OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21785/S-034 (Tablet) 20628/S-011 (Capsule)	Submission Date: June 1, 2012
Brand Name	Invirase®
Generic Name	Saquinavir Mesylate
Pharmacometrics Reviewer	Jeffry Florian, Ph. D.
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OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Roche
Formulation; strength(s)	Eq. 200 mg base capsule; Eq. 500 mg base tablet
Indication	Treatment of HIV-1 infection in adults in combination with ritonavir other antiretroviral medications
Review Type	(b) (4) (pediatric)

Reference ID: 3223120

1 PERTINENT REGULATORY BACKGROUND

Saquinavir (SQV, INVIRASE) is a protease inhibitor approved for the treatment of HIV-1 infection in adults in combination with ritonavir (RTV) and other antiretroviral agents. The recommended SQV/RTV dose is 1000/100 mg b.i.d. in adults (16 years of age and older). Roche submitted (b) (4) three clinical trials evaluating the safety and efficacy of SQV in pediatric patients: PACTG397, HIVNAT017 and NV20911. (b) (4) .

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In addition, during the initial pediatric review the sponsor also provided the Division with results from a thorough QT study (NP21249) that evaluated the effects of SQV/RTV at 1000/100 and 1500/100 mg b.i.d. in healthy volunteers. Results from this study demonstrated significant QTc prolongation effect of SQV/RTV at 1000/100 mg and 1500/100 mg. The largest upper bounds of the 2-sided 90% CI for the mean difference between SQV/RTV 1000/100 mg and placebo, and between SQV/RTV 1500/100 mg and placebo were 22.0 ms at 12 hours and 32.6 ms at 20 hours after dose, respectively. In addition to prolonging the QTc interval, SQV/RTV prolonged the PR intervals in a dose-dependent manner. The largest mean PR interval difference (upper bound of 90% CI) between SQV/RTV 1000/100 mg and placebo, and between SQV/RTV 1500/100 mg and placebo were 28.6 ms (31.6 ms) at 5 hours and 38.4 ms (41.4 ms) at 6 hours after dose, respectively. These observations led to inclusion of the following contraindications and warnings and precautions in the SQV label:

CONTRAINDICATIONS

(b) (4)

- INVIRASE is contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or patients who are at high risk of complete AV block

WARNINGS AND PRECAUTIONS

- QT and PR interval prolongations have been observed in a healthy volunteer study. Use with caution in patients with preexisting conduction system abnormalities and certain heart diseases

(b) (4)

Specifically, the review focuses on comparing observed pediatric exposures at the evaluated doses in NV20911 to SQV exposures in HIV-1 infected adults, (b) (4) .

2 SUMMARY OF FINDINGS

2.1 Key Review Questions

The purpose of this review is to address the following key questions.

2.1.1 Do the studied pediatric saquinavir/ritonavir (SQV/RTV) doses in NV20911 result in similar SQV exposure to that observed in adults?

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 35-194% higher in AUC0-12h and 56-320% higher in C_{max} values than mean adult values (using the range of historical means as comparison).

Table 1: Summary of Pediatrics SQV PK from Study NV20911, Adult SQV PK from the Invirase Label, and Historic Descriptions of Adult SQV PK from the Literature

Age	Dosing Regimen	AUC0-12h (µg·hr/mL) (Range) [CI]	Cmax (µg·hr/mL) (Range) [CI]	Cmin (µg·hr/mL) (Range) [CI]	Source of Data
2 to < 6 yrs	SQV 50 mg/kg BID + RTV [3 mg/kg (body weight 5-<15 kg); 2.5 mg/kg (body weight 15-40 kg)]	37.3 (10.6-65.3)	6.1 (1.6-10.3)	1.8 (0.47-3.4)	NV20911 (n=13)
Adults	Invirase 1000 mg BID + RTV 100 mg BID	14.6 [10.2-20.9]	Not provided	0.37 [0.25-0.56]	Label
Adults	Fortovase 1000 mg BID + RTV 100 mg BID	19.1 [13.9-26.1]	Not provided	0.43 [0.30-0.62]	Label
Adults	Invirase 1000 mg BID + RTV 100 mg BID	12.7-27.7	1.9-3.9	0.31-0.78	Literature

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2.1.4 Is there evidence of an exposure-response relationship for SQV/RTV exposures and either QT or PR prolongation?

The sponsor conducted a thorough QT study (NP21249) in healthy volunteers at SQV/RTV doses of 1000/100 mg and 1500/100 mg. These results demonstrated significant QTc prolongation effect of SQV/RTV (Upper 2-sided 90% CI: 22.0 ms for SQV/RTV 1000/100 and 32.6 ms for SQV/RTV 1500/100 at 12 and 20 h, respectively). However, the maximum observed QT prolongation occurred at 12-20 h post-dose, while maximum concentrations for SQV (and metabolites) and RTV were 4-6 h post-dose. An exposure-response relationship could not be identified between SQV exposure and QT prolongation due to the observed delayed increase in QT prolongation with respect to concentration profiles (from the IRT-QT review):

- The QT effect at 12 h post-dose on Day 3 is expected to be the same as the predose values on the same day. However, this was not observed.
- If the data were true, the QT effect seems to continue to rise even after 3 days coinciding with delayed effects seen with trafficking inhibitors like arsenic trioxide. The maximum response was not captured.

However, a dose-response between SQV and QT prolongation for the two studied doses was observed. In addition to QT prolongation, a concentration-response relationship was identified for PR interval prolongation (Mean (upper 2-sided 90% CI): 28.6 (31.6) ms for SQV/RTV 1000/100 and 38.4 (41.4) ms for SQV/RTV 1500/100 at 5 and 6 h post-dose, respectively).

These assessments were performed at Day 3 of SQV dosing as a previous dose finding study (NP21562) identified that maximum SQV exposures occurs on Day 3 due to the timing of maximal inhibition of CYP3A-mediated metabolism of SQV by the

mechanism-based inhibitor, ritonavir. In addition, healthy volunteers have 75% to 100% higher SQV exposures than HIV-1 infected adults for the same doses. In order to interpret the QT and PR prolongation observations from the thorough QT study in the context of HIV-1 infected adults and pediatrics at day 3 and steady state, we constructed a summary table of C_{max} and AUC based on reported SQV exposures (Table 2). As day 3 exposures in HIV-1 infected adults and pediatrics was unavailable, we assumed the scaling observed in healthy volunteers between day 3 and steady state (AUC: 2.6-3.3 fold; C_{max} 1.8-2.3 fold) would be observed in HIV-1 infected subjects (shown in italics below). The steady-state exposures observed in pediatrics from NV20911 are similar to those observed at steady state in healthy volunteers administered SQV/RTV 1000/100 mg BID, which exceed the adult HIV-1 infected exposures by 35-194%. Without information on the day 3 exposures in HIV-1 infected pediatrics, a conservative assumption is that exposures in HIV-1 infected pediatrics will also be similar to those observed in healthy volunteers at day 3 (which, similarly, exceed those predicted for HIV-1 infected adults).

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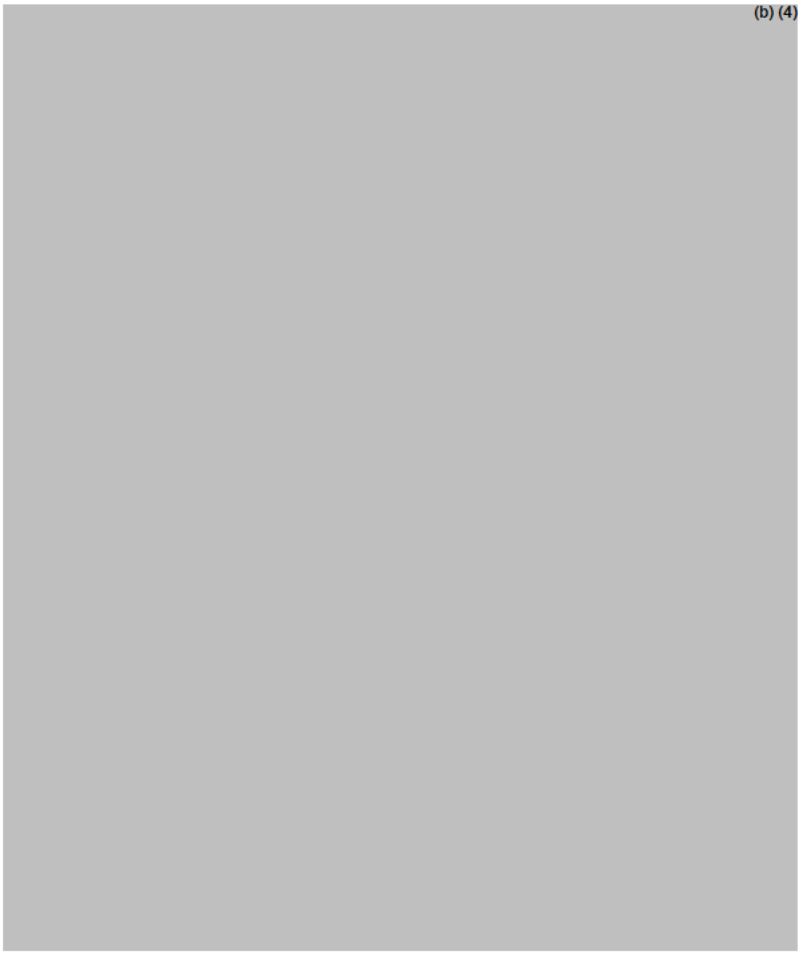
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a dosing regimen that is both safe and efficacious according to the criteria listed above could not be determined using the available data.

(b) (4)

2.2 Recommendations

(b) (4). The pediatric SQV doses (50 mg/kg) evaluated by the sponsor in NV20911 resulted in SQV exposures exceeding those observed in adults. (b) (4)

Therefore, a dosing regimen considered both safe and efficacious in pediatrics could not be determined based on the available data.

2.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

(b) (4)

- Pediatric Use:. Pediatric dose recommendations that are both reliably effective and below thresholds of concern with respect to QT and PR prolongation could not be determined (8.4)

1 INDICATIONS AND USAGE

INVIRASE in combination with ritonavir and other antiretroviral agents is indicated for the treatment of HIV-1 infection in adults (age 16 and older) (b) (4)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose (b) (4)

- INVIRASE 1000-mg twice daily (5 x 200-mg capsules or 2 x 500-mg tablets) in combination with ritonavir 100-mg twice daily.
- Ritonavir should be taken at the same time as INVIRASE.
- INVIRASE and ritonavir should be taken within 2 hours after a meal.

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- No additional ritonavir is recommended when INVIRASE is administered with lopinavir/ritonavir 400/100 mg twice daily
- Pediatric dose recommendations that are both reliably effective and below thresholds of concern for QT and PR interval prolongation could not be determined

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(b) (4)

2.2 Administration for Patients Unable to Swallow Capsules

Open the INVIRASE capsules and place the contents into an empty container. Add 15 mL of either sugar syrup or sorbitol syrup (for patients with Type 1 diabetes or glucose intolerance) **OR** 3 teaspoons of jam to the contents of INVIRASE capsules that are in the container. Stir with a spoon for 30 to 60 seconds. Administer the full amount prepared for each dose. Suspensions should be at room temperature before administering.

8.4 Pediatric Use

(b) (4)

Steady state saquinavir exposures observed in pediatric trials were substantially higher than historical data in adults where dose- and exposure-dependent QTc and PR prolongation were observed [*see Warnings and Precautions (5.3), Clinical Pharmacology (12.2, 12.3)*]. Although electrocardiogram abnormalities were not reported in these pediatric trials, the trials were small and not designed to evaluate QT or PR intervals. Modeling and simulation assessment of pharmacokinetic/pharmacodynamic relationships in pediatric subjects suggest that reducing the INVIRASE dose to minimize risk of QT prolongation is likely to reduce antiviral efficacy. In addition, no clinical efficacy data are available at Invirase doses less than 50 mg per kg in pediatric subjects. Therefore, pediatric dose recommendations that are both reliably effective and below thresholds of concern with respect to QT and PR prolongation could not be determined.

12.3 Pharmacokinetics

Pediatric Patients

Steady-state pharmacokinetic information is available from HIV-infected pediatric subjects (b) (4) from study NV20911. In this study, 5 subjects (b) (4) less than 2 years of age and 13 were between 2 and less than 6 years of age and received 50 mg/kg

saquinavir twice daily (not to exceed 1000 mg twice daily) boosted with ritonavir at 3 mg/kg for patients with body weight ranging from 5 to <15 kg or 2.5 mg/kg for patients with body weight ranging from 15 to 40 kg (not to exceed 100 mg twice daily). For subjects unable to swallow the INVIRASE capsules, the contents of INVIRASE 200 mg capsules were mixed with sugar syrup, or sorbitol syrup (for subjects with Type I diabetes or glucose intolerance), jam, or baby formula. (b) (4) The mean steady state saquinavir PK parameters for pediatric subjects 2 to less than 6 years of age were: $AUC_{0\text{-}12h}$ 37269 ± 18232 ng·h/mL; C_{trough} 1811 ± 998 ng/mL; C_{max} 5464 ± 2782 ng/mL, and day 3 exposures may be within the range of exposure associated with QT and PR prolongation [see *Clinical Pharmacology: Pharmcodynamics (12.2)]*. The subject number was too low and the pharmacokinetic data too variable in the lowest age group (less than 2 years) to establish an appropriate dosing recommendation for this age group. Pharmacokinetic data for subjects ages 6 to 16 years were not available for comparisons with observations from NV20911 [*see Use in Specific Populations: Pediatric Use (8.4)]* as the data from HIVNAT 017 could not be validated.

(b) (4)

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3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Introduction

Roche has performed a population pharmacokinetic bridging analysis using data from adults and available pediatric data from NV-20911 study with the aim of simulating saquinavir exposures of HIV-infected patients [HIVNAT 017] for whom pharmacokinetic (PK) data are lacking but clinical data are available (e.g. efficacy and safety, including demographics and efficacy). Included in this submission is population pharmacokinetic modeling report for saquiniavir boosted with ritonavir in adults and pediatrics infected with HIV-1.

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3.2 Population Pharmacokinetic Model

Report m-s-analysis-v3-20120301.pdf: Modelling and Simulation Analysis Report: Population pharmacokinetic modelling of ritonavir-boosted saquinavir in paediatric and adult HIV-infected patients (bridging pharmacokinetics between adults & children)

3.2.1 Data Sets

The adult data set used in the population PK analysis included 48 patients with 1-6 pharmacokinetic profiles contributing 1309 SQV plasma concentrations. Participants were administered 500 mg film coated tablets with ritonavir at 1000/100 mg b.i.d. daily. Pharmacokinetic sampling was performed at steady-state following a meal containing 20g, 40g or 66g of fat or under fasting conditions depending on the study. Blood was collected pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose. Depending on the study, SQV measurements may have been made on more than one occasion resulting in more than one pharmacokinetic profile for a patient. In addition, some patients participated in more than one study therefore also resulting in multiple profiles.

The pediatric data set consisted of 18 pediatric patients with between 1-2 full pharmacokinetic profiles plus sparse sampling and totaled 178 plasma concentrations. Concentration-time data from 5 patients were removed as the children were aged below 2 years. The dataset was therefore reduced to 13 pediatric patients with 1-2 profiles, 49 sparse samples and a total of 134 plasma concentrations. These data were added to the final adult dataset to perform the pooled adult and pediatric pharmacokinetic modeling analysis. Pharmacokinetic sampling was undertaken during a 48 week dosing period at steady-state following a meal (day 14 of dosing if not previously on an nonnucleoside reverse transcriptase inhibitor or 28 of dosing if previously received a nonnucleoside reverse transcriptase inhibitor) pre-dose and 3, 4, 8 and 12 h post-dose. Additional pre-dose sampling was performed during weeks 8, 12 and 24 plus a 4h postdose sample at week 24. If any paediatric patients required a dose adjustment a predose sample and full profile were repeated within 14 days. If patients could not swallow capsules the capsule contents were mixed with sugar syrup (or sorbitol syrup for those glucose intolerant or with Type I diabetes), jam or baby formula.

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Table 7: Summary of demographic parameters for HIV-infected adults and children included in the pharmacokinetic modeling analysis of ritonavir-boosted saquinavir

Parameter	ADULT	PAEDIATRIC
	Median (range)*	
Sex [n (%)]		
Male	38 (79)	5 (38)
Female	10 (21)	8 (62)
Age (years)	44 (22-63)	4 (2-5)
Weight (kg)	72 (45-108)	15 (11-21)
Body mass index (kg/m^2)	23 (14-39)	16 (14-19)
Saquinavir concentration (mg/L)	1.09 (0.020-15.77)	2.43 (0.036-16.00)
Ritonavir AUC_{0-12} (mg.h/L)	9.03 (1.56-22.53)	8.84 (0.65-15.80)

* Unless stated otherwise
AUC_{0-12}, area under the concentration-time curve over the 12h dosing interval

Sponsor's m-s-analysis-v3-20120301.pdf, page 31

3.2.2 Population PK Model Development

Nonlinear mixed effects modeling was applied using NONMEM (version VI 2.0). First-order conditional estimation with interaction (FOCE-I) was used throughout the modeling process. The previously published adult model used a one-compartment model with zero-order absorption to describe the SQV data (using first order estimation, FO) however a two-compartment model was also explored with the reduced adult dataset along with first-order absorption, zero-order absorption and sequential first and zero-order absorption. The minimal objective function value (OFV; equal to -2 log likelihood) was used as a goodness-of-fit diagnostic with a decrease of 3.84 points corresponding to a statistically significant difference between nested models.

Parametric modeling methods were used and it was assumed that the random effects of the parameters followed a normal (parametric) distribution. For this analysis all interindividual and interoccasion variability (IIV and IOV, respectively) terms (random effects) were described by an exponential model

The following covariates were to be explored: age, weight, body mass index (BMI), body surface area (BSA), fat free mass (FFM), sex, ritonavir area under the curve over the dosing interval (AUC0-12) and food type (fasting; 20g fat; 40g fat; 66g fat). The fat content of the pediatric meals (e.g. baby formula) was not known so it was assumed to approximate to the 20g fat food type of the adults. For the pediatric dataset, ritonavir

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AUC0-12 was only generated on the intensive sampling days and so these values were also used for the sparse sampling days.

All final models determined from the modeling methods outlined previously were assessed by internal validation processes using simulations and visual predictive check If possible bootstrap with re-sampling and replacement from the original dataset was also performed. One thousand patients per model were simulated with the same distribution of covariates as the original dataset (if any were found to be significant) and also with the same distribution of occasions. A 90% prediction interval (P5-P95) was constructed and observed data superimposed. It is indicative of an adequate model if at least 90% of observations are within the prediction interval.

For models for which bootstrapping could be carried out, two hundred bootstrap runs were performed using Perl-Speaks-NONMEM and mean (95% confidence intervals; CI) of fixed and random effects were calculated and compared to the original model estimates. Results from runs that failed to minimize successfully were also be included in the calculations.

The final model best describing the pharmacokinetics of ritonavir-boosted SQV in HIV-infected children 2 to <6 years was taken forward to simulate SQV exposures for HIV-infected patients aged between 2-16 years (100 simulations per patient). Pharmacokinetic data were not available for these patients however demographic data, such as age and weight were available. If data for a covariate included in the model were lacking, values were simulated from the distribution of the covariate from the original dataset. In addition secondary pharmacokinetic parameters, SQV AUC0-12, maximum concentration (Cmax), time of maximum concentration (Tmax), trough concentration (Ctrough) and half-life were calculated using the following analytical solutions:

$AUC_{0\text{-}12} = Dose/CL/F$

$C_{max} = (Dose*k_a/(V/F*(k_a-k)))*((\exp(-k*T_{max}))/(1-\exp(-k*\tau)))-(\exp(-k_a*T_{max})/(1-k_a-\exp(-k_a*\tau)))$

$Tmax = (1/(ka-k))*Ln((ka*(1-\exp(-k*\tau)))/(k*(1-\exp(-ka*\tau))))$

$Ctrough = Dose/V/F*(ka/(ka-k))*((\exp(-k*\tau)/(1-\exp(-k*\tau)))-(\exp(-ka*\tau)/(1-\exp(-ka*\tau))))$

3.2.3 Population PK Model Results

Adult Model

Based on the previous full model of 97 patients and visual inspection of the concentration-time plots a one-compartment model parameterized by apparent oral clearance (CL/F), apparent volume of distribution (V/F) and absorption rate constant (ka) was considered appropriate to describe the data. Inclusion of a lag-time and then use of sequential first and zero-order significantly improved the fit.

Following univariate analysis, weight, BMI and FFM were evaluated for their association with SQV CL/F and V/F using allometric scaling and a linear function. None of the covariates produced a significant drop in OFV or reduced variability. Furthermore no significant relationship between sex and CL/F, V/F or ka was observed. Ritonavir AUC0-

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12 was significantly associated with SQV CL/F and V/F and ultimately included as a power relationship for both parameters.

Pooled Adult and Pediatric Data

A starting point of a one-compartment first-order absorption model (IIV included on CL/F) with a proportional error was used. Changing the absorption process to zero-order significantly improved the fit, and this was further improved by moving to sequential first-order and zero-order absorption.

Use of the mixture model for CL/F randomized patients to two groups – POP1 and POP2. The distribution in POP1 was 3% (n=2 pediatric patients) and 97% in POP2 (n=11 pediatric patients, n=48 adult patients). Following univariate analysis, weight (allometric scaling), age (power relationship), FFM (power relationship), ritonavir AUC0-12 (power relationship), sex and BMI (power relationship) showed significant associations with SQV CL/F, and ritonavir AUC0-12 with V/F (power relationship), however model runs tended to be unstable and full convergence was often difficult. Once multivariate analysis was performed allometric scaling with weight (POP1 and POP2) and ritonavir AUC0-12 (POP2) remained on CL/F and ritonavir AUC0-12 (POP2) remained on V/F.

Pediatric Model Based On Prior Adult Data

SQV data from pediatric patients were modeled separately to adult data; however information from the adult model was included as a prior for all or some of the pediatric pharmacokinetic parameters. Priors were included on fixed effects and IOV CL/F and random effects were only included on IIV CL/F. The zero-order absorption process was removed due to limited absorption data in the pediatric data set. Ritonavir AUC0-12 was the only covariate with a significant association with SQV CL/F and was included using a power law function. Final model parameters are summarized in Table 8.

Table 8: Final saquinavir parameter estimates and associated relative standard errors for HIV-infected paediatric patients (excluding patient #4302) using prior information from an adult model for absorption rate constant and interoccasion variability on apparent oral clearance.

	Estimate (RSE%)	*IIV (%) (RSE%)*	*IOV (%) (RSE%)*
Parameter			
CL/F (L/h)	18.9 (10.3)	50.1 (18.7)	21.4 (41.1)
V/F (L)	169 (17.1)		
k_a (h^{-1})	2.35 (24.5)		
Covariates			
θ_{RTVAUC} on CL/F	-0.0509 (35.2)		
Proportional error (%)	52.9 (18.0)		

RSE% = $SE_{ESTIMATE}$/ESTIMATE * 100 IIV/IOV: Interindividual/Interoccasion variability
RSE%: Relative standard error

Sponsor's m-s-analysis-v3-20120301.pdf, page 41

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Simulations of SQV Exposures in Pediatric Subjects 2 Through 16 Years

The parameter estimates from the final selected model were used to simulate SQV concentration-time curves in 50 HIV-infected pediatric patients [median (range) age and weight 9 years (4-15) and 20 kg (11-55), respectively]. Of the 50 patients 74%, 22% and 4% were receiving 1000 mg, 800 mg and 600 mg of boosted SQV, respectively. Ritonavir AUC_{0-12} data were not available and as this was a covariate in the model ritonavir AUC_{0-12} were simulated using the distribution of AUC_{0-12} from the original pediatric dataset. SQV CL/F and secondary pharmacokinetic parameters AUC_{0-12}, C_{max}, C_{trough}, T_{max}, half-life and simulated ritonavir AUC_{0-12} are summarized in Table 9

Table 9: Summary of simulated saquinavir pharmacokinetic parameters generated for 50 HIV-infected pediatric patients for whom saquinavir concentration-time data were unavailable.

Parameter	Median	Range	Mean	s.d.	CV%	P5	P95
Ritonavir AUC_{0-12} (mg.h/L)*	8.64	0.66-15.80	8.57	3.57	41.61	2.43	14.43
CL/F (L/h)	19.13	7.50-46.55	19.82	5.62	28.38	12.07	30.19
Saquinavir AUC_{0-12} (mg.h/L)	49.10	13.12-133.35	51.29	15.83	30.87	29.50	80.40
C_{max} (mg/L)	6.97	3.23-13.80	7.08	1.37	19.37	4.96	9.49
T_{max} (h)	1.22	1.02-1.34	1.22	0.05	4.08	1.13	1.29
C_{trough} (mg/L)	1.99	0.16-8.58	2.22	1.12	50.49	0.79	4.31
Half-life (h)	6.12	2.52-15.62	6.39	1.82	28.42	3.88	9.71

* Simulated from the distribution of ritonavir AUC_{0-12} of the original paediatric dataset

Sponsor's m-s-analysis-v3-20120301.pdf, page 44

A summary of observed SQV exposures in pediatrics from NV20911 (2 through 5 years) and model predictions based on demographics in HIVNAT017 are described below in Table 10.

Table 10: Pharmacokinetic parameters of saquinavir at steady-state in HIV-infected pediatric patients.

			Mean ± SD Saquinavir Pharmacokinetic Parameters		
Study	**Age Group** (Years)	**N**	**AUC_{0-12h} (ng•h/mL)**	**C_{trough} (ng/mL)**	**C_{max} (ng/mL)**
NV20911	2 to < 6	13	37269 ± 18232	1811 ± 998	5464 ± 2782
Modeling	4-15	50	51290 ± 15830	2220 ± 1120	7080 ± 1370

Sponsor's 20120529-clinical-rsponse-fda-req-info.pdf, page 5

Reviewer's Comments: (b) (4)

(b) (4)

4 REVIEWER'S ANALYSIS

4.1 Introduction

The sponsor conducted 2 pediatric PK and safety studies (HIVNAT017 and NV20911) along with 3 supportive non-pivotal studies evaluating SQV (SQV, Invirase®). (b) (4)

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.

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This review extends the sponsor's provided PK modeling to include body weight covariates (b) (4)

4.2 Objectives

Analysis objectives are:

1. Evaluate the sponsor's population PK model developed using data from adults and pediatrics 2 through 5 years of age

2. Compare model predicted and observed pediatric SQV exposure data to that from HIV-1 infected adults and healthy volunteers to inform efficacy and safety of the exposures, respectively
3. [redacted] (b) (4)

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 11.

Table 11. 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
Population PK	Poppkad1.xpt, poppkad2.xpt, poppkped.xpt	\\Cdsesub1\evsprod\NDA020628\0010\m5\datasets\m-s-analysis\analysis
Population PK	Poppkad1.txt, poppkad2.txt, poppkped.txt	\\Cdsesub1\evsprod\NDA020628\0010\m5\datasets\m-s-analysis\analysis\programs
MaxCmin1	Hivrna.xpt, demo2.xpt, resp.xpt	\\Fdswa150\nonectd\N20628\S_020\2003-10-15\Other\datasets
MaxCmin1	Pk.xpt	\\Fdswa150\nonectd\N21785\N_000\2004-08-12\crt\datasets\MaxCMin1 PK

4.3.2 Software

Population PK analyses were performed using NONMEM v 7.2 (Icon, Ellicott City, MD). Simulations, graphing, and statistical analysis were performed in R (version 12.1; www.r-project.org).

4.3.3 Models

4.3.3.1 Population PK Model for SQV

To bridge exposures observed in pediatrics 2 through 5 years and adults (i.e., to inform pediatric dosing in pediatrics 6 through 16 years) a population pharmacokinetic modeling approach was employed. The model evaluation used the full pediatric and adult data set provided by the sponsor and discussed above in Table 7. In addition, initial model exploration began with the final HIV-1 infected adult model identified by the sponsor. The model was later altered to remove the zero order absorption term due to limited absorption observations available between the combined pediatric and adult data set. All random effects from the original adult model (IIV on k_a, CL/F, and V/F; IOV on CL/F and V/F) were included during evaluation.

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Due to the limited data available and the focus of this population PK evaluation (i.e., development of a population PK model suitable for informing SQV exposures in pediatrics 2 through 16 and exploring alternative SQV dosing scenarios), a full covariate exploration was not performed. Instead, covariate evaluation was limited to those identified during the original model analysis (RTV as a power law covariate on CL/F and V/F) and the inclusion of body weight as a power law covariate on CL/F and V/F.

SQV AUC was calculated according to Dose/(CL/F).

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4.3.3.3 Exposure-Response Relationships for SQV: Safety

Pediatric and adult SQV exposures were related to previously identified dose-response and exposure-response relationships identified during the Interdisciplinary Review Team (IRT) QT review for SQV.

The sponsor conducted a thorough QT study (NP21249) in healthy volunteers at SQV/RTV doses of 1000/100 mg and 1500/100 mg. These results demonstrated significant QTc prolongation effect of SQV/RTV (Upper 2-sided 90% CI: 22.0 ms for SQV/RTV 1000/100 and 32.6 ms for SQV/RTV 1500/100 at 12 and 20 h, respectively). However, the maximum observed QT prolongation occurred at 12-20 h post-dose, while maximum concentrations for SQV (and metabolites) and RTV were 4-6 h post-dose. An exposure-response relationship could not be identified between SQV exposure and QT prolongation due to the observed delayed increase in QT prolongation with respect to concentration profiles (from the IRT-QT review). However, a dose-response between SQV and QT prolongation for the two studied doses was observed. In addition to QT prolongation, an exposure-response relationship was identified for PR interval prolongation (Mean (upper 2-sided 90% CI): 28.6 (31.6) ms for SQV/RTV 1000/100 and 38.4 (41.4) ms for SQV/RTV 1500/100 at 5 and 6 h post-dose, respectively).

A table of exposures for HIV-1 infected adults and pediatrics and healthy volunteers at steady state and day 3 was constructed based on data available from NP21562 and NP21249 (dose finding and thorough QT study in healthy volunteers), the SQV label, literature, and the results of NV20911. Not included in this assessment were the predicted pediatric exposures from HIVNAT017 based on the sponsor's provided population PK modeling.

Table 12: Summary of SQV PK in HIV-1 Infected Pediatrics and Adults and Healthy Volunteers

Population	Regimen, SQV/RTV (mg, b.i.d.)	Saquinavir AUC, ug*hr/mL (SD) [CI] Day 3	Saquinavir AUC, ug*hr/mL (SD) [CI] Steady state	Saquinavir Cmax, ug/mL (SD) [CI] Day 3	Saquinavir Cmax, ug/mL (SD) [CI] Steady state
Healthy vounteers (NP21562)	1000/100	-	36 6 (9 7)	-	6 1 (1 5)
Healthy vounteers (NP21249)	1000/100	94 8 (30 6)	-	11 2 (3 3)	-
Healthy vounteers (NP21562)	1500/100	-	42 7 (20 9)	-	6 8 (3 1)
Healthy vounteers (NP21249)	1500/100	141 0 (44 3)	-	15 9 (4 4)	-
HIV-1 Infected Adults (Label)	1000/100	*37.8-48.2*	14 6 [10 2-20 9]	-	Not provided
HIV-1 Infected Adults (Literature)	1000/100	*32.9-91.5*	12 7-27 7	*3.5-9.1*	1 9-3 9
HIV-1 Infected Pediatrics 2 to <6 Years (NV20911)	50 mg/kg, 3 mg/kg (body weight 5-<15 kg) or 2 5 mg/kg (body weight 15-40 kg	*96.6-123.2*	37 3 [10 6-65 3]	*11.2-14.3*	6 1 [1 6-10 3]

4.3.3.4 Pediatric SQV Exposure Simulations

Mean SQV $AUC_{0\text{-}12h}$ for pediatrics 6 through 16 years were simulated using the developed SQV population PK. Exposures were simulated over a body weight range of 10 through 70 kg. (b) (4)

(b) (4)

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.

RTV exposures were included during model evaluation using a RTV AUC versus body-weight relationship identified based on observations in adults and pediatrics. A linear mixed-effects modeling approach was used to determine the relationship between RTV CL and body weight after log-transformation based on provided subject demographics (body weight), studied RTV dose, and reported RTV AUC. This analysis identified a typical RTV CL/F of 8.2 L/hr for a subject weight 40 kg, a body weight power law relationship with exponent of 0.55, and an interindividual variability in RTV CL of 30% (with the data available, a covariance could not be identified between IIV of RTV CL/F and SQV CL/F).

In addition, as the sponsor's pediatric doses evaluated in NV20911 resulted in exposures exceeding those observed in adults, alternative pediatric SQV/RTV dosing was also evaluated. These evaluated dosing scenarios targeted either a typical SQV $AUC_{0\text{-}12h}$ of 20 or 30 µg·hr/mL. These dosing scenarios corresponded to pediatric dosing nomograms described below in section 4.4.3.

4.4 Results

4.4.1.1 Population PK Model for SQV

Final model parameters based on the full adult and pediatric data sets are shown below in Table 13 with diagnostic graphs in Figure 6. Individual and population predicted concentrations agree well with observed concentrations and are symmetric around the line of unity. Similarly, weighted residuals versus observed concentrations were distributed symmetrically around zero and were not skewed at high/low concentration observations. Relative standard errors were typically less than 20% for most model fixed effects except for parameters describing food effects on SQV exposure. These were included in the model as they were identified from the original adult data, one of the adults studies (SSAT013) was a dedicated food effect study where differences in SQV exposure based on accompanying meal was observed, and inclusion of these parameters reduced the interindividual variability in clearance (otherwise, inflated due to known food effects on SQV clearance). As the impact of a medium fat meal relative to a low fat meal resulted in only a 4% decrease, this food effect parameter was removed from the model to improve stability. RTV AUC was identified as a covariate on both clearance and volume of distribution, similar to the original model proposed by the sponsor. The inclusion of this covariate on both terms likely means that RTV is impacting both bioavailability and clearance. As the number of parameters would be equivalent if the covariate was included on both bioavailability and clearance instead of volume and clearance, the model structure was left unchanged.

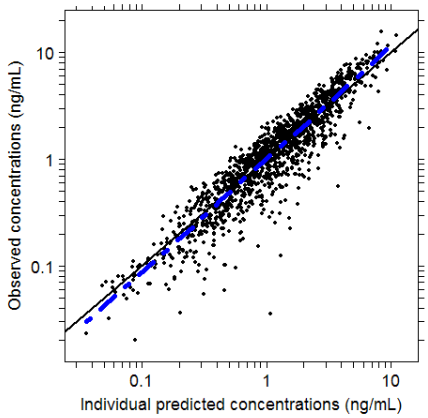
Table 13: Parameter estimates for the reviewer's analysis from the combined adult and pediatric data sets.

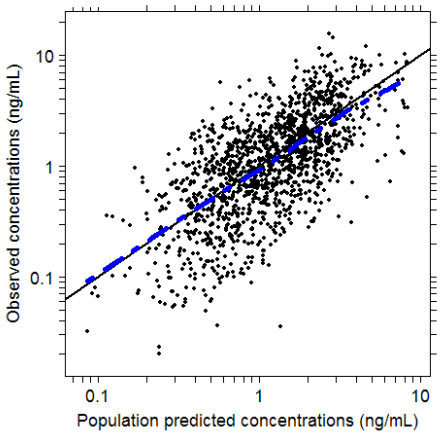
Fixed-Effects Parameters	Estimate	RSE(%)	CI95
Typical CL (Clearance)	42.5	7.6	(36.1-48.9)
Normalized body weight (40 kg) on clearance	0.69	15.7	(0.48-0.90)
Normalized RTV AUC on clearance	-0.89	9.1	(-1.04--0.73)
$CL = TVCL * (WT/40)^{0.69}(RTV\ AUC/8.9)^{-0.89}$			
V (Central volume)	106	14.9	(75.0-137.0)
Normalized body weight (40 kg) on volume	0.46	31	(0.18-0.74)
Normalized RTV AUC on volume	-0.72	13.1	(-0.90--0.54)
$V = TVV * (WT/40)^{0.46}(RTV\ AUC/8.9)^{-0.72}$			
KA (Oral Absorption)	0.24	8.6	(0.19-0.28)
ALAG1 (Time Delay)	0.84	2.2	(0.81-0.88)
F1 (Bioavailability for low or medium meal)	1	-	-
Meal with fat (relative to low fat meal)	1.28	24.5	(0.66-1.90)
Fasting (relative to low fat meal)	-0.19	65.9	(-0.44-0.06)

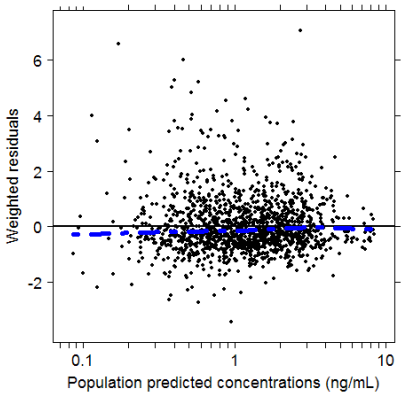
Inter-Individual Variability Parameters (CV%)	Estimate	RSE(%)	Shrinkage(%)
CL	46	10.3	4.8
Corr(CL-V)	0.8	15.5	-
V	34	22.9	18
KA	17	28.9	39
Interoccasion variability - CL	54	9.5	15
Interoccasion variability - V	72	8.1	10

Intra-Individual Variability Parameters	Estimate	RSE(%)	Shrinkage(%)
Additive Error	0.011	117	
Proportional Error	0.38	2.5	

Figure 6: Diagnostic plots for the final PK model.







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(b) (4)

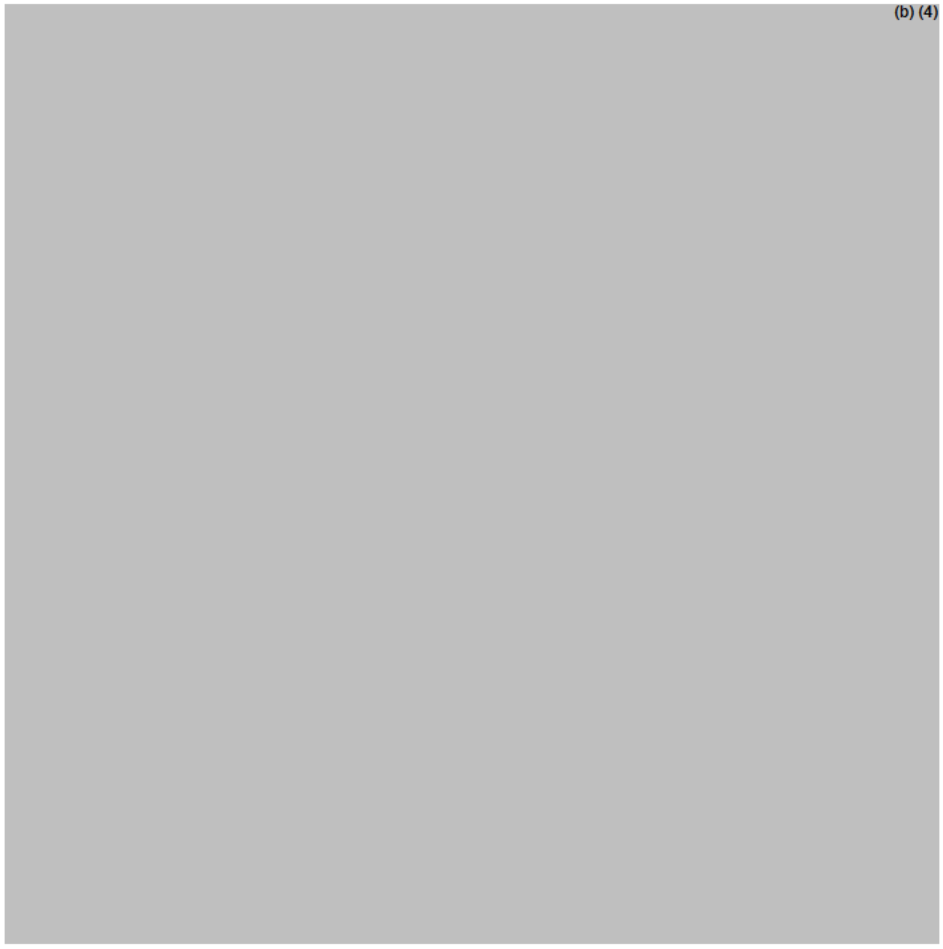
4.4.3 Pediatric SQV Exposure Simulations

Alternative SQV dosing in pediatrics patients was evaluated targeting either an AUC of 30 or 20 µg·hr/mL. The rationale for each of these exposure targets was an intermediate exposure between the exposures observed in NV20911 and the typical exposure in adults and exposure-matching with those observed in adults. It was recognized that exposures exceeding those in adults may have increased safety concerns related to QT prolongation, while exposures similar to adults would be predicted to have decreased efficacy compared to that observed for pediatric exposures observed in NV20911. The dosing nomogram for each of these pediatric targets is summarized below in Table 14.

Table 14: Pediatric SQV Dosing Nomograms to Target AUC of 20 or 30 µg·hr/mL.

Scenario 1: AUC 30 µg·hr/mL		Scenario 2: AUC 20 µg·hr/mL	
<15 kg	SQV 600 mg	<15 kg	SQV 400 mg
15-29 kg	SQV 800 mg	15-34 kg	SQV 600 mg
30-49 kg	SQV 1000 mg	35-49 kg	SQV 800 mg
50 kg and above	SQV 1000 mg	50 kg and above	SQV 1000 mg

(b) (4)



Predicted mean $AUC_{0\text{-}12h}$ for a 70 kg adult administered 1000/100 mg SQV/RTV BID was 16.2 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 31.5–40.0 µg·hr/mL compared to observed mean exposures of 37.3 µg·hr/mL. For the (b) (4) pediatric doses, the median SQV exposure in all pediatrics weighing 40 kg or more is anticipated to exceed 30 µg·hr/mL.

(b) (4)

the prediction interval is wider for pediatrics than is predicted for adults (upper 95% prediction interval for adults weighing 60-80 kg was 30.7-43.4 µg·hr/mL). While an exposure response relationship could not be identified based on the sponsor's thorough QT study, a dose-response relationship was observed with larger prolongation associated with high SQV exposures. (b) (4)

Table 15: Summary of SQV AUC for Two Dosing Nomograms Targeting an AUC of 20 or 30 µg·hr/mL.

Scenario 1: AUC 30 ug.hr/mL			Scenario 2: AUC 20 ug.hr/mL		
Body weight	Median AUC	Upper 95% Prediction Interval Range	Body Weight	Median AUC	Upper 95% Prediction Interval Range
<15 kg	29.4-32.4	70.0-77.8	<15 kg	19.6-21.6	46.6-51.9
15-29 kg	27.0-32.6	63.0-77.4	15-34 kg	19.8-24.5	47.9-55.7
30-50 kg	24.2-34.0	58.8-78.9	35-50 kg	19.3-26.5	45.6-60.3

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Run1017 mod, run1017.lst, patab1017, sdtab1017, cotab1017, catab1017, Poppkpeds.csv	Population PK control stream, results files, and output tables from the final pediatric and adult combined model	Saquinavir_NDA021785_JAF\PPK Analyses\Structure Model
Run1018 mod, run1018.lst, poppkpeds2.csv	Population PK control stream and dataset with adult subjects from MaxCmin1 included	Saquinavir_NDA021785_JAF\PPK Analyses\Structure Model
PopPK_SQV_Run1017.R	Function for running the popPK tool to generate diagnostic plots for Run1017.mod	Saquinavir_NDA021785_JAF\PPK Analyses\Structure Model
Pediatric_SQV_AUC_sim.R	Evaluates different pediatric dosing scenarios based on the completed RTV and SQV models	Saquinavir_NDA021785_JAF\ER Analyses
Adult_Efficacy_Analysis.R	Plots for the adult efficacy analysis (only adults)	Saquinavir_NDA021785_JAF\ER Analyses
Pediatric_Efficacy_Analysis.R	Plots for the pediatric efficacy analysis (only pediatrics)	Saquinavir_NDA021785_JAF\ER Analyses
PopPK_w_MaxCmin1.R	Plots for the combined or overlaid adult and pediatric efficacy analyses	Saquinavir_NDA021785_JAF\ER Analyses

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/s/

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