µg*hr/mL and Ctrough from 700 to 2000 ng/mL. At the approved adult dose of 1000/100 mg BID, individual $AUC_{0\text{-}12h}$ ranges from 10.2 to 56.6 µg*hr/mL and individual Ctrough values range from 70 to 2600 ng/mL.

Key Inclusion Criteria

-Confirmed HIV-1 infection by HIV-DNA polymerase chain reaction (PCR) if patient was <18 months old or by HIV enzyme-linked immunosorbent assay (ELISA) confirmed by Western Blot analysis if patient was >18 months old
-Subject was 4 months to <6 years of age at the day of the first dosing
-Subject for whom SQV/RTV together with ≥2 background ARVs, including NRTIs, and which might include a RTV-boosted PI was considered appropriate, at the discretion of the investigator. For subjects with extensive prior nucleoside use, double boosted PIs (e.g. saquinavir in combination with lopinavir/ritonavir) in addition to nucleosides could be used
-For subjects who could not swallow Invirase capsules, parent/caregiver was able and willing to open Invirase capsules, mix the contents in a vehicle and administer the medication with RTV as directed in the protocol

Key Exclusion Criteria

-Subject whose weight was less than 4 kg/8.8 pounds
-Relevant history or pre-existing condition that might interfere with drug absorption, distribution, metabolism or excretion
-Any pre-existing clinical or laboratory parameter of PACTG Grade 4, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
-Use of any concomitant medications that might interfere with the PK of SQV or RTV, including but not limited to the drugs listed below, within 28 days prior to the first dose of study drug:

–Clarithromycin
–Indinavir
–Ketaconazole
–Nelfinavir
–Rifabutin

–Rifampicin
–Atazanavir
–Fosamprenavir
–Phenobarbital
–Phenytoine
–Carbamazepine
–Glucocortocoids

-Any active OI and/or clinically significant finding within 28 days before study entry
-Subjects with malabsorption, (severe chronic diarrhea or vomiting more than two episodes of moderate or severe intensity, not attributed to medication therapy and lasting more than four days) within 28 days of the study.

Blood Sampling for PK

All subjects underwent 0-12 hour PK sampling at steady-state to determine whether dose adjustment was necessary. Sampling occurred on day 14 ± 2 days if the patient was not using NNRTIs in a previous regimen or after day 28 + 2 days if the patient had switched from a NNRTI-containing regimen (at baseline). If a SQV dose adjustment was required due to exposures found outside or at the extremes of the expected range, a repeat 0-12 hr PK sampling was performed at a minimum of 14 days after the day of the dose adjustment. Additional blood samples for PK analysis of Ctrough were taken pre-dose at weeks 8, 12 and 24, and additionally a 4 hour post-dose for SQV and RTV PK analysis was taken at week 24. Blood samples for SQV and RTV intensive PK assessments were taken at pre-dose, 3, 4, 8 and 12 hours post-dose.

Bioanalytical Validation

Quantitative determination of SQV and RTV in human plasma was performed using an LC/MS/MS method. Plasma samples were stored (at -20° C) and analyzed from July 24, 2008 to November 5, 2009 at the PRA International in The Netherlands.

Two assays were used for the determination of both SQV and RTV concentrations (low range and high range). For the low range assay, the calibration range was 1.0-100 ng/mL for SQV and RTV and the LLOQ was 1.0 ng/mL for both compounds, using 25 µL plasma. For the high range assay, the calibration range was 10.0-10,000 ng/mL for SQV and RTV and the LLOQ was 10.0 ng/mL for both compounds, using 25 µL plasma. The accuracy and precision results for the calibration standards and QC's from the sample runs are presented below.

Concentrations of Saquinavir in Calibration Standards in Human Plasma in Study NV20911: Low Range Assay

Date of Analysis	Run ID	1.00 [ng/mL]	2.00 [ng/mL]	5.00 [ng/mL]	15.0 [ng/mL]	25.0 [ng/mL]	50.0 [ng/mL]	80.0 [ng/mL]	100 [ng/mL]
14Jan09	AQ14-009	0.951	1.92	4.77	15.4	25.5	50.1	81.7	98.2
		1.09	1.97	4.86	15.2	25.3	51.2	79.9	98.8
Mean Conc. [ng/mL]		1.02	1.95	4.82	15.3	25.4	50.6	80.8	98.5
Precision [%]		9.4	1.9	1.3	0.7	0.4	1.5	1.5	0.4
Accuracy [%]		101.9	97.3	96.4	102.1	101.6	101.3	101.0	98.5
Deviation [%]		1.9	-2.7	-3.6	2.1	1.6	1.3	1.0	-1.5
N		2	2	2	2	2	2	2	2

Concentrations of Ritonavir in Calibration Standards in Human Plasma in Study NV20911: Low Range Assay

Date of Analysis	Run ID	1.00 [ng/mL]	2.00 [ng/mL]	5.00 [ng/mL]	15.0 [ng/mL]	25.0 [ng/mL]	50.0 [ng/mL]	80.0 [ng/mL]	100 [ng/mL]
13Mar09	AQ12-004	1.13	1.93	4.72	14.1	25.4	50.5	81.3	102
		0.941	1.85	4.88	14.8	26.4	52.1	81.1	102
14Jan09	AQ14-009	1.01	1.96	4.77	14.9	25.1	47.5	78.8	97.2
		1.00	2.00	5.22	15.4	26.3	50.6	83.1	98.2
Mean Conc. [ng/mL]		1.02	1.94	4.89	14.8	25.8	50.2	81.1	99.9
Precision [%]		7.8	3.2	4.6	3.9	2.6	3.8	2.2	2.6
Accuracy [%]		102.0	96.8	97.9	98.6	103.1	100.4	101.4	99.9
Deviation [%]		2.0	-3.2	-2.1	-1.4	3.1	0.4	1.4	-0.1
N		4	4	4	4	4	4	4	4

Concentrations of Saquinavir in Calibration Standards in Human Plasma in Study NV20911: High Range Assay

Date of Analysis	Run ID	10.0 [ng/mL]	20.0 [ng/mL]	50.0 [ng/mL]	200 [ng/mL]	500 [ng/mL]	2000 [ng/mL]	5000 [ng/mL]	8000 [ng/mL]	10000 [ng/mL]
12Jan09	AQ14-008	9.80	20.8	(40.9) [1)]	197	475	1890	4830	7700	11200
		10.1	20.3	45.2	200	510	1980	4740	8190	11400
Mean Conc. [ng/mL]		10.1	19.9	49.1	200	503	1990	4940	8060	10300
Precision [%]		6.0	6.5	5.9	3.8	3.6	2.8	4.0	3.3	5.5
Accuracy [%]		100.7	99.3	98.1	99.9	100.5	99.4	98.8	100.8	102.7
Deviation [%]		0.7	-0.7	-1.9	-0.1	0.5	-0.6	-1.2	0.8	2.7
N		51	51	51	51	52	51	52	52	46

Concentrations of Ritonavir in Calibration Standards in Human Plasma in Study NV20911: High Range Assay

Date of Analysis	Run ID	10.0 [ng/mL]	20.0 [ng/mL]	50.0 [ng/mL]	200 [ng/mL]	500 [ng/mL]	2000 [ng/mL]	5000 [ng/mL]	8000 [ng/mL]	10000 [ng/mL]
Mean Conc. [ng/mL]		10.1	19.7	48.6	198	492	1960	5000	8290	10400
Precision [%]		7.3	5.5	6.2	3.6	4.5	4.3	4.1	4.3	5.5
Accuracy [%]		101.4	98.5	97.2	99.0	98.4	97.8	100.1	103.6	104.4
Deviation [%]		1.4	-1.5	-2.8	-1.0	-1.6	-2.2	0.1	3.6	4.4
N		49	48	49	50	49	49	50	50	45

Performance of Saquinavir in Quality Control Samples in Human Plasma in Study NV20911: Low Range Assay

Date of Analysis	Run ID	3.00 [ng/mL]	20.0 [ng/mL]	80.0 [ng/mL]
14Jan09	AQ14-009	3.02	19.8	79.8
		2.71	20.3	81.8
Mean Conc. [ng/mL]		2.86	20.1	80.8
Precision [%]		7.7	1.8	1.8
Accuracy [%]		95.5	100.3	101.0
Deviation [%]		-4.5	0.3	1.0
N		2	2	2

Performance of Ritonavir in Quality Control Samples in Human Plasma in Study NV20911: Low Range Assay

Date of Analysis	Run ID	3.00 [ng/mL]	20.0 [ng/mL]	80.0 [ng/mL]
13Mar09	AQ12-004	3.02	19.0	77.2
		2.93	19.0	79.0
14Jan09	AQ14-009	2.99	19.7	77.7
		2.82	19.9	80.5
Mean Conc. [ng/mL]		2.94	19.4	78.6
Precision [%]		3.0	2.4	1.9
Accuracy [%]		97.9	97.0	98.3
Deviation [%]		-2.1	-3.0	-1.7
N		4	4	4

Performance of Saquinavir in Quality Control Samples in Human Plasma in Study NV20911: High Range Assay

Date of Analysis	Run ID	30.0 [ng/mL]	500 [ng/mL]	8000 [ng/mL]
		32.2	510	7920
12Nov08	AQ14-006	29.3	451	7350
		27.4	473	7440
28Nov08	AQ14-007	29.0	469	7480
		30.7	464	7590
12Jan09	AQ14-008	29.6	451	7580
		28.9	466	7320
Mean Conc. [ng/mL]		29.7	494	7820
Precision [%]		8.5	5.1	5.2
Accuracy [%]		98.9	98.8	97.7
Deviation [%]		-1.1	-1.2	-2.3
N		52	52	51

Performance of Ritonavir in Quality Control Samples in Human Plasma in Study NV20911: High Range Assay

Date of Analysis	Run ID	30.0 [ng/mL]	500 [ng/mL]	8000 [ng/mL]
12Nov08	AQ14-006	28.3	477	7020
		30.0	472	7350
28Nov08	AQ14-007	27.3	482	7630
		29.3	482	7080
12Jan09	AQ14-008	27.8	461	7180
		28.9	441	6880
Mean Conc. [ng/mL]		29.0	485	7700
Precision [%]		5.3	5.4	6.4
Accuracy [%]		96.6	97.0	96.3
Deviation [%]		-3.4	-3.0	-3.7
N		50	50	49

All precision and accuracy values are within acceptable limits (<15% deviation for all concentrations). Long-term storage stability for both SQV and RTV were demonstrated at -20^{o} C for 356 days.

Reviewer's Comments:
-The longest a potential study sample could have been stored at -20^{o} C before being analyzed is 469 days (based on the dates of assay). SQV and RTV both demonstrated stability for only 356 days. The DSI investigator has been notified that the storage of samples exceeded the long-term storage stability validation time and additional stability data was requested of the sponsor.
-DSI's inspection results revealed that some of the method validation data are invalid. In particular, the inspector cited failure to use freshly prepared calibration standards in the validation experiments and failing validations for stability of saquinavir and ritonavir stock solution. (Please see 1-20-2011 review by Dr. Michael Skelly and Dr. Martin Yau for full details.) The sponsor can perform additional re-validation experiments to validate the PK data from this study.

Results

A total of 18 patients were recruited from 3 centers in Argentina, 1 center in Spain, and 4 centers in Thailand. Five of eight planned subjects were enrolled in the low age group (≥ 4 months to <2 years) and 13 of 16 planned subjects were enrolled in the high age group (≥ 2 years to <6 years).

Demographics

Below is a table detailing the demographics of all subjects in both groups.

	LOW N = 5	HIGH N = 13	All Patients N = 18
Sex			
FEMALE	3	8 (62%)	11 (61%)
MALE	2	5 (38%)	7 (39%)
n	5	13	18
Race			
CAUCASIAN	3	5 (38%)	8 (44%)
ORIENTAL	2	8 (62%)	10 (56%)
n	5	13	18
Age (years) at Randomization			
Mean	0.8	4.0	3.1
SD	0.45	1.08	1.75
SEM	0.20	0.30	0.41
Median	1.0	4.0	4.0
Min-Max	0 - 1	2 - 5	0 - 5
n	5	13	18
Weight in kg			
Mean	9.36	15.23	13.60
SD	2.298	3.049	3.890
SEM	1.028	0.846	0.917
Median	9.00	15.20	14.00
Min-Max	6.3 - 12.3	10.5 - 20.0	6.3 - 20.0
n	5	13	18
Height in cm			
Mean	76.6	97.7	91.8
SD	8.88	9.55	13.32
SEM	3.97	2.65	3.14
Median	78.0	100.0	91.0
Min-Max	62 - 86	81 - 116	62 - 116
n	5	13	18

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

Concomitant Antiretroviral Treatments

A total of 94% (17/18) of all patients reported at least one previous ART at screening. One subject in the high age group had no previous antiretroviral experience. The most commonly reported previous NRTI treatment was with lamivudine (67%; 12/18) and zidovudine (39%; 7/18) among both age groups. Four of the five subjects in the low age group and 7/13

patients in the high age group had previous experience with a protease inhibitor. Ten of these subjects had received Kaletra®. One subject in the high age group received nelfinavir.

Efficacy

Mean viral load at baseline for the low age group was 3.42 log_{10} copies/mL and 3.53 log_{10} copies/mL for the high age group. Through 48 weeks, the decrease in mean viral load was similar in both age groups (high age group: mean change from baseline of -1.39 log_{10} copies/mL; low age group: mean change from baseline of -1.27 log_{10} copies/mL). At baseline, no subject in the low age group and 4 subjects in the high age group had a viral load <50 copies/mL. In the combined all patient population, 11 of the 16 subjects (68.8%) with a week 48 assessment had a viral load <50 copies/mL. Two of the three subjects in the low age group and 9 of the 13 subjects in the high age group with a week 48 assessment had a viral load <50 copies/mL. In the all patient population, 4/18 patients were classified as virological failures at week 48 (3/5 patients in the low age group and 1/13 patients in the high age group).

Safety

All 5 subjects in the low age group (100%) and 9/13 subjects (69%) in the high age group reported adverse events. “Infections and Infestations” was the class of adverse event most frequently recorded, being reported in 56% (10/18) of subjects. Gastrointestinal disorders were the next most frequently recorded adverse events being reported by 44% (8/18) of subjects. Please refer to the medical officer’s review for further details.

Reviewer’s Comments:
-Although the exposures in the high age group were significantly higher than the low age group and adults, the proportion of GI disorders reported by the high age group (~31%) was not higher than the number reported by the low age group (~80%) or adults, as listed in the Invirase label (~32%).

Pharmacokinetics

In the low age group, SQV doses ranged from 400 mg to 600 mg and the mean (range) dose of RTV administered in this study was 3.0 mg/kg (2.3-3.7 mg/kg). SQV exposure parameters exhibited a large inter-subject variability: $AUC_{0\text{-}12h}$ ranged from 2.10 to 43.8 hr*ug/mL, Cmax ranged from 331 to 6860 ng/mL, and average Ctrough ranged from 26.6 to 1090 ng/mL (Table 3). SQV half-life was comparable across subjects, ranging from 2.27 to 2.66 hours. The 50 mg/kg dose of SQV (boosted w/ RTV) achieved the target Ctrough in 4 out of 5 of the subjects in the low age group. RTV exposures also demonstrated large inter-subject variability. The range in $AUC_{0\text{-}12h}$ was between 19.1 and 361 µg*h/mL (mean 181.68 µg*h/mL) and the range in Ctrough was between 0.423 to 10.2 ng/mL (mean 4.93 ng/mL). Two subjects in this group required a SQV dose adjustment; however, one did not return for follow-up PK assessment.

- Subject #4101 had a dose adjustment from 400 mg to 600 mg but this increase subsequently resulted in a 65% decrease in their Cmax concentration. A similar trend was observed with this subject’s RTV concentration, suggesting that this may be due to non-compliance. The subject’s viral load was 410 copies/mL at baseline, 50 copies/mL at week 8, and 85 copies/mL at week 12. SQV and RTV were discontinued and were replaced with Kaletra® at week 12.

In the high age group, SQV doses ranged from 600 mg to 1000 mg and the mean (range) dose of RTV administered in this study was 2.6 mg/kg (2.3-3.3 mg/kg). Similar to the low age group, SQV exposure parameters exhibited a large inter-subject variability: $AUC_{0\text{-}12h}$ ranged from 4.77 to 83.2 hr*ug/mL, Cmax ranged from 954 to 12,100 ng/mL, and Ctrough

ranged from 470 to 6420 ng/mL (Table 3). The half-life across subjects ranged from 2.15 to 5.25. The 50 mg/kg dose of SQV (boosted w/ RTV) achieved the target Ctrough in 10 out of 13 of the subjects in the high age group. RTV $AUC_{0\text{-}12h}$ exposures were between 4.77 and 83.2 µg*h/mL (mean 8.77 µg*h/mL) and the range in Ctrough was between 63.7 to 916 ng/mL (mean 420.9 ng/mL). Three subjects required a dose adjustment in the high age group:

- Subject #1202 received a dose adjustment from 1000 mg to 800 mg due to the subject's Ctrough value exceeding the upper range. This 20% reduction in SQV dose resulted in a 90% reduction in Ctrough and 79% reduction in $AUC_{0\text{-}12h}$ values. Although this subject's RTV dose was not changed, RTV exposure also decreased (63% in $AUC_{0\text{-}12h}$ and 38% in Ctrough). The viral load declined from >100,000 copies/mL at baseline to 1204 copies/mL at week 8 and increased to 6468 copies/mL by week 48 in this subject.
- Subject #4103 required a dose adjustment from 800 mg to 600 mg. Similar to subject #1202, a 25% decrease in SQV dose resulted in a disproportionately higher decrease in exposure. $AUC_{0\text{-}12h}$ was reduced by 85%, and Ctrough was reduced by 78%. RTV dose was not decreased but its exposure was reduced; ~26% for $AUC_{0\text{-}12h}$ and ~18% for Ctrough. The viral load remained <50 copies/mL in this subject at week 8 and beyond.
- Subject #4302 had a dose adjustment from 800 mg to 600 mg. This reduction resulted in the SQV exposure to drop to within the expected range for $AUC_{0\text{-}12h}$; however, the average Ctrough concentration fell outside the target range. The viral load remained <50 copies/mL in this patient at week 8 and beyond.

Table 3 Dose Normalized (50 mg/kg) SQV PK Parameters following Multiple Oral Doses of SQV

Group	PATIENT	Visit	C_{max} (ng/mL)	C_{trough} (ng/mL)	$AUC_{0\text{-}12h}$ (h*ug/mL)
A	1301	Day 14/28	1890	1020	12.8
	1302	Day 14/28	514	23.6	2.48
	3101	Day 14/28	7720	1120	49.3
	4101*	Repeat Visit	251	101	1.59
	4203	Day 14/28	4200	969	27.5
	N		5	5	5
	Mean		2910	645	18.7
	SD		3110	536	20.0
	Min		251	23.6	1.59
	Median		1890	969	12.8
	Max		7720	1120	49.3
	CV%		106.6	83.0	106.9
B	1101	Day 14/28	4710	1310	31.3
	1201	Day 14/28	8980	3070	58.8
	1202*	Repeat Visit	2390	608	21.2
	1203	Day 14/28	3270	1640	28.0
	1204	Day 14/28	7330	2490	51.3
	4102	Day 14/28	7700	2870	50.7
	4103*	Repeat Visit	2000	701	13.5
	4201	Day 14/28	8110	2510	61.5
	4202	Day 14/28	2230	1260	16.4
	4301	Day 14/28	2820	1300	18.3
	4302*	Repeat Visit	9160	3980	56.5
	4303	Day 14/28	8130	1880	55.7
	4401*	Repeat Visit	5640	563	31.4
	N		13	13	13
	Mean		5570	1860	38.0
	SD		2780	1060	18.1
	Min		2000	563	13.5
	Median		5640	1640	31.4
	Max		9160	3980	61.5
	CV%		49.9	56.8	47.5

Reviewer's Comments:
*-The mean exposure to SQV was similar between the non-dose normalized data and the dose-normalized data. The non-dose normalized AUC_{0-12h} was 15.07 µg*h/mL in the low age group and 42.5 µg*h/mL in the high age group. The dose-normalized AUC_{0-12h} was 18.7 µg*h/mL in the low age group and 38.0 µg*h/mL in the high age group. Similarly, the Ctrough values differed by only 18.8% and 16.3% between the low and high age groups, respectively.*
-The mean actual dose received by the low age group was 51.6 mg/kg while the mean actual dose administered to the high age group was 48.9 mg/kg. Thus, there were no significant differences in the actual dose received between the two age groups.
-When the actual RTV dose administered in this study was compared with the proposed pediatric RTV dose, the actual doses received and the proposed doses corresponded well with each other and with the RTV dose portion of the recommended pediatric dose of Kaletra.
-The higher mean SQV exposure in the older children may partially be a result of the low subject number combined with high variability in the younger age group. In addition, hepatic CYP3A4 activity peaks in children at approximately 1 year of age, where the catalytic activity exceeds that of adults. Given the higher enzymatic activity in pediatric subjects younger than 2 y.o.a., lower exposures to SQV in this population is not unexpected.
-The low subject number (n=5) and high interindividual variability in the low age group do not provide enough assurance that 50 mg/kg is an adequate dose for pediatric patients who are in the 4 months to <2 years of age group.
*-Mean adult SQV AUC_{0-12h} values range from 12.7-27.7 µg*h/mL (individual values range: 10.2-56.6 µg*h/mL) and mean Ctrough ranges from 70 to 2600 ng/mL. Thus, the upper range of AUC_{0-12h} observed in adults following a SQV/RTV 1000/100 mg dose still exceeds the mean AUC_{0-12h} observed in pediatric subjects in the high age group (38.0 µg*h/mL). In addition, the mean Cmax value in pediatric subjects (across both age groups) was 43% lower than the day 3 Cmax observed in the tQTc study in healthy adults given the therapeutic dose of SQV/RTV (day 3 Cmax in adults in that study was ~11.2 ng/mL).*
- 68% of patients in the high age group were Thai, which may have contributed to higher exposure in this group of children, based on observed disparities in Thai and Caucasian adult patients (as described in the review of HIVNAT017 above).

Conclusion

Based on the results from HIVNAT017, the SQV 50 mg/kg dose and a corresponding RTV dose (Kaletra equivalent) from that study was chosen for this study. Target Ctrough and AUC_{0-12h} values were also derived from the PK data from HIVNAT017 where nearly all subjects achieved a Ctrough within the range observed in adults and no new or unexpected AE's emerged.

Dosing in the youngest age group (4 months to <2 years of age) resulted in highly variable exposures. Coupled with the low subject number (n=5), the data are insufficient to make a dosing recommendation based on the information provided. In the high age group (2 to <6 years of age), the AUC_{0-12h} and Ctrough exposures were higher than historical mean adult values; however, the means are contained within the range of exposures previously observed in adults (historical studies) and did not result in any new, unexpected, or higher frequency of AEs. In addition, efficacy results are similar to what has been reported for adults taking the SQV/RTV 1000/100 mg regimen (historical results in Invirase label). Thus, in agreement with study HIVNAT017, the SQV 50 mg/kg dose in combination with the studied dose of RTV (3 mg/kg q12h for children weighing 5 to <15 kg; 2.5 mg/kg q12h for children weighing 15 to 40 kg) is appropriate for this age range. However, without positive bioanalytical method re-validation results, the PK data are currently not valid in supporting a dosing recommendation.

4.3 Individual Study Review—Non-Pivotal Study (PACTG 397)

Title (Study PACTG 397)

"A Randomized Trial of Saquinavir-Containing Combination Treatment Regimens in Children with HIV Infection."

Objectives

The main objectives of this study were to assess the PK, safety, tolerability, bioavailability, and efficacy of SQV soft gel capsules alone and in combination with nelfinavir (NFV) in children ages 3 to 16 years old for 48 weeks.

Study Dates and Location(s):

Enrollment for the dose-adjusted cohort (rollover from cohort 1 to cohort 1A) took place from December 1999 to May 2000. Study sites were located at 13 hospitals and medical centers throughout the U.S.

Study Design

This study was a 48-week, randomized, two-arm trial in HIV-infected children ages 3 to 16 years old with a target enrollment of 50 subjects. Subjects were randomized in Cohort 1 to receive either:

- Arm 1: SQV 50 mg/kg TID (to a maximum of 1200 mg TID) in combination with 2 NRTIs

or

- Arm 2: SQV 50 mg/kg BID (to a maximum of 1200 mg BID) in combination with NFV 55 mg/kg BID (to maximum of 1500 mg BID) and 1 or 2 NRTIs

Preliminary analysis of the PK data demonstrated inadequate SQV exposures in both arms. The study was amended and subjects that were still on treatment were given the option to rollover into Cohort 1A, which would include:

- Arm 1: dosing SQV 50 mg/kg (up to a maximum of 1200 mg) with RTV 100 mg/m^2 BID in combination with 1 or 2 NRTIs
- Arm 2: SQV 50 mg/kg BID (to a maximum of 1600 mg BID) in combination with NFV 55 mg/kg BID (to maximum of 1500 mg BID) and 1 or 2 NRTIs

Formulation(s) Used

Saquinavir 200-mg soft-gel capsules (Fortovase®) were used in this study.

Reviewer's Comments:
-Fortovase and Invirase were not bioequivalent and could not be used interchangeably due to differing bioavailabilities. In addition, Fortovase was discontinued by Roche in 2006. However, based on literature reports (and the label for Invirase), Fortovase had approximately 30% higher bioavailability than Invirase when administered as 1000/100 mg with RTV.

Blood Sampling for PK

Intensive PK sampling was performed on day 14 of cohort 1 in 12 subjects in the SQV+NFV arm (arm 2) and in all subjects on day 14 in cohort 1A. Blood samples were collected at 2, 4, 6, 8, 10, and 12 hours post-dose. In addition, blood samples were collected at weeks 4, 8, 12, 16, 24, 32, and 40 for assessment of SQV trough levels.

Bioanalytical Validation

No bioanalytical method validation or within-study validation was submitted with the final study report.

Results

A total of 51 subjects were enrolled in cohort 1 of the study. Twenty-two of these subjects rolled over into cohort 1A. Fourteen subjects were in the SQV+RTV arm and 8 subjects were in the SQV+NFV arm. The demographics for cohort 1A are given below.

Baseline Demographics

	1A: Saq + RTV		1A: Saq + Nel		Total	
	N	%	N	%	N	%
Gender						
Male	7	50.0	4	50.0	11	50.0
Female	7	50.0	4	50.0	11	50.0
Race/ethnicity						
White Non-Hispanic	4	28.6	1	12.5	5	22.7
Black Non-Hispanic	5	35.7	6	75.0	11	50.0
Hispanic(Regardless of Race)	4	28.6	0	0	4	18.2
Asian, Pacific Islander	1	7.1	1	12.5	2	9.1
Age (years)						
>5 - 10	5	35.7	3	37.5	8	36.4
>10	9	64.3	5	62.5	14	63.6

Concomitant Antiretroviral Treatments

In the SQV+RTV arm of cohort 1A, 4 subjects had stavudine and lamivudine in their background ARV regimen, 4 subjects had stavudine and didanosine, 3 subjects had zidovudine and lamivudine, 1 subject had zidovudine and abacavir, and 1 subject had stavudine and abacavir. One subject had an unknown regimen. In the SQV+NFV arm, 3 subjects had stavudine in their background ARV regimen, 3 subjects had zidovudine and lamivudine, 1 subject had didanosine, and 1 subject had lamivudine and abacavir.

Efficacy

Forty-three percent (6/14) of the subjects in the SQV+RTV arm and 25% (2/8) of subjects in the SQV+NFV arm had HIV RNA values <400 copies/mL at entry into cohort 1A. Out of these 8 subjects with <400 copies/mL at baseline, 4 continued to maintain their virological status through week 48. An additional 4 subjects out of the remaining 14 subjects with HIV RNA >400 copies/mL also achieved <400 copies/mL from week 16 through 48.

Safety

The most common minor AEs were cough, swollen lymph nodes, and ANC abnormalities. Two subjects in the SQV+RTV arm developed a grade 3 or higher toxicity during the course of the study. However, neither event was judged to be related to study treatment. Two additional subjects experienced grade 3 or higher CPK and headaches, but both these events occurred within 30 days of starting treatment and therefore were not treated as new events. Two subjects in the SQV+NFV arm developed grade 4 toxicities but neither was judged to be related to drug treatment. Please refer to the medical officer's review for further details.

Pharmacokinetics

Every patient in cohort 1A ended up receiving a SQV dose of 1200 mg BID. The mean (range) dose of RTV administered in this study was 3.6 mg/kg (1.4-11.7 mg/kg). Table 4 below shows the summary PK statistics for trough concentrations collected in cohorts 1 and 1A. As expected, median SQV Cmin values were significantly higher when given in combination with RTV in cohort 1A than without RTV in cohort 1 and higher than when SQV was given in combination with NFV in either cohort 1 or 1A. Table 5 shows that median SQV Cmin values in the SQV+RTV group were approximately 6-fold higher in the HIV-1 RNA <400 copies/mL group than in the >400 copies/mL group (1684 ng/mL vs. 272 ng/mL). Similarly, SQV Cmin values in the SQV+NFV group were 7-fold higher in the HIV-1 RNA <400 copies/mL group than the >400 copies/mL group (739 ng/mL vs. 103 ng/mL). Again, as expected, SQV AUC was significantly higher when SQV was boosted with RTV than when given in combination with NFV (Table 6).

Table 4 Summary Statistics for Trough Concentrations for Cohorts 1 and 1A

TRT	Cohort	DRUG	N	MEDIAN	MIN	MAX
Coh1: Saq	1	Saq	16	26.50	BLQ	174.50
	1A	RTV	12	707.10	BLQ	2509.95
		Saq	12	1102.93	BLQ	2256.70
Coh1: Saq + Nel	1	M8	21	368.60	BLQ	4405.20
		Nel	21	822.80	BLQ	6060.70
		Nel+M8	21	1251.70	BLQ	10465.90
		Saq	21	87.90	BLQ	6143.00
	1A	M8	8	513.50	BLQ	2234.90
		Nel	8	2015.35	BLQ	4336.70
		Nel+M8	8	2253.35	12.00	6571.60
		Saq	8	257.38	25.15	909.00

Table 5 Trough Concentrations by Virologic Status at Week 16

STEP2TRT	DRUG	RNA	N	MEDIAN	MIN	MAX	p-value
1A: Saq + RTV	RTV	<400	5	818.20	302.60	2286.80	0.513
		>=400	7	351.75	0.00	2509.95	
	Saq	<400	5	1683.85	649.70	2256.70	0.012
		>=400	7	272.00	0.00	1936.85	
1A: Saq + Nel	M8	<400	3	1618.25	730.90	2234.90	0.036
		>=400	5	275.90	0.00	551.00	
	Nel	<400	3	3803.55	3235.05	4336.70	0.037
		>=400	5	736.75	0.00	3213.30	
	Nel+M8	<400	3	4853.30	4534.45	6571.60	0.037
		>=400	5	1134.00	12.00	3213.30	
	Saq	<400	3	739.45	619.80	909.00	0.037
		>=400	5	103.00	25.15	381.85	

Table 6 Summary Statistics for AUC in Cohorts 1 and 1A

TRT	Cohort	DRUG	N	MIN	MEDIAN	MAX
Saq + Nel	1	Nelfinavir	9	13.32	30.74	75.08
		Saquinavir	9	0.63	3.11	37.38
Saq + RTV	1A	Ritonavir	13	3.94	11.48	29.24
		Saquinavir	13	4.86	20.15	61.97
Saq + Nel	1A	Nelfinavir	8	11.13	41.85	99.82
		Saquinavir	8	2.63	9.51	22.12

Conclusion

Overall, both treatments (SQV+RTV and SQV+NFV) were well-tolerated. SQV Cmin and AUC were significantly higher when boosted with RTV as compared with not boosting or with dosing in combination with NFV. In addition, higher median Cmin values were observed in subjects with controlled viral load after 16 weeks of treatment (HIV-1 RNA <400 copies/mL).

4.4 Individual Study Review—Non-Pivotal Study (BP20594)

Title (Study BP20594)

"Assessment of the bioavailability of open 200 mg saquinavir capsules suspended in three different vehicles combined with ritonavir relative to unopened 200 mg saquinavir capsules combined with ritonavir."

Objectives

- To determine the bioavailability of opened 200 mg saquinavir capsules suspended in 3 different vehicles combined with ritonavir relative to unopened saquinavir 200 mg capsules combined with ritonavir.
- To assess the palatability of opened 200 mg saquinavir capsules suspended in 3 different vehicles combined with ritonavir relative to unopened saquinavir 200 mg capsules combined with ritonavir.

Study Dates and Location(s):

The study took place from September 6, 2006 to November 16, 2006 at Christchurch Clinical Studies Trust (CCST), Christchurch, New Zealand.

Study Design

This study was a single-center, open-label, randomized, 4-sequence, 4-period, 4-treatment crossover study in healthy male and female subjects aged 18 to 65 years inclusive. A total of 30 subjects were enrolled in the study. The 4 treatment sequences were ABCD, BDAC, CADB, and DCBA. The treatments were as follows:
–**Treatment A**: 5, unopened saquinavir 200 mg (Invirase) capsules + ritonavir 100 mg oral solution (Norvir) (reference treatment)
–**Treatment B**: saquinavir 1000 mg from 5, opened 200 mg (Invirase) capsules suspended in 15 mL of simple sugar syrup + ritonavir 100 mg oral solution (Norvir) (test treatment)
–**Treatment C**: saquinavir 1000 mg from 5, opened 200 mg (Invirase) capsules suspended in 15 mL of baby formula + ritonavir 100 mg oral solution (Norvir) (test treatment)
–**Treatment D**: saquinavir 1000 mg from 5, opened 200 mg (Invirase) capsules suspended in 15 g of strawberry-flavored jelly jam + ritonavir 100 mg oral solution (Norvir) (test treatment)

Formulation(s) Used

Commercially available Invirase® 200 mg capsules (batch no. B1204), Norvir® 100 mg soft gelatin capsules (batch no. 354612E21), and Norvir® 80 mg/mL oral solution (batch no. 41131AW21) were used in this study.

Doses Used

A single dose of 1000 mg SQV was administered as 5 intact 200-mg Invirase® capsules (Treatment A) on one occasion (in the morning of either day 14, 18, 22, or 26, depending upon the sequence) immediately following 100 mg ritonavir, administered as oral solution. SQV was administered 30 minutes after the start of a high-fat breakfast. RTV, 100 mg was administered BID with food on days 1 to 27 (only morning dose given on day 27). RTV was administered as oral solution on the mornings of days 14, 18, 22 and 26; all other times, RTV was administered as soft capsules.

Key Inclusion Criteria
-Were male or female volunteers of any race
-Were aged 18 to 65 years, inclusive

-Were healthy as determined by the screening assessments
-Were non-tobacco users, ie, had abstained from using tobacco for a minimum of 6 months prior to Day 1
-If female, either:

a) postmenopausal (had not had a spontaneous menstrual period for at least 1 year)
b) surgically sterile (tubal ligation or removal of ovaries or uterus)
c) committed to practice 2 barrier forms of contraception during the study and for at least1 month after the end of study treatment. Note: Due to PK drug-drug interactions with ritonavir, hormonal contraception was not acceptable.

Key Exclusion Criteria
-History of clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrinological or hematological or allergic disease, metabolic disorder, cancer or cirrhosis
-Disease or medical condition (eg, gall bladder removal, malabsorption syndrome) capable of altering the absorption, metabolism or elimination of drugs
-Experienced a cold or any other condition affecting taste within 2 weeks prior to screening;
-Female of child-bearing potential with positive pregnancy test at baseline or on Day 1 or lactating
-Female subjects on hormonal replacement therapy
-Clinically relevant laboratory abnormality identified at screening (including positive test for HIV, hepatitis B or hepatitis C)
-Used a CYP3A4 inhibitor within 4 weeks prior to Day 1, including but not limited to the following: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine or cimetidine
-Used a CYP3A4 inducer within 4 weeks prior to Day 1, including but not limited to the following: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin and phenobarbital
-Used any herbal product containing St. John's Wort or garlic (alimentary garlic excluded) within 4 weeks prior to Day 1
-Used any medication, other than inhibitors or inducers of microsomal enzymes or P-gp, within 1 week or within 6 times the elimination half life (whichever was longer) prior to Day 1 of the study. Vitamin/mineral supplements and occasional use of aspirin or paracetamol were allowed up to 48 hour before dosing

Blood Sampling for PK

Intensive PK sampling was conducted on days 14, 18, 22, and 26. The sampling times were: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

Bioanalytical Validation

The high calibration range contained SQV concentrations from 10.0 ng/ml to 10,000 ng/ml. The precision of the high range assay was ≤ 6.8%. The accuracy of the high range assay was between 97.3% and 102.1%. The low calibration range contained SQV concentrations from from 1.00 ng/ml to 100 ng/ml. The precision of the low range assay was ≤ 6.1%. The accuracy of the low range assay was between 93.1% and 98.2%. The within-study validation results are acceptable.

Results

A total of 30 subjects completed treatment. The demographics are given in the table below.

Demographics

	ALL TREATMENTS N = 30
Sex	
MALE	21 (70%)
FEMALE	9 (30%)
n	30
Race	
CAUCASIAN	27 (90%)
MAORI	1 (3%)
PART MAORI	1 (3%)
SAMOAN	1 (3%)
n	30
Age in years	
Mean	30.0
SD	13.54
SEM	2.47
Median	23.5
Min-Max	18 - 61
n	30
Weight in kg	
Mean	76.95
SD	12.827
SEM	2.342
Median	75.25
Min-Max	51.0 - 107.0
n	30
Height in cm	
Mean	174.2
SD	8.94
SEM	1.63
Median	176.0
Min-Max	154 - 187
n	30
Female Reproductive Status	
POSTMENOPAUSAL	1
SURGICALLY STERIL.	3
WITH CONT. PROT.	5
n	9
Does Subject Smoke ?	
NO	30 (100%)
n	30
HIV	
NEGATIVE	30 (100%)
n	30
Hepatitis B	
NEGATIVE	30 (100%)
n	30
Hepatitis C	
NEGATIVE	30 (100%)
n	30
Body mass Index (kg/m2)	
Mean	25.34
SD	3.822
SEM	0.698
Median	24.55
Min-Max	20.2 - 34.6
n	30

Safety

Headache was the most common AE reported during treatment with RTV 100 mg BID alone prior to the first dose of SQV/RTV on Days 1-14 (20%); all other individual AEs for RTV 100 mg BID alone were reported by fewer than 10% of subjects. Headache and diarrhea were the most common AEs reported following treatment with SQV/RTV 1000/100 mg; following treatments A, B, C or D, headache was reported by 10% to 17% of subjects and diarrhea was reported by 7% to 10% of subjects. Four AEs in 3 subjects were reported to be severe; 1 of

these severe AEs occurred in a subject within the approximate 12-hour interval following single-dose treatment with SQV/RTV and the other 3 AEs occurred while on treatment with RTV alone. Please refer to the medical officer's review for further details.

Pharmacokinetics

Compared to the unopened Invirase capsule (treatment A), the bioavailability (based on AUC_{inf}) of opened Invirase capsules suspended in simple sugar syrup (treatment B), baby formula (treatment C), or strawberry-flavored jelly jam (treatment D) was 12%, 59%, and 44% higher, respectively. Summary PK parameters for SQV are presented in Table 7 below.

Table 7 Summary PK Parameters for SQV Following Administration of Closed Invirase Capsules with RTV and Opened Invirase Capsules with RTV Suspended in 3 Different Vehicles

Treatment[a]		T_{max} (h)	C_{max} (ng/mL)	AUC_{0_24}[b] (h*ng/mL)	AUC_{inf} (h*ng/mL)	$T_{1/2}$ (h)	Cl/F (L/h)
A	N	30	30	30	30	30	30
	Mean	4.96	3150	24600	26200	5.21	45.2
	SD	1.74	1160	9340	10400	1.25	21.5
	Min	3.00	1260	8070	8390	3.27	18.4
	Median	5.00	3020	23700	24500	4.89	40.8
	Max	11.9	5540	45600	54500	9.25	119
	CV%	35.1	36.7	38.0	39.9	24.0	47.5
	Geometric Mean	4.73	2930	22800	24200	5.08	41.4
B	N	30	30	30	30	30	30
	Mean	4.87	3350	27100	28700	5.28	38.7
	SD	1.41	1170	8850	9610	0.781	13.3
	Min	3.00	1770	13000	13300	3.74	18.7
	Median	5.00	3330	25100	26500	5.13	37.8
	Max	10.0	7030	50100	53400	6.79	75.0
	CV%	28.9	35.0	32.6	33.4	14.8	34.3
	Geometric Mean	4.71	3170	25800	27300	5.22	36.7
C	N	30	30	30	30	30	30
	Mean	4.64	4540	38500	40900	5.26	27.2
	SD	1.27	1310	12600	14200	0.891	8.99
	Min	2.00	2190	21100	21800	3.95	12.9
	Median	5.00	4600	37600	39700	5.32	25.2
	Max	8.00	8020	67800	77400	7.04	45.8
	CV%	27.5	28.8	32.7	34.7	16.9	33.0
	Geometric Mean	4.45	4350	36600	38700	5.19	25.8
D	N	30	30	30	30	30	30
	Mean	4.37	4380	35100	37500	5.43	30.7
	SD	1.00	1500	12900	14700	1.26	11.8
	Min	2.00	2090	17200	17700	3.37	13.5
	Median	5.00	4150	32900	34800	5.17	28.8
	Max	6.00	9340	68700	74000	9.29	56.3
	CV%	22.9	34.3	36.7	39.2	23.3	38.4
	Geometric Mean	4.24	4150	32900	34900	5.30	28.6

[a] *Reference Treatment*: 5, unopened saquinavir 200 mg (Invirase) capsules (Treatment A).
Test Treatments: Saquinavir 1000 mg from 5, opened 200 mg (Invirase) capsules suspended in 15 mL of simple sugar syrup (Treatment B), **or** 15 mL of baby formula (Treatment C), **or** 15 g of jelly jam (Treatment D).
Ritonavir 100 mg b.i.d. was administered throughout the study.

[b] $AUC_{last} \sim AUC_{0\text{-}24}$ and therefore was not included on this table.

The relative bioavailability of SQV in the simple sugar syrup suspension compared to unopened Invirase capsules was 108% and 112% for Cmax and AUC_{inf}, respectively. The bioavailability of SQV in the baby formula suspension was higher than that from unopened Invirase capsules, with values of 148% and 159% for Cmax and AUC_{inf}, respectively. The bioavailability of SQV from the jelly jam suspension was higher than that from unopened Invirase capsules, with values of 142% and 144% for Cmax and AUC_{inf}, respectively. However, the bioavailability of SQV from the baby formula and the jelly jam suspension was similar. Within-subject variability was moderate, with coefficients of variation of 25.0% for Cmax and 22.6% for AUC_{inf}.

Palatability

The most palatable treatment was simple syrup followed by jelly jam, then unopened capsules and lastly baby formula. The median duration of aftertaste was similar for all vehicles (~1.5 - 2h), all of which were at least an hour longer than the unopened capsules.

Conclusion

Of the 3 treatments tested, SQV in simple sugar syrup was similar in bioavailability to the unopened capsules, whereas SQV in baby formula and jelly jam had higher bioavailability compared to unopened capsules. Overall, it is highly unlikely that treatment with SQV suspended in any of the vehicles tested (intended for pediatric use) would result in SQV exposures lower than that produced by unopened Invirase® capsules.

4.5 Brief Study Synopsis—Non-Pivotal Palatability Study (BP20226)

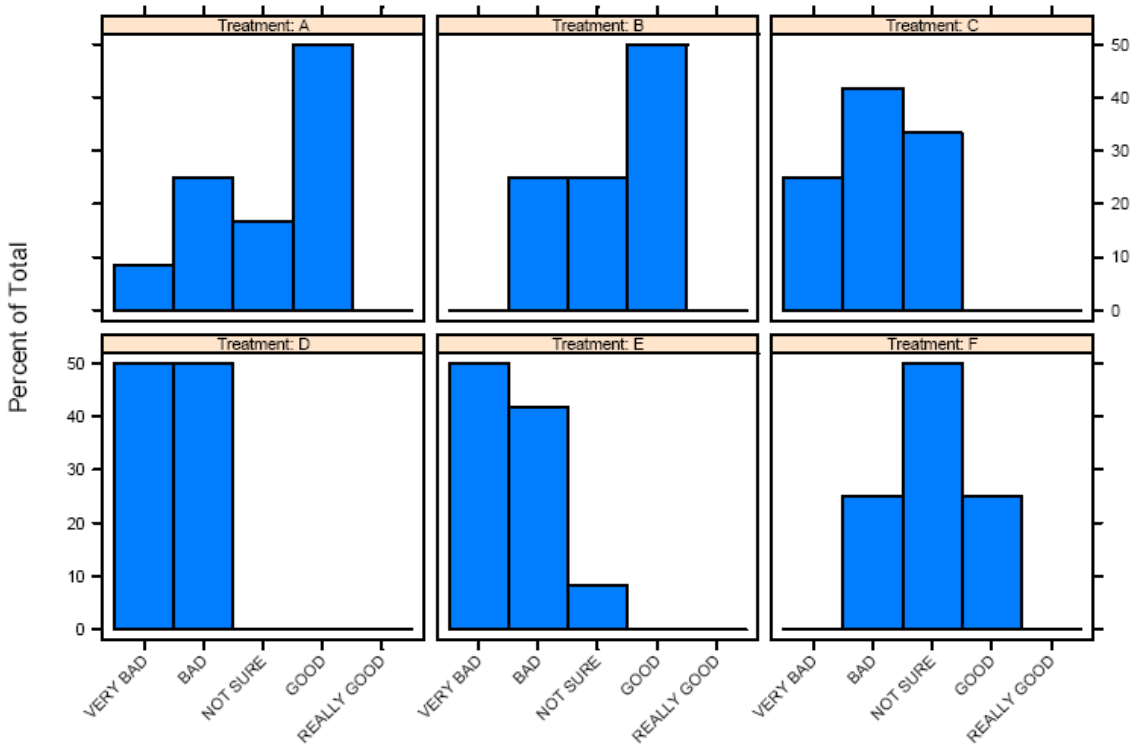
Study Design

This palatability study was a single-center, open-label, randomized, 6-sequence, 6-period, 6-treatment crossover study in healthy male and female subjects aged 18 to 65 years inclusive. A total of 12 subjects were enrolled in the study. All eligible subjects were administered saquinavir (1000 mg) once daily for 6 consecutive days mixed with one of the following test vehicles in either a plastic container or a spoon: simple sugar syrup (treatment A), sorbitol syrup (treatment B), apple puree (treatment C), carrot puree (treatment D), baby formula (treatment E), and jelly jam (treatment F). Each subject received each of the treatments once. After each administration, subjects were asked to verbally rate the taste of the treatment using a verbal smile face scale. Subjects were also asked for aftertaste at regular intervals for a period of 3 hours after drug administration.

Results & Conclusion

Taste assessments are presented in an individual listing and as a frequency summary by treatment (see Figure 2 below). In order to investigate the data and estimate odds of 'not bad' versus 'bad' with 95% confidence intervals for each treatment, the original 5-categorical taste assessments were dichotomized into 'bad' (combining 'very bad' and 'bad') and 'not bad' (combining 'not sure', 'good', and 'very good') and analyzed using a generalized linear mixed effects model with a logit link function including a fixed factor for treatment and a random factor for subject. Based on the estimated odds of 'not bad' versus 'bad', the ranking of the vehicles with respect to palatability is as follows: B=F>A>C>E>D.

Figure 2 Taste of SQV Opened Capsules in Different Food Vehicles



A: simple sugar syrup; B: simple sorbitol syrup; C: apple puree; D: carrot puree; E: baby formula; F: strawberry flavored jelly jam

4.6 Pharmacometrics Review

Introduction

The sponsor conducted 2 pivotal, pediatric PK and safety studies (HIVNAT017 and NV20911) along with 3 supportive non-pivotal studies evaluating saquinavir (SQV, Invirase®). SQV exposures were available from 18 subjects in NV20911 (<2 years: n=5; ≥2 through <6 years: n=13) and 19 subjects in HIVNAT017 (≥2 through <6 years: n=1; ≥6 through <10 years: n=13; ≥10 through <16 years: n=5). Pediatric subjects in NV20911 were administered SQV 50 mg/kg q12h and ritonavir (RTV) at either 3 mg/kg q12h for children weighing 5 to <15 kg or 2.5 mg/kg q12h for children weighing 15 to 40 kg. Pediatric subjects in HIVNA017 were administered LPV/RTV 230/57.5 mg/m^2 q12h and SQV 50 mg/kg q12h.

In addition to the pediatric exposure from the pivotal studies, one of the supportive studies (PACTG 397) included pediatric exposure measurements over 4–15 years (n=13); however, a separate formulation (Fortovase®) with increased bioavailability (30% higher) was used in this study. Pediatric subjects in PACTG 397 were administered SQV 50 mg/kg (up to a maximum of 1200 mg) q12h with RTV 100 mg/m^2 q12h in combination with 1 or 2 NRTIs.

A failed DSI inspection has questioned the validity of data from the two pivotal studies (HIVNAT017 and NV20911), and data from the supportive study (PACTG 397) has also not been validated. The reviewer analyzed if validation of data from NV20911 would allow for PK bridging between relevant adult and validated pediatric (2 through 5 years) SQV exposures to SQV exposures in pediatrics where data may be limited or unavailable (6 through 16 years). In addition, exposure-response relationships based on the pivotal pediatrics studies were developed as a supportive measure of the effectiveness of the proposed pediatric doses.

Objectives

Analysis objectives are:

1. Evaluate if the SQV exposures for pediatrics 2 through 5 and 6 through 16 years using the sponsor's dosing recommendations could be predicted based on population pharmacokinetic analysis from adults
2. Evaluate the exposure-response relationship between percentage of patients achieving virologic success (HIV-1 RNA <50 copies/mL at Week 48) and SQV exposure from HIVNAT017 and NV20911

Methods

Data Sets
Data sets used are summarized in Table 1.

Table 1. Analysis Data Sets

Study Number	Name	Link to EDR
NV20911	Demo.xpt, efval.xpt	\\Fdswa150\nonectd\N20628\S_034\2010-07-29\N20628 sNDA 072910\crt\Datasets\nv20911
HIVNAT017	Demo.xpt, efval.xpt	\\Fdswa150\nonectd\N20628\S_034\2010-07-29\N20628 sNDA 072910\crt\Datasets\HIV-NAT 017

PACTG 397	Patient.xpt, growth.xpt, pkdeauc.xpt, virol.xpt	\\Fdswa150\nonectd\N20628\S_034\2010-07-29\N20628 sNDA 072910\crt\Datasets\pactg397

Software
Simulations, graphing, and statistical analysis were performed in R (version 10.1).

Models

Pediatric SQV Exposure Simulations
Data from HIVNAT017 was found to be inadmissible as a result of the Division of Scientific Investigation (DSI) inspection findings. The bioanalytical results from study NV20911 was also called into question, though these deficiencies may be resolved by the bioanalytical site. To address the scenario where validated exposure data from pediatrics 6 through 16 year (mean population body weight: 20 through 60 kg) is unavailable, a population pharmacokinetic modeling approach was employed to use available adult and pediatric 2 through 6 year data for bridging pharmacokinetic exposures in pediatrics 6 through 16 years. There were three objectives using these population pharmacokinetic models:

1. Evaluate if the available models accurately predict mean SQV $AUC_{0\text{-}12h}$ for adults administered 1000/100 mg SQV/RTV q12h.

2. Evaluate mean SQV $AUC_{0\text{-}12h}$ predictions from the model in pediatrics 2 through 6 years using the sponsor's doses. Compare these predictions to mean SQV $AUC_{0\text{-}12h}$ from NV20911

3. Simulate mean SQV $AUC_{0\text{-}12h}$ for pediatrics 6 through 16 years and evaluate the range of exposures.

Typical population clearances for ritonavir and saquinavir based on population pharmacokinetic modeling were obtained from the literature. Equations for ritonavir (CL_{RTV}, Kappelhoff *et al.* (2005)) and saquinavir (CL_{SQV}, Dickinson *et al.* (2008)) are shown below:
$CL_{RTV} = 10.8 \cdot (WT/70)^{0.75}$
$CL_{SQV} = 69.8 \cdot (AUC_{RTV}/8.95)^{-0.4} \cdot (WT/70)^{0.75}$
Exposures were simulated over a body weight range of 10 through 70 kg. The sponsor's dosing recommendations for pediatrics (shown below) were used for determining SQV $AUC_{0\text{-}12h}$.

(b) (4)

[redacted]

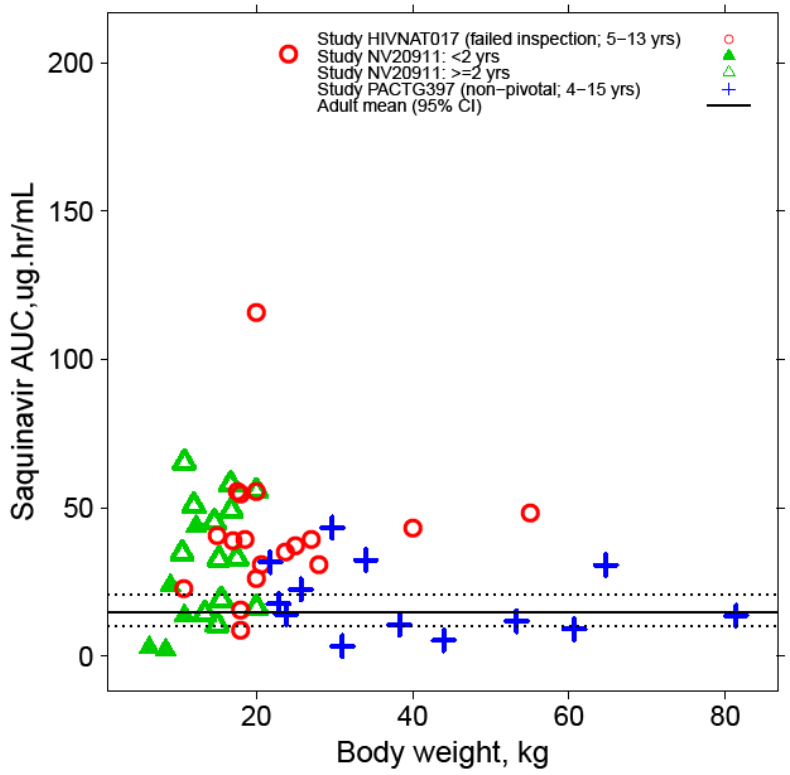
SQV dose was capped at 1000 mg q12h (reached at 20 kg) and RTV capped at 100 mg q12h (reached at 40 kg). Pediatrics weighing ≥40 kg are administered the adult dose of 1000/100 mg SQV/RTV q12h.

Logistic Regression: Efficacy Exposure-Response Relationships
Logistic regression models for virologic success (<50 copies/mL) were performed using the sponsor's pediatric HIVNAT017 and NV20911 trial data. $AUC_{0\text{-}12h}$ was the only independent variable explored in the logistic regression analysis.

Results

$AUC_{0\text{-}12h}$ from the two pivotal studies and $AUC_{0\text{-}12h}$ from PACTG 397 (Fortovase® formulation) adjusted based on the difference in bioavailability from the Invirase® (30% increase)formulation are plotted versus the respective pediatric body weights in Figure 1. Also shown are adult SQV exposures (mean AUC (95% CI): 14.6 (10.2; 20.9) µg·hr/mL) obtained from the SQV label. While the dosing recommendations are based on pediatric age intervals, a plot of SQV AUC versus body weight was constructed as: i) body weight/body mass index is the primary SQV covariate for clearance and volume of distribution; and ii) SQV is predominantly hepatically eliminated which would be influenced by liver maturation only at <2 years.

Figure 1: SQV exposures in pediatrics from studies HIVNAT017 (red circles), NV20911 (green triangles), and PACTG 397 (blue, plus marks) versus body weight. SQV treatment in all pediatric studies was 50 mg/kg q12h with differing RTV regimens. Mean (black, solid) and 95% CI (black, dashed) SQV exposure were obtained from the SQV label.

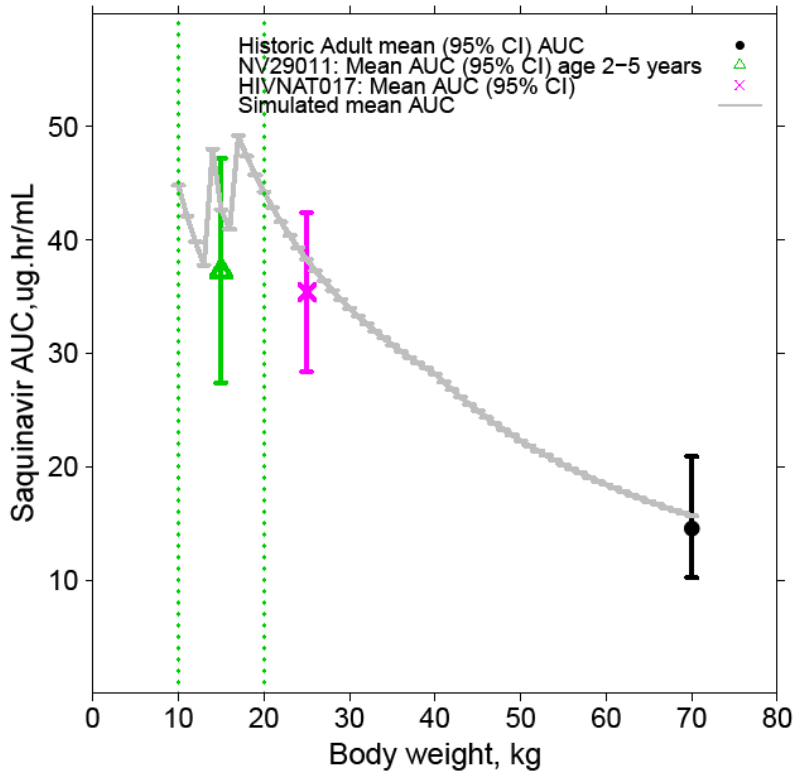


The SQV doses selected for the pediatric trials result in an increased exposure in pediatrics relative to adults for pediatrics >10 kg. Data from NV20911 and HIVNAT017 are in good agreement over 10–20 kg. Eight of the pediatric subjects from HIVNAT017 have body weight >20 kg (heaviest pediatric from NV20911), though only two of these pediatric subjects have body weight >30 kg. While a majority of the data for pediatrics >30 kg is from the PACTG 397, the exposures from this study demonstrate that the selected pediatric doses are similar to adult exposures for pediatrics 2–16 years.

Pediatric SQV Exposure Simulations

Predicted mean $AUC_{0\text{-}12h}$ for a 70 kg adult administered 1000/100 mg SQV/RTV q12h was 15.7 µg·hr/mL, which is in good agreement with the mean SQV $AUC_{0\text{-}12h}$ for the same dose and formulation from the SQV label (mean (95% CI): 14.6 (10.2; 20.9) µg·hr/mL). Likewise, mean $AUC_{0\text{-}12h}$ for pediatrics 2 through 5 years are predicted to range between 37.8–49.2 µg·hr/mL compared to observed mean exposures of 37.3 µg·hr/mL. These results, in addition to simulated mean $AUC_{0\text{-}12h}$ in pediatrics 6 through 16 years for the proposed sponsor's doses are shown in Figure . A similar plot but with data from HIVNAT017 is shown in Figure 2. Only pediatrics weighing 20–30 kg were included in the mean $AUC_{0\text{-}12h}$ calculation (mean (95% CI): 36.6 (30.2; 43.0) µg·hr/mL). In addition, the two pediatrics with the highest exposures were removed from the analysis (increase mean $AUC_{0\text{-}12h}$ to 49.6 µg·hr/mL). Predicted mean exposure for a pediatric weighing 25 kg receiving the sponsor's recommended dosing was 38.3 µg·hr/mL, which is also in reasonable agreement with the observed exposures.

Figure 2: Simulated mean SQV exposures for the proposed sponsor's pediatric dosing versus body weight. Observed mean and 95% CI SQV exposures from NV20911 (pediatrics, green triangle), HIVNAT017 (20-30 kg, cross), and the SQV label (adults, black circle) are shown for a 15 kg and 70 kg subject, respectively. SQV dosing in NV20911 was 600, 800, and 1000 mg q12h for pediatrics ≥10 through <14 kg, ≥14 through <17 kg, and ≥17 through <20 kg, respectively.



Exposure-Response Analysis Pediatric SQV Exposure Simulations

Significant exposure-response relationships between the percent of patients achieving virologic success and SQV $AUC_{0\text{-}12h}$ was identified using data from both pivotal pediatric studies, or data only from NV20911 (Figure 1 and Figure . A steeper exposure-response relationship was

observed when only data from NV20911 was analyzed, and this result is likely a result of the difference in treatments between NV20911 (lopinavir included in background regimen in 8 subjects) compared to HIVNAT017 (all subjects taking concomitant lopinavir). The predicted response rate at the adult mean exposure was 49% and 35% for the combined analysis and using only NV20911 data, respectively. Both of these predicted response rates are less than the response rate in adults (61%). However, the results of the exposure response relationships developed for pediatrics may be influenced by the small sample size. In addition, the adult response rate was based on HIV-1 RNA <400 copies/mL at Week 48, and a more stringent metric of <50 copies/mL would likely result in a lower response rate.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Pediatric_Data_Mapping.R	Assembles pediatric analysis data set and plot ER, AUC vs. body weight, and, simulated exposure vs. body weight figures	Reviews\Ongoing PM Reviews\Saquinavir_NDA20628_JAF\ER Analyses

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SHIRLEY K SEO
01/27/2011

JEFFRY FLORIAN
01/27/2011

JOGARAO V GOBBURU
01/27/2011

SARAH M ROBERTSON
01/27/2011