EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/623173/2010
Evaluation of Medicines for Human Use

# CHMP variation assessment report

Invented name/Name: **Invirase**
International non-proprietary name/Common name: **saquinavir**

## Type II Variation: EMEA/H/C/000113/II/0085

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|---|---|
| **Indication summary (as last approved):** | Treatment of HIV-1 infection |
| **Marketing Authorisation Holder (MAH):** | Roche Registration Ltd. |

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

## 1. Scope of the variation and changes to the dossier

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|---|---|
| **Scope of the variation:** | **Update of Summary of Product Characteristics and Package Leaflet**<br>Update of the sections 4.3, 4.4, 4.5 and 5.1 of the SmPC based on a thorough QT/QTc study with ritonavir boosted saquinavir in healthy volunteers. Consequently, the PL was updated. |
| **Rapporteur**: | Milena Stain |
| **Product presentations affected:** | EU/1/96/026/001-2 |
| **Dossier modules/sections affected:** | Module 1, 2 and 5 |
| **Product Information affected:** | SmPC and Package Leaflet |

## 2. Steps taken for the assessment

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| **Submission date:** | 5 November 2009 |
| **Start of procedure:** | 22 November 2009 |
| **Rapporteur's preliminary assessment report circulated on:** | 23 December 2009 |
| **Rapporteur's updated assessment report circulated on:** | 14 January 2010 |
| **Request for supplementary information and extension of timetable adopted by** | 20 January 2010 |

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

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| **the CHMP on:** | |
| **MAH's responses submitted to the CHMP on:** | 24 March 2010 |
| **Rapporteur's preliminary assessment report on the MAH's responses circulated on:** | 30 April 2010 |
| **Rapporteur's updated assessment report on the MAH's responses circulated on:** | 12 May 2010 |
| **Follow-on request for supplementary information and extension of timetable adopted by the CHMP on:** | 20 May 2010 |
| **MAH's responses submitted to the CHMP on:** | 31 May 2010 |
| **Rapporteur's preliminary assessment report on the MAH's responses circulated on:** | 4 June 2010 |
| **Rapporteur's updated assessment report on the MAH's responses circulated on:** | 15 June 2010 |
| **CHMP opinion:** | 24 June 2010 |

# 3. Scientific discussion

## *3.1. Introduction*

Invirase (saquinavir, SQV) is a potent inhibitor of human immunodeficiency virus (HIV) viral protease. Two formulations of SQV are currently marketed for oral administration, Invirase 200 mg hard capsule and Invirase 500 mg film-coated tablets. The oral bioavailability of SQV is limited by extensive first pass metabolism, mediated primarily by CYP3A4. Ritonavir (Norvir, RTV), a protease inhibitor (PI) with antiviral activity against HIV-1 and HIV-2, is a potent inhibitor of CYP3A4 and P-glycoprotein (P-gp). SQV is administered in combination with low dose RTV to increase SQV exposure. The approved therapeutic dose in the United States (US) and European Union (EU) is SQV 1000 mg twice daily (BID) in combination with RTV 100 mg BID.

In this variation dossier the MAH presented two clinical trials. NP21249, a thorough QT/QTc study, was conducted to investigate the proarrhythmic potential of ritonavir-boosted saquinavir in a therapeutic and a supratherapeutic dosing regimen. In the preceding trial NP21562 a feasible supratherapeutic dose of SQV was determined. The studies were conducted in accordance with the ICH-GCP guidelines. Full bioanalytical reports for each study were provided, and the assessments were done applying validated methods.
The MAH asked to update the SmPC/PL based on the finding of thorough QT/QTc study NP21279 conducted with Invirase.

## *3.2. Clinical aspects*

### 3.2.1 NP 21562- Multiple-ascending-dose (MAD) study

- **Protocol**

Study NP21562 was a 14-day, randomised, double-blind, MAD study designed to address any potential for the accumulation of saquinavir or its metabolites that could possibly affect the QTc interval. The study was conducted to determine an appropriate supratherapeutic dose of SQV/rtv to be carried forward into the thorough QT/QTc study, NP21249.

The trial was designed for up to 36 subjects to be randomised into one of three planned cohorts. Each cohort was to include 12 subjects. The decision to escalate to the next dose level was to be made based on the thorough review of safety data (i.e. laboratory safety data, vital signs, ECGs), tolerability data (i.e. adverse events), and saquinavir pharmacokinetic (PK) data of all previous dose levels to minimise the risk to healthy subjects. An overview of the study design is given in Table 1.

**Table 1 Overview of Study Design**

| | Evaluating Dose SQV/rtv (9 subjects) | Positive Control SQV/rtv (3 subjects) |
|---|---|---|
| Cohort 1 | 1500/100 mg | 1000/100 mg |
| Cohort 2 | 2000/100 mg | 1000/100 mg |
| Cohort 3 | 2500/100 mg | 1000/100 mg |

Subjects were healthy male and female volunteers of Body Mass Index (BMI) between 18 to 32 kg/m2, aged 18 to 65 years, who were not using tobacco and not taking any CYP3A4 inducers or inhibitors within 4 weeks prior to dosing. Participants were either sterile, postmenopausal or used acceptable contraception. A total of 12 healthy volunteers, 10 male and 2 female, aged 21 through 65 years were enrolled and received treatment.

After completion of the first dose cohort of SQV/rtv (1500/100 mg bid, n = 9; and 1000/100 mg bid, n = 3), two pre-defined stopping criteria for the dose escalation were met (please see below) and no further dose levels were investigated. All 12 subjects enrolled under cohort 1 were included in the PK analysis population.

- **Stopping criteria**

After completion of the first dose cohort (1500/100 mg SQV/rtv bid), the stopping criteria for dose escalation were met, in that the PK data suggested that further dose escalation could result in SQV exposure greater than the highest exposure observed in 4-week dog toxicokinetic studies (AUC0-24 = 168 µg.h/mL).

The maximum AUCinf and AUC12h in two subjects who received the 1500/100 mg SQV/rtv bid dose were 83.4 µg.h/mL and 80.2 µg.h/mL, respectively. On the assumption that the absorption of the next higher planned dose (2000/100 mg SQV/rtv bid) would be as good as the absorption at the 1500/100 mg SQV/rtv bid dose, the predicted AUCinf and AUC12h were estimated to be 98.6 and 91.7 µg.h/mL, respectively. Hence, further dose escalation of SQV/rtv to 2000/100 mg bid mg could result in daily exposures exceeding the highest exposure tested in the dog toxicology studies (AUC = 84 µg.h/mL for a 12-hour dosing interval).

- **Objectives**

The primary objective of study NP21562 was to evaluate the safety and tolerability of multiple doses of saquinavir boosted with ritonavir (SQV/rtv) between 1500/100 mg and 2500/100 mg bid for 14 days, compared to the safety and tolerability of the recommended dose of SQV/rtv (1000/100 mg bid) as positive control in healthy subjects.

Secondary objectives were to characterize the pharmacokinetics (PK) of saquinavir, its major metabolites, and ritonavir after multiple dose administration of SQV/rtv up to 2500/100 mg bid for 14

days. PK sampling strategy included both intensive PK samples (up to 12 h post-morning dose) on Day 1 and Day 14 and trough PK samples pre-morning dose on Day 2 to Day 13.

- **Dosing regimen**

Study drug SQV/rtv was administered to the subjects bid at approximately 12 (± 1) hour intervals for 14 days consecutively (evening dose on Day 14 was not administered).

On all dosing days subjects received a standardised breakfast within 30 minutes prior to morning dosing at the Clinical Unit. Study medication was administered with approximately 240 mL of water at least 10 minutes after the completion of the standardised breakfast. On Day 1 and Day 14, no food was allowed for at least 4 hours post-dose, although subjects were allowed water ad libitum, from 2 hours post morning dose. Subjects fasted overnight (for at least 10 hours) before receiving their morning dose on Days 1, 8 and 14.

On Day 2, after administration of the morning dose of study drugs, subjects could be discharged from the Clinical Unit upon the Investigator's approval.
In the evening on Days 1 and 13, subjects were resident in the Clinical Unit and received a standard dinner at 11.5 hours post-morning dose. Subjects were required to complete the standard dinner at least 10 minutes prior to study drugs administration. The evening dose of the study drugs was administered 12 hours post-morning dose.
For all other dosing days, subjects self-administered the evening dose at home with a full glass of water at 12 hours post-morning dose. Subjects were recommended to take the evening dose of study drug at least 10 minutes after the completion of the evening meal.

Dose escalation was to be stopped if one of the following conditions occurred irrespective of the suspected relationship to the study drugs:

1. Severe AEs of same character in 2 or more subjects.
2. Clinically significant laboratory abnormalities of same character in 3 or more subjects.
3. Clinically significant changes in vital signs or ECGs of same character in 3 or more subjects.
4. Clinically significant QT/QTc interval prolongation (QT/QTc > 500 ms or > 60 ms over baseline) during treatment with the study drug in one or more subjects. Baseline was defined as the mean QTc interval derived from the Day 1 pre-dose triplicate ECG recordings.
5. Four occurrences of any of the above.
6. PK data indicated that further dose escalation would not result in a further increase in plasma concentration.
7. PK data suggested the further dose escalation might result in a saquinavir exposure greater than the highest exposure (AUC0-24h = 168 µg·hr/mL) observed in dogs in the 4-week toxicity and toxicokinetic study

- **Study Procedures**

Blood samples for PK analysis were to be collected on Day 1 and 14 predose (0), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours post-dose. Pre-dose samples were to be collected every morning on Days 2 through 13 to determine trough plasma concentrations of saquinavir, its major metabolites, and ritonavir.

Estimated PK parameters derived from plasma concentrations of saquinavir, ritonavir and saquinavir metabolites: AUCinf, (Day 1 only); AUCτ (Day 14 only); $C_{max}$ (Days 1 and 14); Cmin (Days 2 to 14); $T_{max}$ (Days 1 and 14); T½ (ln2)/λz (Days 1 and 14).

CLss/F (Day 14, for saquinavir and ritonavir only).
Vz/F (Day 14, for saquinavir and ritonavir only);
M/P ratio (where P is saquinavir and M is its metabolite [M4, M6, or M10]).
For all metabolites, the computed parameters include AUCinf, $C_{max}$, $T_{max}$, and T½ on Day 1 and AUCτ, $C_{max}$, $T_{max}$, and T½ on Day 14.

Tolerability of saquinavir boosted with ritonavir was assessed by monitoring adverse events, vital signs, laboratory tests, and ECGs.

- **Study Results**

Plasma samples were analysed for saquinavir, its metabolites (M4, M6 and M10), and ritonavir using a validated specific HPLC-MS/MS method. The lower limit of quantification was 50.0 ng/mL for saquinavir and ritonavir and 5.00 ng/mL for M4, M6, and M10. The inter-assay precision ranged from 3.7% to 9.7%. Overall accuracy (% Relative Error) ranged from -5.9% to 3.3%.

**SQV Pharmacokinetics**

*Cmax*

On Day 1, the maximum plasma concentration ($C_{max}$) was reached at approximately 4 to 4.8 hours post dosing for two dose groups (Table 1). The plasma exposure of saquinavir increased with doses; the values of $C_{max}$ increased from 4260 ng/mL (1000 mg saquinavir dose group) to 4910 ng/mL (1500 mg saquinavir dose group). Similarly, the values of AUCinf increased from 34.6 µg.h/mL (1000 mg saquinavir dose group) to 42.3 µg.h/mL (1500 mg saquinavir dose group).

On Day 14, $C_{max}$ was reached at around 4 hours post dosing for both dose groups (Table 2). The values of $C_{max}$ increased from 6050 ng/mL in the 1000 mg saquinavir dose group to 6750 ng/mL in the 1500 mg saquinavir dose group. Similarly, the values of AUCτ increased from 36.6 µg.h/mL in the 1000 mg saquinavir dose group to 42.7 µg.h/mL in the 1500 mg saquinavir dose group.

The elimination half-life of saquinavir following multiple dose administration (T1/2) was 3.48 hours in the 1000 mg saquinavir dose group and 4.89 hours in the 1500 mg saquinavir dose group. Apparent clearance at steady state (CLss/F) was around 28.5 L/hour in the 1000 mg saquinavir group and 46.8 L/hour in the 1500 mg saquinavir group. Apparent volume of distribution (Vz/F) was 142 L in the 1000 mg saquinavir group and 295 L in the 1500 mg saquinavir group.

**Table 1** **Summary Statistics of Saquinavir Pharmacokinetic Parameters on Day 1 following 1000 mg or 1500 mg Saquinavir Boosted with 100 mg Ritonavir Twice Daily in Healthy Volunteers**

| Dose (mg) | | $AUC_{inf}$ (µg•h/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $T_{1/2}$ (h) |
|---|---|---|---|---|---|
| 1000 | N | 3 | 3 | 3 | 3 |
| | Mean | 34.6 | 4260 | 4.02 | 3.70 |
| | SD | 19.9 | 1590 | 0.98 | 1.03 |
| | Min | 22.1 | 3240 | 3.03 | 3.02 |
| | Max | 57.5 | 6090 | 5.00 | 4.89 |
| | CV% | 57.5 | 37.2 | 24.5 | 27.9 |
| 1500 | N | 9 | 9 | 9 | 9 |
| | Mean | 42.3 | 4910 | 4.78 | 4.65 |
| | SD | 25.2 | 2050 | 0.97 | 1.58 |
| | Min | 12.7 | 2020 | 3.00 | 2.83 |
| | Max | 83.4 | 7930 | 6.00 | 7.75 |
| | CV% | 59.5 | 41.7 | 20.3 | 33.9 |

Derived Parameters Source: NCA.Model.200.MT.ZeroTime.SQVD1

**Table 2** **Summary Statistics of Saquinavir Pharmacokinetic Parameters on Day 14 following 1000 mg or 1500 mg Saquinavir Boosted with 100 mg Ritonavir Twice Daily in Healthy Volunteers**

| Dose (mg) | | AUCτ (µg•h/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $T_{1/2}$ (h) | $CL_{ss}/F$ (L/h) | $V_z/F$ (L) |
|---|---|---|---|---|---|---|---|
| 1000 | N | 3 | 3 | 3 | 3 | 3 | 3 |
| | Mean | 36.6 | 6050 | 4.00 | 3.48 | 28.5 | 142 |
| | SD | 9.66 | 1460 | 0.00 | 0.184 | 6.87 | 28.7 |
| | Min | 28.9 | 5180 | 4.00 | 3.27 | 21.1 | 109 |
| | Max | 47.4 | 7740 | 4.00 | 3.60 | 34.6 | 163 |
| | CV% | 26.4 | 24.1 | 0.0 | 5.3 | 24.1 | 20.2 |
| 1500 | N | 8 | 8 | 8 | 8 | 8 | 8 |
| | Mean | 42.7 | 6750 | 3.75 | 4.89 | 46.8 | 295 |
| | SD | 20.9 | 3080 | 0.70 | 1.37 | 32.3 | 128 |
| | Min | 12.6 | 2230 | 3.00 | 2.92 | 18.7 | 152 |
| | Max | 80.2 | 11800 | 5.00 | 6.73 | 119 | 501 |
| | CV% | 49.0 | 45.7 | 18.8 | 28.1 | 69.0 | 43.5 |

Derived Parameters Source: NCA.Model.200.MT.ZeroTime.Day14

The Cmax and $AUC_{0-12}$ have also been submitted upon a CHMP request since the study NP21562 explored values everyday for 14 days with maximal value at day 3 (i.e. at maximum plasma concentration).

The time course of ritonavir (RTV)-boosted saquinavir (SQV) PK was established in study NP21562, based on the $C_{trough}$, over the 14-day dosing, and maximum plasma concentrations on Day 3. Assessments of $C_{max}$ or $AUC_{0-12}$ were performed on Day 1 and Day 14 for the 1000/100 mg and 1500/100 mg SQV/RTV regimens. In the subsequent QTC study, NP21249, $C_{max}$ and $AUC_{0-12}$ were assessed on Day 3 (i.e. at maximum plasma concentration) of the 1000/100 mg and 1500/100 mg SQV/RTV regimens. These data are summarised in Table 3.

Table 3: $C_{max}$and $AUC_{0-12}$ Estimates of SQV following Multiple Dosing of 1000/100 mg and 1500/100 mg Regimens of SQV/RTV in Healthy Subjects

| Study | Regimen, N | Day | Cmax* (ng/mL) | AUC*$_{0-12}$ (µg·h/mL) | $C_{trough}$ (ng/mL) | Cmax/ $C_{trough}$ Ratio |
|---|---|---|---|---|---|---|
| NP21562 [1] | 1000/100, bid, N=3 | 1<br>14 | 4260 ± 159<br>6050 ± 1460 | 34.6 ± 19.9<br>36.6 ± 9.66 | 1210 ± 850**<br>1300 ± 316** | 3.52<br>4.65 |
| NP21562 [1] | 1500/100, bid, N=9 | 1<br>14 | 4910 ± 2050<br>6750 ± 3080 | 42.3 ± 25.2<br>42.7 ± 20.9 | 1690 ± 1170**<br>2060 ± 1540** | 2.91<br>3.28 |
| NP21249 [2] | 1000/100, bid, N= 57 | 3 | 11200 ± 3260 | 94.8 ± 30.6 | 5940 ± 2860*** | 1.88 |
| NP21249 [2] | 1500/100, bid, N=60 | 3 | 15900 ± 4360 | 141± 44.3 | 9520 ± 4140*** | 1.67 |

* mean ± standard deviation
** 12 hour post-dose data from PK Table 2.1 (p 483) and PK Table 2.3 (p 485) in the study report [1].
*** 12 hour post-dose data from individual listing of SQV plasma concentrations table on p 472 and p 474 of the study report [2].

The MAH has reviewed the available PK information from Roche internal reports and publications describing the PK of RTV-boosted SQV and provided additional information from two published studies listed below.

Kilby et al. reported $C_{trough}$ values for the first two weeks following once daily (QD) and three times daily (TID) administration of 1200 to 1800 mg doses of SQV with 100 to 200 mg of RTV in HIV-

infected patients. Although the dose regimens utilised in this study was quite different from the approved/recommended SQV/RTV 1000/100 mg twice daily (BID) regimen, the data show that plasma concentrations decline from initial values before reaching steady state after 10 days of dosing, which is consistent with the findings of study NP21562.

Boffito et al. measured steady state SQV plasma concentrations for the QD and BID regimen in HIV-infected patients. This study showed that the PK profile of SQV from the evening dose is similar to that achieved with the morning dose.

During the assessment it has been considered that these data are consistent with the concomitant inhibition and induction of CYP3A by ritonavir.

*Cmin*

The mean predose saquinavir plasma concentrations ($C_{min}$) on Days 2 – 14 are summarised in Table 4. In the SQV/rtv 1000/100 mg dose group, the mean $C_{min}$ ranged from 2890 ng/mL on Day 2 to 827 ng/mL on Day 14 with the highest value of 3920 ng/mL on Day 3. Similarly, in the SQV/rtv 1000/100 mg dose group, the mean Cmin ranged from 5070 ng/mL on Day 2 to 1470 ng/mL on Day 14 with the highest value of 6100 ng/mL.

Table 4: Summary statistics of Saquinavir Concentrations (ng/mL) at PRedose on Day 2-14. Following 1000 mg or 1500mg Saquinavir Boosted with 100 mg Ritonavir. Twice Daily in Healthy Volunteers

| Days | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 mg Dose Group | | | | | | | | | | | | | |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Mean | 2890 | 3920 | 3520 | 2710 | 1920 | 1960 | 1290 | 1560 | 1160 | 1530 | 674 | 1050 | 827 |
| SD | 1390 | 621 | 1050 | 1020 | 1120 | 473 | 754 | 135 | 502 | 533 | 279 | 840 | 205 |
| Min | 1790 | 3200 | 2390 | 1850 | 671 | 1420 | 444 | 1420 | 580 | 1110 | 497 | 78.5 | 600 |
| Max | 4450 | 4290 | 4470 | 3830 | 2830 | 2300 | 1890 | 1690 | 1450 | 2130 | 996 | 1590 | 999 |
| CV% | 48 | 15.9 | 29.9 | 37.6 | 58.3 | 24.1 | 58.4 | 8.7 | 43.3 | 34.9 | 41.4 | 80.3 | 24.8 |
| 1500 mg Dose Group | | | | | | | | | | | | | |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 8 | 8 | 8 | 8 | 8 |
| Mean | 5070 | 6100 | 5360 | 4690 | 3810 | 3170 | 3240 | 2980 | 2800 | 2630 | 2150 | 1960 | 1470 |
| SD | 2200 | 2510 | 2820 | 3230 | 2530 | 1930 | 2090 | 2540 | 1960 | 1750 | 1310 | 1590 | 936 |
| Min | 1130 | 2560 | 1550 | 424 | 765 | 933 | 1280 | 380 | 548 | 852 | 598 | 453 | 653 |
| Max | 7330 | 9240 | 10000 | 9960 | 8060 | 5940 | 7970 | 9170 | 6310 | 5550 | 4680 | 4860 | 3550 |
| CV% | 43.4 | 41.1 | 52.7 | 68.8 | 66.2 | 60.8 | 64.5 | 85.1 | 70.1 | 66.7 | 61 | 81.1 | 63.6 |

Concentration Data Source: MT.ZeroTime.Predose

Viewing the table 1, 2, 4, the Cmax for the dose 1500/100 mg BID is around 5000mg/mL at Day 1 and 7000 mg/mL at Day 14. However Cmin is around 5000 and 6000 ng/mL at Day 2-3. This discrepancy is explained by SQV metabolism is primarily mediated by CYP3A4 enzyme and ritonavir (RTV) is a potent CYP3A4 inhibitor as well as enzyme inducer of CYP3A4 in humans. The inhibitory effect predominates at the outset of RTV regimen, 2 to 4 days after initiation of treatment, and enzyme induction effect gradually increases reaching the maximum approximately 10 to 15 days after initiation of RTV regimen. The behavior of $C_{trough}$ values in study NP21562, increasing for first 3 days and then declining to reach a lower steady state level by Day 14, is consistent with these expectations. Since $C_{max}$ was not estimated on Day 2 or Day 3 in study NP21562, it is not possible to compare observed $C_{trough}$ values on these days (5000 to 6000 ng/mL for 1500/100 mg regimen) to the corresponding $C_{max}$ values on these days. However, on study days when both of these values were available, as shown in table 5, $C_{max}$ was considerably higher than the corresponding $C_{trough}$ values. On average, $C_{max}$ was 2- to 3-fold higher than the corresponding $C_{trough}$ for the first 3 days of both the 1000/100 mg and1500/100 mg dosing regimens of SQV/RTV.

Table 5: Cmax, $AUC_{0-12}$ and $C_{trough}$ Estimates of SQV following Multiple Dosing of 1000/100 mg and 1500/100mg Regimens of SQV/TRV in Healthy Subjects

| Study | Regimen, N | Day | Cmax* (ng/mL) | AUC*$_{0-12}$ (µg·h/mL) | $C_{trough}$ (ng/mL) | Cmax/ $C_{trough}$ Ratio |
|---|---|---|---|---|---|---|
| NP21562 [5] | 1000/100, bid, N=3 | 1<br>14<br>3 | 4260 ± 159<br>6050 ± 1460<br>- | 34.6 ± 19.9<br>36.6 ± 9.66<br>- | 1210 ± 850**<br>1300 ± 316**<br>3920 ± 621** | 3.52<br>4.65<br>- |
| NP21562 [5] | 1500/100, bid, N=9 | 1<br>14<br>3 | 4910 ± 2050<br>6750 ± 3080<br>- | 42.3 ± 25.2<br>42.7 ± 20.9<br>- | 1690 ± 1170**<br>2060 ± 1540**<br>6100 ± 2500** | 2.91<br>3.28<br>- |
| NP21249 [6] | 1000/100, bid, N= 57 | 3 | 11200 ± 3260 | 94.8 ± 30.6 | 5940 ± 2860*** | 1.88 |
| NP21249 [6] | 1500/100, bid, N=60 | 3 | 15900 ± 4360 | 141± 44.3 | 9520 ± 4140*** | 1.67 |

* mean ± standard deviation
** from PK Table 2.1 (p 483) and PK Table 2.3 (p 485) in the study report [5].
*** 12 hour post-dose data from individual listing of SQV plasma concentrations table on p 472 and p 474 of the study report [6].

Based on these ratios, the MAH estimates that the $C_{max}$ on Day 2 and Day 3 should be, on average, 2- to 3-fold higher than the corresponding $C_{trough}$ values (5000 to 6000 ng/mL for the 1500/100 mg regimen), i.e. the expected $C_{max}$ should be in the range of 10000 ng/mL to 18000 ng/mL on these days, which is consistent between both studies.

**RTV Pharmacokinetics**

*Cmax*
The same dose (100 mg) ritonavir was administered in combination with 1000 mg saquinavir or 1500 mg saquinavir.

On Day 1, the time to reach $C_{max}$ ($T_{max}$) was independent of saquinavir dose and approximately 5 hour post-dose (Table 6). The mean plasma exposure of ritonavir decreased with increase of saquinavir dose; the mean $C_{max}$ was 925 ng/mL in the 1000 mg saquinavir dose group and 749 ng/mL in the 1500 mg saquinavir dose group. Similarly, the values of AUCinf decreased from 10.9 µg•h/mL in the 1000 mg saquinavir dose group to 8.79 µg•h/mL in the 1500 mg saquinavir dose group.

On Day 14, the $C_{max}$ of ritonavir was reached at approximately 4 hours post-dose (Table 5). $C_{max}$ ritonavir decreased from 2070 ng/mL to 1400 ng/mL as saquinavir dose increased from 1000 mg to 1500 mg. Similarly, $AUC_T$ of ritonavir decreased from 13.3 µg.h/mL to 7.99 µg.h/mL as saquinavir dose increased from 1000 mg to 1500 mg.

The $T_{1/2}$ of ritonavir after multiple dose on Day 14 was similar (approximately 4 hours) in both 1000 mg saquinavir dose group and 1500 mg saquinavir dose group. The CLss/F was around 8.05 L/hour in 1000 mg saquinavir group and 14.2 L/hour in 1500 mg saquinavir dose group. The Vz/F was 46.5 L in 1000 mg saquinavir dose group and 75.1 L in 1500 mg saquinavir dose group (Table 7).

Table 6: Summary Statistics of RTV Pharmacokinetics on Day 1 following 1000mg and 1500 mg SQV Boosted with 100mg RTV Twice Daily in Healthy Volunteers

| Dose | | $AUC_{inf}$ (µg•h/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $T_{1/2}$ (h) |
|---|---|---|---|---|---|
| 1000 mg | N | 3 | 3 | 3 | 3 |
| | Mean | 10.9 | 925 | 5.01 | 6.74 |
| | SD | 1.81 | 92.8 | 0.01 | 2.87 |
| | Min | 9.46 | 854 | 5.00 | 4.60 |
| | Max | 12.9 | 1030 | 5.02 | 10.0 |
| | CV% | 16.7 | 10.0 | 0.2 | 42.6 |
| 1500 mg | N | 9 | 9 | 9 | 9 |
| | Mean | 8.79 | 749 | 4.56 | 7.44 |
| | SD | 6.53 | 390 | 1.59 | 8.15 |
| | Min | 2.16 | 364 | 3.00 | 2.47 |
| | Max | 20.1 | 1520 | 8.00 | 28.7 |
| | CV% | 74.3 | 52.1 | 34.9 | 109.5 |

Derived Parameters Source: NCA.Model.200.MT.ZeroTime.Day1.RTV

Table 7: Summary Statistics of RTV Pharmacokinetics on Day 14 following 1000mg or 1500mg SQV Boosted with 100mg RTV Twice Daily in Healthy Volunteers

| Dose | | $AUC_{\tau}$ (µg•h/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $T_{1/2}$ (h) | $CL_{ss}/F$ (L/h) | $V_{z,ss}/F$ (L) |
|---|---|---|---|---|---|---|---|
| 1000 mg | N | 3 | 3 | 3 | 3 | 3 | 3 |
| | Mean | 13.3 | 2070 | 4.33 | 3.86 | 8.05 | 46.5 |
| | SD | 4.62 | 997 | 1.53 | 0.798 | 2.37 | 20.5 |
| | Min | 10.1 | 1440 | 3.00 | 2.96 | 5.37 | 22.9 |
| | Max | 18.6 | 3220 | 6.00 | 4.46 | 9.89 | 59.5 |
| | CV% | 34.6 | 48.2 | 35.3 | 20.6 | 29.5 | 44.0 |
| 1500 mg | N | 8 | 8 | 8 | 8 | 8 | 8 |
| | Mean | 7.99 | 1400 | 3.63 | 3.82 | 14.2 | 75.1 |
| | SD | 2.61 | 394 | 1.19 | 0.859 | 6.07 | 24.1 |
| | Min | 3.96 | 861 | 2.00 | 2.95 | 8.94 | 42.4 |
| | Max | 11.2 | 2010 | 5.02 | 5.10 | 25.2 | 108 |
| | CV% | 32.6 | 28.1 | 32.7 | 22.5 | 42.8 | 32.0 |

Derived Parameters Source: NCA.Model.200MT.ZeroTime.Day14.RTV

*Cmin*

The mean predose ritonavir plasma concentrations on Days 2 – 14 are summarised in Table 8. Like SQV, the highest mean Cmin for ritonavir plasma concentration was reached on Day 3 in both the 1000 mg and 1500 mg SQV dose group.

Table 8: Summary Statistics of RTV Concentrations (ng/mL) at Predose on Days 2-14 following 1000mg or 1500mg SQV Boosted with 100mg RTV Twice Daily in Healthy Volunteers

| Days | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 mg Dose Group | | | | | | | | | | | | | |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Mean | 1050 | 1200 | 911 | 1080 | 834 | 774 | 567 | 577 | 567 | 625 | 456 | 482 | 633 |
| SD | 152 | 459 | 203 | 476 | 403 | 301 | 232 | 120 | 259 | 242 | 154 | 365 | 286 |
| Min | 966 | 710 | 704 | 608 | 416 | 447 | 318 | 444 | 304 | 427 | 300 | 60.9 | 359 |
| Max | 1230 | 1620 | 1110 | 1560 | 1220 | 1040 | 776 | 678 | 821 | 895 | 607 | 699 | 930 |
| CV% | 14.4 | 38.3 | 22.3 | 44.3 | 48.3 | 38.9 | 40.9 | 20.8 | 45.6 | 38.7 | 33.7 | 75.7 | 45.2 |
| 1500 mg Dose Group | | | | | | | | | | | | | |
| N | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 8 | 8 | 8 | 8 | 8 |
| Mean | 877 | 884 | 743 | 727 | 663 | 585 | 615 | 601 | 463 | 403 | 415 | 430 | 331 |
| SD | 578 | 455 | 464 | 541 | 470 | 359 | 562 | 604 | 263 | 177 | 189 | 245 | 149 |
| Min | 112 | 242 | 157 | 70.2 | 173 | 236 | 141 | 80.8 | 208 | 181 | 174 | 115 | 155 |
| Max | 1670 | 1410 | 1460 | 1860 | 1680 | 1400 | 2000 | 2130 | 903 | 657 | 765 | 789 | 614 |
| CV% | 65.9 | 51.4 | 62.4 | 74.4 | 70.8 | 61.3 | 91.4 | 100.6 | 56.7 | 43.8 | 45.6 | 57.1 | 44.9 |

Concentration Data Source: MT.ZeroTime.Predose

**Saquinavir Metabolites Pharmacokinetics**

The plasma concentrations of M4 were the highest compared to M6 or M10. Most M10 samples were below the limit of quantitation (BLQ). The $T_{max}$ for M4 and M6 were similar (4 to 5 hour post-dose). The exposure of the metabolites (AUCinf, $AUC_{\tau}$, or $C_{max}$) increased with increasing saquinavir dose. In

general, the concentrations of the metabolites were lower on Day 14 than on Day 1. The plasma concentrations of M4, M6, and M10 were low with a mean metabolite/parent (M/P) (%) ratio of less than 0.5 %.

Like saquinavir, the highest mean Cmin for M4 plasma concentration was reached on Day 3.

The mean $C_{min}$ for M6 was BLQ from day 2 to Day 14 in the 1000/100 mg dose group, and BLQ afterward in the 1500/100 mg dose group. The mean $C_{min}$ values for M10 were BLQ from Day 2 to Day 14 in both dose groups which suggest no major concern for the accumulation of metabolites following multiple dose administration of SQV/RTV in humans.

- **Safety**

Both the 1000/100 and 1500/100 mg SQV/rtv bid doses were well tolerated by healthy subjects after 14 days of dosing. All three subjects in the SQV/rtv 1000/100 mg and 7 of 9 subjects, in the SQV/rtv 1500/100 mg treatment group reported at least one adverse event during the study. The most commonly reported adverse events in both treatment arms were nervous system disorders (9 subjects), such as dysgeusia and dizziness.

Four subjects reported gastrointestinal (GI) disorders (diarrhoea, flatulence); the most frequent incidence of these was reported in the SQV/rtv 1500/100 mg treatment group.

All adverse events reported by subjects in the SQV/rtv 1000/100 mg group were of mild intensity except for 2 moderate events (upper respiratory tract infection (URTI) and pharyngolaryngeal pain) both considered unrelated to the study drug by the investigator. Most adverse events observed in the SQV/rtv 1500/100 mg treatment group were also considered of mild intensity (35 events). Three subjects in this treatment group reported three moderate AEs (pharyngolaryngeal pain, cough, URTI) considered unrelated to study drug by the investigator. No severe adverse events were reported during the study.

All but two AEs resolved without sequelae. One event of mild paresthesia and one event of moderate cough, both reported in subjects in the SQV/rtv 1500/100 mg treatment group, were each considered unresolved but stable by the end of the study. No deaths or serious adverse events occurred during the study or follow-up periods

One subject withdrew from the study due to an adverse event of pharyngolaryngeal pain and mild malaise both events were considered as unrelated to study drug. There were no clinically relevant abnormalities in laboratory parameters, vital signs, or ECG findings.

## 3.2.2 NP21249: Thorough QT/QTc Study

To establish a suitable supratherapeutic dose study NP21562 was performed. The results of this study supported a multiple dosing regimen of SQV/rtv 1500/100 and a maximum exposure after 3 days of bid dosing.

- **Protocol**

Study NP21249 "*A double-blind, placebo-controlled, positive controlled, randomized, crossover study to assess the effect of saquinavir boosted by ritonavir at the therapeutic dose and at a supra-therapeutic dose on the QT/QTc interval after multiple dose administration in healthy subjects*" utilised therapeutic and supratherapeutic doses of RTV-boosted SQV, along with both a negative (placebo) and

positive (moxifloxacin, MOXI) control. The positive control group consisted of 400mg moxifloxacin (MOXI), which is common practice for such a trial. The study was undertaken to provide definitive information regarding the potential risk for QT prolongation with RTV-boosted SQV. The supratherapeutic dose regimen for SQV/rtv (1500/100 mg bid) and the choice of ECG monitoring after 3 days of dosing used in this study were based upon results of the multiple-ascending dose (MAD) study, NP21562.

*Overview of the study design:*

- Treatment A (SQV/rtv therapeutic dose regimen): SQV/rtv 1000 mg/100 mg bid on Days 1 to 3 (morning dose only on Day 3);
- Treatment B (SQV/rtv supratherapeutic dose regimen): SQV/rtv 1500/100 mg bid on Days 1 to 3 (morning dose only on Day 3);
- Treatment C (positive control): single morning dose MOXI 400 mg on Day 3;
- Treatment D (negative control): SQV placebo + RTV placebo bid on Days 1 to 3 (morning dose only on Day 3) plus a single morning dose of MOXI placebo on Day 3

The 4 treatment sequences to which eligible subjects were randomly assigned were ABCD, BDAC, CADB, and DCBA.

A washout period of at least 7 days separated each treatment period.

The total duration of the study for each subject was up to 12 weeks:
- 4 weeks for screening period, in-clinic period of 5 days [Day -2 to Day 4] for each treatment period,
- 7 days for washout period between each treatment period,
- safety follow-up period of 7 to 10 days after the last dose of study medication)

In each treatment period, each subject received 3 days of dosing with study medication (bid dosing on Days 1 and 2, single morning dose only on Day 3; total of 5 doses) according to the subject's randomisation sequence (ABCD, BDAC, CADB or DCBA).

The doses of SQV and RTV (or SQV placebo and/or RTV placebo) on Days 1 and 2 were separated by 12 ± 1h.

The first dose of study medication was administered on Day 1 of each treatment period.

A standard breakfast was provided approximately 30 minutes prior to the morning dose on Days 1, 2 and 3, while a standard dinner was provided approximately 30 minutes prior to the evening dose on Days 1 and 2. Subjects were required to complete the breakfast and dinner at least 10 minutes prior to dosing. A standardised lunch was also provided approximately 4h after the morning dose of study drugs on Days 1, 2, and 3. On Day 3, the standard dinner was given 10 minutes after the 12h post-dose ECG time point. Subjects were required to fast overnight for a minimum of 10h before breakfast on Day 3.

*Study population:*
The study population consisted of healthy adult males and females aged 18 to 55 years, inclusive. Consistent with the ICH E14 Guidelines, subjects with a history of risk factors for TdP (heart failure, hypokalemia, family history of long QT syndrome), who exhibited a marked baseline prolongation of the QT/QTc interval, or who were using drugs known to prolong the QT/QTc interval were excluded from participation in this thorough QT/QTc study.

A total of 66 healthy subjects were enrolled at 1 study centre. Of these, 15 subjects were randomly assigned to treatment sequence ABCD, 17 subjects to treatment sequence BDAC, 18 subjects to treatment sequence CADB, and 16 subjects to treatment sequence DCBA.

Discontinuation criteria for marked prolongation of QT/QTc (increases to >500ms or of >60ms over baseline) were included in the protocol. No such incidences were reported.

- **Study Procedure**

Blood samples (3 mL) were collected by venipuncture into an EDTA tube for the measurement of plasma SQV, SQV metabolites (M4, M6, and M10), RTV, and MOXI concentrations at the following time points on Day 3 for all 4 treatment periods: immediately prior to the morning dose of study medication (pre-dose) and at 2, 3, 4, 5, 6, 8, and 12h post-dose. Vital signs, laboratory tests for safety analysis and AEs were evaluated during the study.

Continuous Holter 12-lead digital ECG were used in this study. The ECG extraction time points were based on the available PK profile of SQV and its metabolites observed in the MAD study NP21562 where the mean SQV time to peak concentration ($T_{max}$) was 4h and 4.8h for 1000/100 SQV/RTV and 1500/100 mg SQV/RTV, respectively, and the mean elimination half-life (t½) of SQV was 3.7h and 4.9h for the 2 dose regimens, respectively.

After study completion, a note–to-file was made to add 2 additional ECG extraction time points at 16h and 20h post-dose on Day 3 and their matched time points on Day -1.

ECG data were derived from collection of 12-lead surface ECGs. Measurements were computer assisted and readings were performed by centralised reading from a trained team, which was adequately blinded. Data on the inter- and intra-reader variability was not generated during this study.

To minimise variability in the measurement of the QT/QTc interval, care was taken to keep the subject's activity level, postural position, food ingestion, and circadian patterns consistent between the baseline (Day -1) and on treatment (Day 3) ECG recordings. On Day -1, subjects were given a standard breakfast at -24.5h (relative to first dose of study medication on Day 1), and the baseline continuous 12-lead digital continuous ECG monitoring was done from -24h to pre-dose on Day 1.

Body position was to be consistently maintained for each ECG extraction time point so that changes in HR (Heart Rate) were avoided. Care was also taken within the CPU ( Central Processing Unit) to avoid environmental distractions during the pre-ECG rest and at the ECG extraction time points. A standard lunch and dinner was provided after the -20h and -12h ECG time points, respectively, on Day -1.

On Day 3, 12-lead continuous ECG recording was repeated from just before the morning dose of study medication up through 24h post-dose (Day 4). Triplicate paper ECG readings were extracted during this time period at regular time intervals pre- and post-study drug administration. The body position of subjects during ECG extraction on Day 3, timing of meals, and care taken to minimise potential changes in HR were the same as that specified for the baseline recordings done on Day -1.

The following ECG parameters were measured and recorded from the triplicate extractions of continuous ECG recordings: HR, QT, RR, PR, QRS and assessments of T- and U-wave morphology. QTcB and QTcF interval values (Bazett and Fridericia corrections, respectively) were derived using the QT and RR intervals.

Intrinsic variability of ECG assessment was addressed by standardising assessment conditions (time of recording, body position, meals) and extraction of triplicate ECG recordings.
The ECG extraction time points were based on the investigation of the PK profile of SQV and its metabolites observed in the study NP21562. ECG readings were extracted at 2, 3, 4, 5, 6, 8, and 12h as well as 16 and 20h (note to file after study completion) matched with time points on Day -1.

- **Study Result**

*Pharmacokinetic Results for Saquinavir*

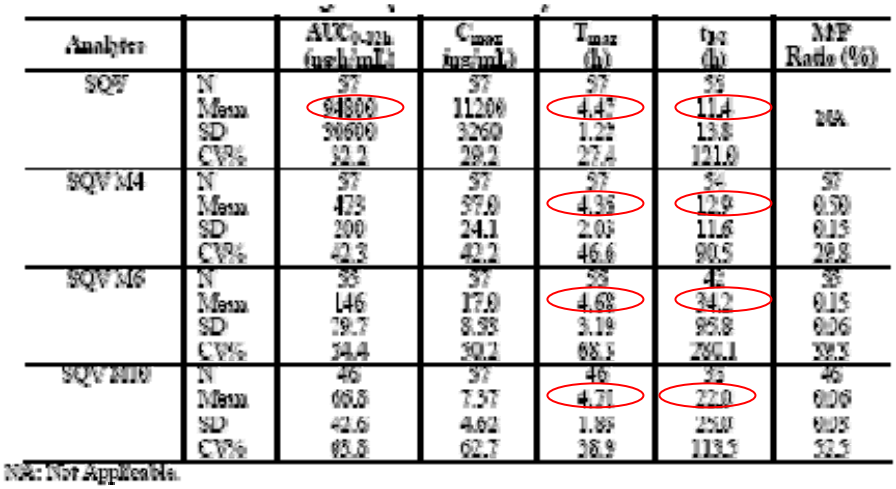
Sixty-one (61) subjects participating in the study had PK data from at least 1 treatment period with SQV/rtv 1000/100 mg bid (Treatment A) or SQV/rtv 1500/100 mg bid (Treatment B) and were included in the PK analysis. Of these, 57 subjects (20 males, 37 females) had PK data from a treatment period with SQV/rtv 1000/100 mg bid and 60 subjects (21 males, 39 females) had PK data from a treatment period with SQV/rtv 1500/100 mg bid.

Only the 2h PK samples from 59 subjects who received Treatment C (MOXI 400 mg) were assayed to confirm the expected $C_{max}$ of MOXI. Only the 2h and 4h samples from Treatment D (placebo), corresponding to the time of the expected $C_{max}$ for MOXI and SQV/rtv, respectively, were assayed to confirm that plasma concentrations were BLQ.

Each of the 59 subjects who received placebo (Treatment D) had plasma concentration data analysed for SQV and MOXI.

PK parameters for SQV and its metabolites (M4, M6, and M10) on Day 3 following treatment with SQV/rtv 1000/100 mg bid (Treatment A) and SQV/rtv 1500/100 mg bid (Treatment B) are summarised in Table 7 and Table 8, respectively. Peak plasma concentrations of SQV were reached at approximately 4h regardless of dose.

Table 9: Summary of Pharmacokinetic Parameters for SQV and its Metabolites (M4, M6, and M10) on Day 3 Following SQV/rtv 1000/100mg bid (Treatment A)



| Analyte | | $AUC_{0-12h}$ (ug·h/mL) | $C_{max}$ (ug/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) | MP Ratio (%) |
|---|---|---|---|---|---|---|
| SQV | N | 57 | 57 | 57 | 59 | |
| | Mean | 94800 | 11200 | 4.47 | 11.4 | NA |
| | SD | 30600 | 3260 | 1.25 | 13.8 | |
| | CV% | 32.2 | 29.2 | 27.4 | 121.0 | |
| SQV M4 | N | 57 | 57 | 57 | 54 | 57 |
| | Mean | 473 | 97.0 | 4.36 | 12.9 | 0.50 |
| | SD | 200 | 24.1 | 2.03 | 11.6 | 0.15 |
| | CV% | 42.3 | 42.2 | 46.6 | 90.5 | 29.8 |
| SQV M6 | N | 55 | 57 | 58 | 42 | 55 |
| | Mean | 146 | 17.0 | 4.68 | 34.2 | 0.15 |
| | SD | 78.7 | 8.58 | 3.19 | 95.8 | 0.06 |
| | CV% | 54.4 | 50.2 | 68.3 | 280.1 | 38.3 |
| SQV M10 | N | 46 | 57 | 46 | 36 | 46 |
| | Mean | 66.8 | 7.57 | 4.71 | 22.0 | 0.06 |
| | SD | 42.6 | 4.62 | 1.99 | 25.0 | 0.05 |
| | CV% | 63.8 | 62.7 | 38.9 | 113.5 | 32.5 |

NA: Not Applicable.

Table 10: Summary of Pharmacokinetic Parameters for SQV and its Metabolites (M4, M6, and M10) on Day 3 Following SQV/rtv 1500/100mg bid (Treatment B)

| Analytes | | $AUC_{0\text{-}12h}$ (ng·h/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) | M/P Ratio (%) |
|---|---|---|---|---|---|---|
| SQV | N | 60 | 60 | 60 | 59 | |
| | Mean | 141000 | 15900 | 4.31 | 13.1 | NA |
| | SD | 44300 | 4360 | 1.50 | 8.18 | |
| | CV% | 31.4 | 27.5 | 34.8 | 62.4 | |
| SQV M4 | N | 60 | 60 | 60 | 58 | 60 |
| | Mean | 849 | 99.1 | 4.14 | 12.0 | 0.60 |
| | SD | 374 | 41.4 | 1.80 | 9.25 | 0.17 |
| | CV% | 44.0 | 41.7 | 43.5 | 77.2 | 28.4 |
| SQV M6 | N | 60 | 60 | 60 | 48 | 60 |
| | Mean | 298 | 32.9 | 4.49 | 29.6 | 0.21 |
| | SD | 155 | 15.0 | 3.68 | 47.7 | 0.08 |
| | CV% | 52.0 | 45.6 | 81.9 | 161.5 | 39.3 |
| SQV M10 | N | 58 | 60 | 58 | 46 | 58 |
| | Mean | 125 | 13.2 | 5.41 | 61.3 | 0.08 |
| | SD | 54.7 | 5.14 | 2.86 | 264 | 0.03 |
| | CV% | 43.7 | 38.8 | 52.9 | 429.8 | 32.1 |

NA: Not Applicable.

*Pharmacokinetic Results for Ritonavir*

Summary statistics for RTV PK parameters on Day 3 following treatment with SQV/rtv 1000/100 mg bid (Treatment A) and SQV/rtv 1500/100 mg bid (Treatment B) are provided in Table 11. The mean AUC0-12h and t1/2 of RTV on Day 3 were comparable for the 2 SQV/rtv regimens, as were the mean $T_{max}$ and $C_{max}$ of RTV on Day 3.

Table 11: Summary of Pharmacokinetic Parameters for RTV on Day 3 Following SQV/rtv 1000/100mg bid (treatment A) and SQV/rtv 1500/100mg bid (Treatment B)

| Treatment | | $AUC_{0\text{-}12h}$ (ng·h/mL) | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| SQV/rtv 1000/100 mg bid | N | 57 | 57 | 57 | 56 |
| | Mean | 18700 | 2610 | 4.01 | 6.45 |
| | SD | 5800 | 764 | 1.13 | 3.11 |
| | CV% | 31.1 | 29.3 | 28.1 | 48.2 |
| SQV/rtv 1500/100 mg bid | N | 60 | 60 | 60 | 59 |
| | Mean | 20300 | 2710 | 3.91 | 8.47 |
| | SD | 7420 | 1060 | 1.17 | 9.75 |
| | CV% | 36.5 | 39.3 | 29.9 | 115.1 |

*QTcS Correction*

The LME (Linear Mixed Effect) model used to determine the study-specific HR correction factor for this study revealed a statistically significant gender ×log(RR) interaction. As such, the final study-specific correction factors were 0.319 for male subjects and 0.337 for female subjects (QTcS = QT/RR0.319 and QTcS = QT/RR0.337, respectively. The chosen correction exponents (0.319 and 0.337) were in good agreement with Fridericia's correction (0.33) in eliminating the effect of HR on the QT interval.

To accommodate possible differences due to age, age (≤ 50 and > 50 years) was added to the model used to develop the QTcS correction. However, the interaction between age group and log(RR) was not statistically significant (sequentially tested), and no age-specific QT correction was derived for the main analysis.

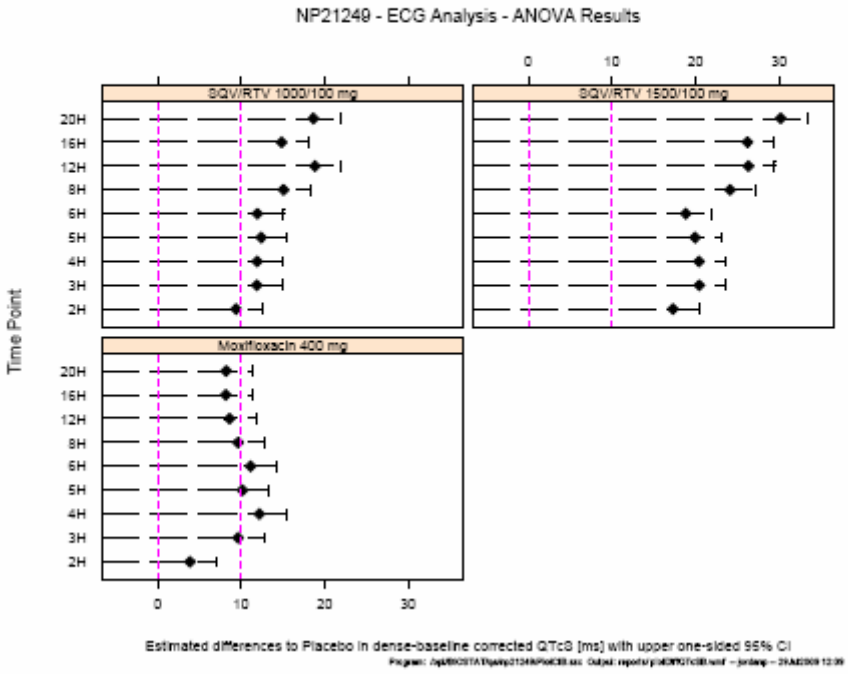
***Primary Study Variable*** *- ANOVA Derived Difference of Dense Pre-Dose Baseline Corrected QTcS Between Active Treatment and Placebo (****ddQTcS dense****)*

ANOVA results for the primary endpoint (ddQTcSdense), evaluating the least squares (LS) mean difference between the change from dense pre-dose baseline in the QTcS interval placebo at corresponding time points, showed the greatest increase in ddQTcSdense at 12h post-dose for the SQV/rtv 1000/100 mg bid group (LS mean: 18.86 ms; upper one-sided 95% CI: 22.01 ms) (Figure 3).

Analysis of changes occurring around the $C_{max}$ for each individual were not performed, but are not considered necessary given the low variation in $T_{max}$.

The study was shown to be sufficiently sensitive to detect an effect of study treatment on the primary variable, ddQTcSdense. Results of the assay sensitivity analysis showed that at 3h and 4h post-dose, the ddQTcSdense for MOXI 400 mg was > 5ms.

Figure 3 **ANOVA Results: Least Squares Mean Estimates (ms) and Upper One-Sided 95% CI for QTcS Change from Dense Pre-Dose Baseline Compared to Placebo ($ddQTcS_{dense}$) on Day 3**

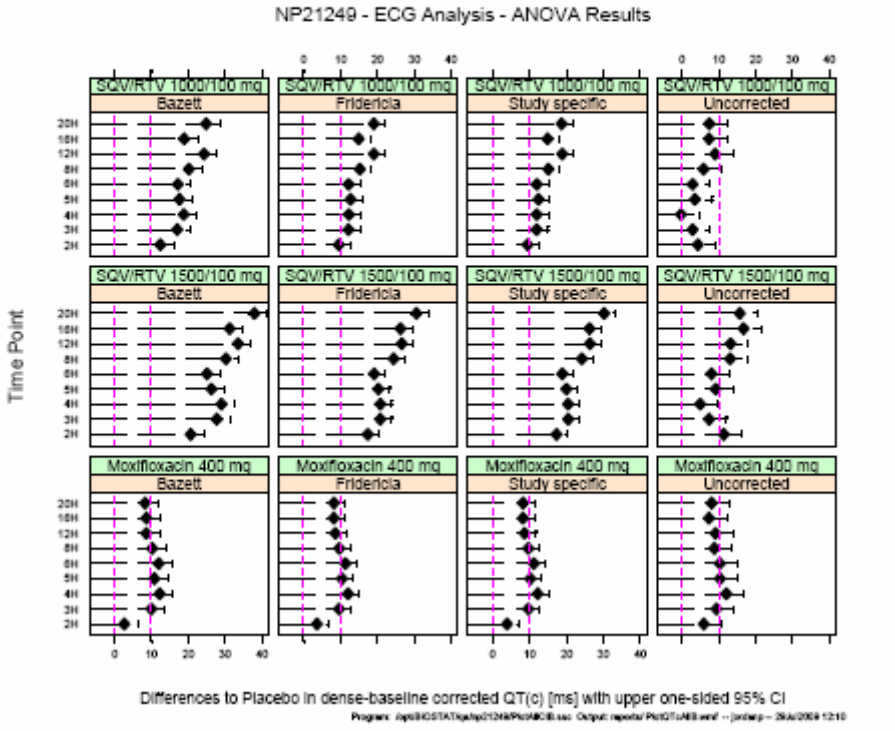



***Secondary Study Variables***

The secondary ECG variables for the study were absolute and change from dense predose baseline for the QT, QTcB, QTcF, RR, PR, and QRS intervals, and HR, as well as changes from baseline in T- and U-wave morphology.

ANOVA results for the secondary endpoint, evaluating the LS mean difference between the change from dense pre-dose baseline for the QTcF and QTcB on active treatment (SQV/rtv and MOXI) and placebo (ddQTcFdense and ddQTcBdense, respectively) at corresponding time points are shown in Figure 4.

Figure 4 ANOVA Results: Estimated Differences From Placebo in Dense Pre-Dose Baseline Corrected QTcS ($ddQTcS_{dense}$), QTcF ($ddQTcF_{dense}$), QTcB ($ddQTcB_{dense}$), and QT ($ddQT_{dense}$) with Upper One-Sided 95% CI on Day 3




The selection of secondary variables is adequate. The results applying Fridericia's (ddQTcFdense) and Bazett's (ddQTcBdense) correction formula led to very similar results for the primary variable (ddQTcSdense).

***Categorical Analysis of QTc Effects***

*Absolute QT/QTc Interval Prolongation*

At each scheduled post-dose time point after administration of SQV/rtv (therapeutic and supratherapeutic dose levels), MOXI 400 mg, or placebo, most subjects had QTcS, QTcF, and QTcB interval values of < 450 ms. No subject had a QT interval value (QT, QTcS, QTcF, QTcB) of > 500 ms (mean triplicate value) at any time point following any of the 4 study treatments.

The mean maximum QTcS, QTcF, and QTcB interval values across all post-dose time points for each of the 4 study treatments are presented in Table 11. The maximum value represents the greatest QTc interval value at any extraction time point following dosing on Day 3. Also shown on this table is the overall frequency distribution for maximum QTcS, QTcF, and QTcB intervals in the range of < 450 ms, > 450 to ≤ 480 ms, > 480 to ≤ 500 ms, and > 500 ms.

Table 11: Summary of Maximum Post-Baseline QTcS, QTcF, and QTcB Interval and Categorical Analysis by Trial Treatment

| | All Periods SQV/rtv 1000/100 mg (N=59) | All Periods SQV/rtv 1500/100 mg (N=60) | All Periods MOXI 400 mg (N=60) | All Periods Placebo 0 mg (N=59) |
|---|---|---|---|---|
| **Maximum QTcS (ms)** | | | | |
| Subjects evaluated | 57 | 60 | 59 | 59 |
| Mean (SD) | 419.7 (23.64) | 427.1 (24.75) | 409.0 (18.93) | 402.2 (19.35) |
| (Minimum, Maximum) | (374 – 470) | (368 – 480) | (351 – 447) | (351 – 441) |
| ≤ 450 ms | 51 (89%) | 48 (80%) | 59 (100%) | 59 (100%) |
| > 450 to 480 ms | 6 (11%) | 11 (18%) | 0 (0%) | 0 (0%) |
| > 480 to 500 ms | 0 (0%) | 1 (2%)[a] | 0 (0%) | 0 (0%) |
| > 500 ms | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Maximum QTcF (ms)** | | | | |
| Subjects evaluated | 57 | 60 | 59 | 59 |
| Mean (SD) | 419.9 (23.54) | 427.2 (24.68) | 409.0 (18.72) | 402.1 (19.41) |
| (Minimum, Maximum) | (375 – 471) | (368 – 480) | (352 – 447) | (351 – 440) |
| ≤ 450 ms | 51 (89%) | 48 (80%) | 59 (100%) | 59 (100%) |
| > 450 to 480 ms | 6 (11%) | 12 (20%) | 0 (0%) | 0 (0%) |
| > 480 to 500 ms | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| > 500 ms | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Maximum QTcB (ms)** | | | | |
| Subjects evaluated | 57 | 60 | 59 | 59 |
| Mean (SD) | 426.5 (25.60) | 434.6 (26.34) | 413.4 (19.27) | 406.6 (20.42) |
| (Minimum, Maximum) | (369 – 480) | (377 – 494) | (362 – 447) | (356 – 453) |
| ≤ 450 ms | 46 (81%) | 45 (75%) | 59 (100%) | 57 (97%) |
| > 450 to 480 ms | 11 (19%) | 12 (20%) | 0 (0%) | 2 (3%) |
| > 480 to 500 ms | 0 (0%) | 3 (5%) | 0 (0%) | 0 (0%) |
| > 500 ms | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

Percentages are based on 'Total no. of subjects evaluated'.
[a] Subject 1039 had a maximum QTcS interval value of 480.2 ms.

***Effect of Trial Treatment on Other ECG Parameters***

*Effects on PR Interval*

PR interval values were elevated after administration of therapeutic and supratherapeutic dose regimens of SQV/rtv.

The pattern of PR interval values on Day 3 from 2h to 20h post-dose mirrored the pattern of PR interval values at matched time points from -22h to -4h on Day -1, indicating a similar circadian pattern on Day -1 (baseline) and Day 3 (on treatment).

The maximum mean PR interval values for the SQV/rtv 1000/100 mg bid and SQV/rtv 1500/100 mg bid treatments were 186 ms and 195 ms, respectively, and occurred at 4h and 5h post-dose, respectively. At these extraction time points, the mean change from dense pre-dose baseline in the PR interval and the percentage of subjects who had a PR interval of > 200 ms were +25 ms and 30% (n=17) for SQV/rtv 1000/100 mg (4h postdose) and +34 ms and 40% (n=24) for SQV/rtv 1500/100 mg (5h post-dose). Across all time points on Day 3, PR intervals > 200 ms were observed for 40% and 47% of subjects following administration of SQV/rtv 1000/100 mg bid or SQV/rtv 1500/100 mg bid administration, respectively, and for 3% and 5% of subjects following treatment with MOXI 400 mg or placebo.

Mean PR intervals were largely unchanged relative to dense pre-dose baseline value following administration of MOXI 400 mg and placebo on Day 3.

*Effects on QRS interval*

The mean QRS interval on Day 3 following administration of the 4 study treatments (2h to 20h post-dose) ranged from 101 to 102 ms for SQV/rtv 1000/100 mg, from 102 to 104 ms for SQV/rtv 1500/100 mg, and from 98 to 100 ms for MOXI 400 mg and placebo.

The maximum increase in the QRS interval in the SQV/rtv treatments occurred at 5h post-dose; the mean QRS interval then decreased toward baseline value at 20h post-dose. There was no evident change in the QRS interval for MOXI and placebo. Small, mean increases ranging from 1 to 3 ms and from 2 to 4 ms were seen at each post-dose extraction time point on Day 3 with the SQV/rtv 1000/100 mg and 1500/100 mg bid treatments.

The percentage of subjects who had QRS intervals elevated above the normal range (40 to 120 ms) was similar for the 4 study treatments (5% to 7%).

However this is not considered clinically relevant.

*T- and U- Wave Morphology*

No subject had an abnormal U-wave at any extraction time point. The percentage of subjects who had a change from baseline in T-wave morphology was higher for the 2 SQV/rtv treatments than for placebo at each post-dose time point on Day 3, and was maximal at 5h post-dose (28% and 27% of subjects with change in T-wave morphology for the SQV/rtv 1000/100 mg and 1500/100 mg treatments, respectively (vs. 14% for placebo). No subject had a change in U-wave morphology on Day 3.

For each treatment, the most common abnormal T-wave morphology was a nonspecific T wave abnormality. On Day 3, no subject had an abnormality consisting of a tall T-wave following treatment with either SQV/rtv regimen, and only 1 to 3 subjects had an abnormality consisting of a flat T-wave or widespread abnormal T-wave pattern.

An increase in heart rate together with a decrease in RR intervals was observed Still, no subject had a HR value of > 100 bpm and no AEs associated with increased HR were reported. Findings on QRS interval and T-Wave morphology were both not considered clinically meaningful.

**Safety Results**

*Generalities*

Sixty-four (64) subjects reported a total of 339 AEs during the study. The percentage of subjects who experienced at least 1 AE was greater during the periods with SQV/rtv dosing than during periods of dosing with MOXI 400 mg or placebo.

AEs in the body systems, nervous system disorders and gastrointestinal disorders, were the most common AEs reported with SQV/rtv treatment, and occurred at higher rates with both SQV/rtv dose regimens than with MOXI 400 mg or placebo treatment. Differences in the reporting frequencies of AEs in other body systems between the SQV/rtv treatments and MOXI 400 mg and placebo were either not apparent or were not notable.

- The overall frequency of gastrointestinal AEs was similar for the 1000/100 mg bid (46%) and 1500/100 mg bid regimens (53%);

- However, the overall frequency of nervous system AEs was higher with the 1500/100 mg bid regimen (68%) than with the 1000/100 mg bid regimen (41%).
- Of the most common AEs (i.e., those reported in ≥ 5% subjects in any treatment group), the frequency of the following events was at least 2-fold higher for the SQV/rtv 1500/100 mg bid treatment than for the SQV/rtv 1000/100 mg bid treatment: dysgeusia (50% vs 22%, respectively), dizziness (22% vs 5%, respectively), presyncope (7% vs 3%, respectively), accommodation disorders (8% vs 2%, respectively), oral dysaesthesia (7% vs 2%, respectively), and feeling drunk (5% vs 2%, respectively). Dysgeusia, dizziness, and presyncope were also reported on placebo.

As a function of treatment period, results indicated that, except for nervous system disorders, the reporting frequency for AEs in most body systems showed no consistent pattern of difference across the 4 treatment periods. The frequency of nervous system disorder AEs was highest in Period 1 (44% vs. 35%, 34%, and 27% for Periods 2, 3 and 4, respectively). This difference was due to an imbalance in the reporting frequencies for syncope and presyncope; syncope was reported in the first treatment period for 8 of the 13 subjects with this AE while presyncope was reported in the first treatment period for 7 of the 10 subjects with this AE.

The majority of AEs (290 of 339, 86%) were assessed as mild in intensity by the investigator. Six (6) subjects had a total of 7 AEs assessed as severe in intensity. These were severe syncope and presyncope (both in the same subject), severe presyncope, severe dizziness and severe abdominal pain in subjects receiving SQV/rtv 1500/100 mg bid. Severe syncope in two subjects receiving SQV/rtv 1000/100 mg bid and severe syncope in one subject receiving MOXI 400 mg. Each of these severe AEs was assessed by the investigator as possibly related to treatment and resolved without treatment or sequelae.

No deaths or serious adverse events were reported during the trial or follow-up periods.

Three (3) subjects were withdrawn from the study due to AEs. Each of the AEs leading to premature discontinuation occurred during the first period during treatment with SQV/rtv 1000/100 mg bid (presyncope, first degree AV block; both moderate intensity), SQV/rtv 1500/100 mg bid (urticaria; moderate intensity) or MOXI 400 mg (sinus tachycardia; mild intensity).

There were no clinically significant, treatment-emergent, or abnormal laboratory results that would suggest a safety concern with either dose level of SQV/rtv.

*Syncope and presyncope*

Syncope and presyncope were reported at a higher than expected rates in study NP21249. AEs of syncope and presyncope were reported more frequently in subjects while receiving SQV/rtv;

- 11 of the 13 reports of syncope were during treatment with SQV/rtv 1000/100 mg bid (n=4) or 1500/100 mg bid (n=7).
- The remaining 2 reports of syncope occurred during treatment with MOXI 400 mg (n=1) and placebo (n=1).

- Of the 10 reports of presyncope, 6 were reported during treatment with SQV/rtv 1000/100 mg bid (n=2) or 1500/100 mg bid (n=4);
- the remaining 4 presyncope events were reported during treatment with placebo (n=2) or MOXI 400 mg (n=2).

Of the 23 reported AEs of syncope or presyncope, 17 (74%) were found to have an environmental etiology, including 14 that were associated with cannula insertion or blood sampling. The remaining 6 events (3 syncope, 3 presyncope) in 4 subjects had no obvious environmental etiology.

Three (3) of these events occurring in 3 subjects were associated with documented or suspected loss of consciousness. Review of the data revealed one additional AE that resulted in a documented loss of consciousness. No intervention was required for the loss of consciousness in these 4 subjects, and subjects were not hospitalised as a result of the event. All were non-serious, and only 1 was associated with a new abnormal Holter recording (PVCs, missed beats, and PR interval prolongation). Of these 4 events, 3 occurred during treatment with SQV/rtv 1500/100 mg bid and 1 occurred during treatment with SQV/rtv 1000/100 mg bid.

Central nervous system (CNS) effects might be more common with the higher dosing regimen. Furthermore, it seems reasonable to suspect that syncope could be caused or enhanced by saquinavir/ritonavir (SQV/RTV) and could be dose-dependent.Therefore detailed information for the syncope cases have been provided to clarify how syncope and presyncope were defined and at what day of exposure (of any suspected substance) the events occurred. SQV exposures in subjects with syncope have been compared to that seen in those without such an event. QTc findings and PR-intervals in subject with syncope have been compared to subjects without syncope.

Central nervous system (CNS) effects might be more common with the higher dosing regimen. Furthermore, it seems reasonable to suspect that syncope could be caused or enhanced by saquinavir/ritonavir (SQV/RTV) and could be dose-dependent. Therefore detailed information for the syncope case have been provided to clarify how syncope and presyncope were defined and at what day of exposure (of any suspected substance) the events occurred. SQV exposures in subjects with syncope have been compared to that seen in those without such an event. QTc findings and PR-intervals in subject with syncope have been compared to subjects without syncope.

- A post-hoc analysis of prolonged PR interval findings from subjects with and without syncope who were enrolled in the Study NP21249 was performed with the following hypothesis: Syncope/presyncope with prolonged PR interval could be caused or enhanced by SQV/RTV and could be dose-dependent.

Information on the safety and ECG data from the NP21249 study report was reviewed. In order to keep the review focused, only those subjects with triplicate ECGs available on Day 3 with PR > 200 msec were reviewed. Three subjects were already identified to have syncope/presyncope and who presented with Holter findings, PR interval > 200 msec; however, they did not have evaluable triplicate ECGs on Day 3. Five additional subjects were identified to have episodes of syncope or presyncope, but without PR > 200 msec.

For the post-hoc analysis, ECG data on PQ (PR) findings, was further reviewed. Subjects with PR interval > 200 msec were identified per randomised Treatment groups: ABCD, BDAC, CADB, and DCBA.

A total of 28 subjects were identified to have a PR interval of >200 msec. From these 28 subjects, 60 entries of prolonged PR were further identified based on the assigned randomized treatment group. Of 60 entries, 59 were evaluated for syncope/presyncope. The percentage of subjects with syncope/presyncope in those with prolonged PR interval is similar (or equivalent) regardless of treatment group. There is no dose effect of SQV/RTV and there is no difference compared to placebo or

moxifloxacin. Conversely, 80% with prolonged PR interval did not have syncope regardless of treatment group.

Table 12: Subjects with PR Interval>200 msec, by triplicates ECG only on Day 3 with and without Syncope/Presyncope (Study NP21249)

| Treatment[3] | Subjects with Syncope/Presyncope (n, %) | Subjects without Syncope/Presyncope (n, %) | Total No. of Subjects[4] (n, %) |
|---|---|---|---|
| 1000 mg SQV/ 100 mg RTV | 3 (13.6%) | 19 (86.4%) | 22 (37.3%) |
| 1500 mg SQV/ 100 mg RTV | 5 (18.5%) | 22 (81.5%) | 27 (45.8%) |
| 400 mg moxifloxacin | 1 (20.0 %) | 4 (80.0%) | 5 (8.5%) |
| Placebo | 1 (20.0 %) | 4 (80.0%) | 5 (8.5%) |
| TOTAL | 10[5] | 49 | 59[6] (100%) |

[1]Excludes drop-out subjects 1004, 1013, and 1038; (no ECGs available Day 3)
[2]PR interval data from ECG, as extracted from see vs03c_eabi "Listing of Triplicates of ECG Data by CRTN/Subject Number with Scheduled Visit" in the Secondary Data Displays of the NP21249 study report
[3]Trial treatment of the subject at the time of prolonged PR interval, with or without syncope, based on the assigned randomized treatment group.
[4]Total number of subjects with PR interval > 200 msec at a specified trial treatment: 1000/100 mg SQV/RTV, 1500/100 mg SQV/RTV, 400 mg moxifloxacin, and placebo. See attached listing of prolonged PR by subject number and trial treatment (Appendix 2 and Appendix 3).
[5]This total number reflects 2 subjects (1031, 1041) who were counted twice on different trial treatments. See highlighted entries in Appendix 3.
[6]This total reflects the total number of entries of PR prolongation. There maybe multiple entries per subject.

Correlated with the day of the reported event, the AE of syncope or presyncope on a specified trial treatment revealed that most episodes of syncope/presyncope occurred on Day 2. Only 6 subjects had syncope/presyncope on Day 3: 2 on placebo, 2 on moxifloxacin 400 mg and 2 on 1500/100 mg SQV/RTV.

- *Saquinavir exposures in subjects with PR >200 msec and syncope/presyncope vs those without syncope/presyncope.* A post hoc analysis of the PK data on Day 3 was performed on a subset of subjects that had PR > 200 msec (N=28) based on triplicate ECG and further subcategorized by subjects that had syncope or presyncope on at least one SQV/RTV dose, and compared to those subjects without syncope on any SQV/RTV dose, with the following hypothesis SQV PK (AUC, Cmax) is different in subjects with PR interval > 200 msec with syncope/presyncope compared to those with PR interval > 200 msec without syncope/presyncope while on SQV/RTV

PK exposure parameters in subjects with PR interval > 200 msec without syncope/presyncope (Group 1) were compared to those with PR interval > 200 msec with syncope/presyncope (Group 2).

A total of 28 subjects had PR interval > 200 msec. Of these 28 subjects, 21 experienced no syncope/presyncope (Group 1) and 7 experienced syncope/presyncope (Group 2).

Table 13 shows that there was no appreciable difference in the PK between exposures in subjects with PR > 200 msec with syncope/presyncope and without syncope/presyncope.

| SQV/RTV Regimen | | AUC (ng·h/mL) | | Cmax (ng/mL) | |
|---|---|---|---|---|---|
| | | Group 1 | Group 2 | Group 1 | Group 2 |
| 1000/100 mg | N | 21 | 7 | 21 | 7 |
| | Mean | 91890 | 97400 | 10903 | 10931 |
| | SD | 31059 | 32318 | 3462 | 3254 |
| | Minimum | 45400 | 63500 | 5400 | 7170 |
| | Maximum | 153000 | 140000 | 17000 | 15300 |
| 1500/100 mg | N | 21 | 7 | 21 | 7 |
| | Mean | 141214 | 154543 | 15924 | 16186 |
| | SD | 37489 | 41049 | 3619 | 3554 |
| | Minimum | 71000 | 93800 | 9050 | 12000 |
| | Maximum | 197000 | 219000 | 20600 | 21100 |

- Saquinavir exposures in subjects with and without syncope/presyncope. A post-hoc analysis of the PK data on Day 3 was performed on a subset of subjects that had syncope/presyncope on at least one SQV/RTV dose and compared to those subjects without syncope/presyncope on any SQV/RTV dose. Since 2 subjects with early discontinuation had no data on either dose, the number of subjects with syncope/presyncope on at least one SQV/RTV dose was 12, therefore n=10. The subjects with syncope/presyncope with moxifloxacin and placebo were placed in the control group with the following hypothesis: SQV PK (AUC, Cmax) is different in subjects with syncope/presyncope while on SQV/RTV.

PK exposure parameters in subjects without syncope/presyncope were compared to those with syncope/presyncope while on SQV/RTV regimen. Syncope/presyncope was reported in 16 subjects; 13 were on SQV/RTV. PK information is available from 10 subjects for the 1000/100 mg regimen and 12 subjects for the 1500/100 mg regimen.

Table 14 shows that there was no appreciable difference in the PK between subjects with and without syncope/presyncope.

| SQV/RTV Regimen | | AUC (ng·h/mL) | | Cmax (ng/mL) | |
|---|---|---|---|---|---|
| | | Group 1 | Group 2 | Group 1 | Group 2 |
| 1000/100 mg | N | 47 | 10 | 47 | 10 |
| | Mean | 94428 | 96680 | 11205 | 10992 |
| | SD | 29860 | 35097 | 3271 | 3355 |
| | Minimum | 42700 | 59800 | 5400 | 7170 |
| | Maximum | 158000 | 15100 | 20100 | 16100 |
| 1500/100 mg | N | 48 | 12 | 48 | 12 |
| | Mean | 136129 | 161758 | 15407 | 17650 |
| | SD | 41142 | 52355 | 3999 | 5407 |
| | Minimum | 61000 | 92300 | 8620 | 11500 |
| | Maximum | 260000 | 234000 | 25500 | 27200 |

Post-hoc analyses were performed on the data from this study. Based on these analyses described below, the occurrence of syncope was not dose-dependent and was not different for the SQV arms vs. the moxifloxacin or placebo arms. Most episodes of syncope/presyncope occurred on Day 2; only 6 subjects had events on Day 3 (2 on placebo, 2 on moxifloxacin, and 2 on 1500/100 mg SQV/RTV).

No subject had a QT/QTc value (QT, QTcS, QTcF, or QTcB interval) > 500 msec after any treatment. Only 1 subject had a QTcS interval value of 480 msec after treatment with SQV/RTV (1500/100 mg) BID regimen. The subject did not have adverse events associated with the QT prolongation.

There were no appreciable differences in the PK in subjects with PR interval > 200 msec and syncope/presyncope vs those without syncope/presyncope. In addition, there were no appreciable differences in the PK between exposures in subjects with syncope and without syncope.

It is agreed that the SQV exposure was similar in patients with and without syncope/presyncope. However, it was much more frequently seen during treatment with saquinavir, and especially with the higher dose than in the control arms. Therefore, a causal relationship cannot be ruled out.

It is difficult to conclude whether the syncope events, seen in a high frequency during treatment of saquinavir/r, were related to cardiac disturbances (such as a higher tendency for syncope around a vasovagal reaction) or rather caused by a more direct CNS related effect. The ECG findings would be caused by disturbances on various ion channels - perhaps similar disturbances could in fact be seen in the CNS. Therefore the SmPC should raise the potential sycope (see section III of the AR).

Patient with concomitant methadone therapy

The quantitatively most important such drug in the relevant patient population is methadone, which shows a dose dependent QTc-prolongation. The putative additive effects of saquinavir and methadone on the QT interval is discussed below. Of notice, HIV patients in such studies are fairly young and therefore cardiovascular disease is rare in this population. In future, the HIV population will be older and consequently show a higher frequency of chronic conditions, more risk factors, and concomitant medication.
There were four large well-control clinical trials in HIV patients. One with unboosted saquinavir (registration studies from 1998) and three with RTV-boosted SQV (MaxCmin1, MaxCmin2, and Gemini Study).

| | MAXCMIN1 | MAXCMIN2 | GEMINI |
|---|---|---|---|
| **Nervous System** | | | |
| Peripheral Neuropathy | 2,8 | 1,8 | - |
| Paresthesia | 0,7 | 2,4 | - |
| Dysgeusia | 2,8 | 1,2 | - |
| Headache | 2,1 | 5,4 | 2 |
| Dizziness | 1,4 | 3,6 | - |
| Syncope | - | - | <1 |
| **TOTAL** | **9,8** | **14,4** | **8** |
| | | | |
| **Cardiac Events** | | | |
| Palpitations | 0,7 | 0,7 | |
| Atrial Tachycardia | - | - | <1 |
| **TOTAL** | **0,7** | **0,7** | **<1** |

Although there are differences in the way adverse reactions and events were reported over time with boosted and unboosted SQV in the four large studies, there did not appear to be a change in either cardiac or nervous system disorder adverse reactions or events between boosted and unboosted SQV, although concomitant HAART therapy has changed over time. In the smaller studies involving rifampin, ketoconazole, and

There is no obvious difference in the frequencies reported during treatment with saquinavir/r versus that seen with indinavir/r or lopinavir/r. Only one case of syncope was reported (Gemini); neither syncope nor lipothymia (term used previously by Roche) occurred in the reports of the other two studies. Dizziness, which could be related to presyncope was uncommon and of low grade (1-2).

In one of the studies (MaxCmin 2) all 6 deaths occurred in the saquinavir/r arm (no case in lopinavir/r arm), four of whom died in aids related conditions, where other medicines with potential ECG disturbances would be commonly used. However, this pattern was not seen in the other two studies, where it seemed very unlikely that sauinavir/r could have contributed to the deaths.

In summary the results obtained in the clinical studies seems reassuring with regard to the issues under study.

The PSUR data on on cardiovascular and central nervous system (CNS) events have been revisit. Of particular interest was one death of Torsades de Pointes from 1996 (before RTV was added to boost SQV) that occurred in a 31 year-old male receiving unboosted SQV 600 mg three times daily (TID) which is lower than current recommendations of boosted SQV/RTV of 1000/100 mg twice daily (BID). The patient had a long history of AIDS, injection drug use on methadone maintenance, and CNS toxoplasmosis with a CD4 count of 10 mm3 and viral load of 142,000/mL. Cumulatively, in almost 14 years of clinical experience with SQV, there was no post marketing experience reports of PR prolongation or atrioventricular block associated with SQV or SQV/RTV.

## *3.3. Overall Conclusion*

Saquinavir was the first protease inhibitor approved for marketing in 1995. Early bioavailabilty issues were resolved with ritonavir boosting of Invirase. In the 14 years of marketing experience since approval of Invirase, there have been 1.7 million person years of exposure to saquinavir in combination with other antiretrovirals. Since approval, post marketing surveillance, including 5 issue work-ups included in PSURs from 2006 through 2010 has not found a causal relationship between QT prolongation or Torsades de Pointes. Despite the introduction of a number of new protease inhibitors to the market, ritonavir boosted Invirase remains an alternate PI. Of the nine protease inhibitors on the market, post marketing surveillance identified Torsades de Pointes cases with use of atazanavir, nelfinavir, indinavir and lopinavir/ritonavir.

Completion of a recent thorough study of ECGs in healthy volunteers demonstrated dose dependent QT and PR prolongation with the therapeutic dose of saquinavir 1000 mg boosted with ritonavir 100 mg bid on day 3 and has identified an average maximum prolongation of QT interval by 18.86 milliseconds (ms) at 12 hours post dose compared to a single dose of moxifloxacin 400 mg of 12.18 ms at 4 hrs post dose. There was no QT prolongation >500 ms and no Torsades de Pointes seen in this study.

The QT prolongation seen in this study was greater than that seen with moxifloxacin contol. Dedicated QT studies of other protease inhibitors have not shown this degree of prolongation, however cross-study comparisons should be interpreted with caution due to differences in study drugs, doses chosen, timing of ECG monitoring relative to maximal plasma concentrations, design, conduct and analysis.

Given the findings from the dedicated QT study in healthy volunteers, the company revised wording in the Core Data Sheet, reflecting the MAH position, in order to minimise the potential risk posed by the findings of prolongation of QT and PR intervals found in the study. Therefore the SmPC has been updated as explained below.

Furthermore the CHMP decided that this information should be communicated to the HIV treating physicians and cardiologists via a Dear Health Care Professional letter. This letter raised the following point:

- Invirase is contraindicated in patients with congenital or documented acquired QT prolongation, electrolyte disturbances, clinically relevant bradycardia, clinically relevant heart failure with reduced left-ventricular ejection fraction, previous history of symptomatic arrhythmias, as well as concurrent therapy with other drugs that prolong the QT and/or PR interval.

- Patients initiating therapy with ritonavir boosted Invirase should be warned of the potential arrhythmogenic risk and told to report any signs of cardiac arrhythmias (e.g., chest palpitations, syncope, presyncope) to their physician. Ritonavir boosted Invirase should be discontinued in case of significant arrhythmias, QT or PR prolongation.
- Consideration should be given for performing baseline and follow-up electrocardiograms after initiation of treatment in patients with predisposing risk factors or in patients taking concomitant medication known to increase the exposure of saquinavir. An ECG and continuous monitoring should be performed if signs or symptoms suggesting cardiac arrhythmia occur.

This letter should be circulated to all HIV treating physicians and cardiologists in all Member States on the 15 July 2010.

The CHMP will continue to monitor this safety issue.

# 4. Changes to the product information

The SmPC has been updated as described below. Consequently the Package Leaflet has been amended.

### 4.1 Section 4.3 Contraindication

The contraindications section has been amended with all medical conditions proposed by the CHMP (congenital or documented acquired QT prolongation, electrolyte disturbances, particularly uncorrected hypokalaemia, clinically relevant bradycardia, clinically relevant heart failure with reduced left-ventricular ejection fraction, previous history of symptomatic arrhythmias).

Moreover, concurrent therapy with medicinal products with a known potential for QT or PR prolongation, and with known or suspected increase in the plasma concentration in the presence of Invirase/ritonavir has been contraindicated due to potentially life threatening cardiac arrhythmias.

Medicinal products with known potential for QT or PR prolongation, but with *no* known or suspected increase in the plasma concentration in the presence of Invirase/ritonavir (or if dose adjustments have been previously accepted in the label) have *not* been contraindicated. They are however listed in SPC section 4.5 with the recommendation "Use with caution. Additive effects on QT and/or PR prolongation may occur with Invirase/ritonavir."

Some conditions have been listed as contraindications for SQV use, taking into account the availability of alternative HIV-treatment options as:

*Invirase is contraindicated in patients with:*
*• hypersensitivity to the active substance or to any of the excipients*
*• decompensated liver disease (see section 4.4)*
*• congenital or documented acquired QT prolongation*
*• electrolyte disturbances, particularly uncorrected hypokalaemia*
*• clinically relevant bradycardia*
*• clinically relevant heart failure with reduced left-ventricular ejection fraction*
*• previous history of symptomatic arrhythmias*
*• concurrent therapy with any of the following other drugs, which may interact and result in potentially life-threatening undesirable effects that both have pharmacokinetic interactions and prolong the QT and/or PR interval (see sections 4.4, and 4.5 and 4.8):*
*- drugs that prolong the QT and/or PR interval (see section 4.4 and 4.5)*

### 4.2 Section 4.4: Special warning and precaution for use

In order to reflect the findings of TQT study NP21249, the following precautionary wording is proposed for Section 4.4 'Special Warnings and Precautions' of the Invirase SmPC. Some issues was addressed like:

- Caution is recommended for special populations with an increased risk for drug-induced arrhythmia.
- Prolongation of QT and PR intervals clearly increased with dose of SQV. Therefore the following sentences should be included.
- As elaborated in the NfG CHMP/ICH/2/04 torsades the pointes is very infrequently captured in clinical databases. The failure to observe such episodes in a drug application database is not considered sufficient to dismiss the possible arrhythmogenic risk shown by this trial.

Therefore the following wording has been proposed:

> **4.4 Special warnings and precautions for use**
> ……
> *Cardiac conduction and repolarisation abnormalities:*
> Dose-dependent prolongations of QT and PR intervals have been observed in healthy volunteers receiving ritonavir-boosted Invirase (see section 5.1). The magnitude of QT and PR prolongation may increase with increasing concentrations of saquinavir. Therefore, the recommended dose of Invirase/ritonavir should not be exceeded, and other medicinal products known to increase the plasma concentration of ritonavir-boosted Invirase should be used with caution. Concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is contraindicated (see section 4.3). Women and elderly patients may be more susceptible to drug-associated effects on the QT and/or PR interval. Patients initiating therapy with ritonavir boosted Invirase should be warned of the arrhythmogenic risk associated with QT and PR prolongation and told to report any sign or symptom suspicious of cardiac arrhythmia (e.g., chest palpitations, syncope, presyncope) to their physician. Consideration should be given for performing baseline and follow-up electrocardiograms after initiation of treatment, e.g. in patients taking concomitant medication known to increase the exposure of saquinavir (see section 4.5). If signs or symptoms suggesting cardiac arrhythmia occur, continuous monitoring of ECG should be performed. Ritonavir boosted Invirase should be discontinued if arrhythmias are demonstrated, or if prolongation occurs in the QT or PR interval

### 4.3 Section 4.5: Interaction with other medicinal products and other form of interaction

In addition, in section 4.5, the possibility of an additive effect of SQV with other medicinal products with a potential for QT-prolongation have been discussed. A list of conditions known to increase the proarrhythmic risk (e.g. congestive heart failure, Long QT Syndrome, hypokalemia) has been added.

> ***"4.5 Interaction with other medicinal products and other form of interaction***
>
> ***…….***
>
> *Based on the finding of dose-dependent prolongations of QT and PR intervals in healthy volunteers receiving Invirase/ritonavir (see sections 4.3, 4.4 and 5.1), additive effects on QT and PR interval prolongation may occur. Therefore, concomitant use of ritonavir-boosted Invirase with other medicinal products that prolong the QT and/or PR interval is contraindicated. The combination of Invirase/ritonavir with drugs known to increase the exposure of saquinavir is not recommended and should be avoided when alternative treatment options are available. If concomitant use is deemed necessary because the potential benefit to the patient outweighs the risk, particular caution is warranted (see section 4.4; for information on individual drugs, see Table 1).*

Moreover, drugs with a known potential for QT or PR prolongation (as per the CHMP Request for Supplementary Information and additional information from literature) have been listed in "Table 1: Interactions and dose recommendations with other medicinal products", in conjunction with precautionary wording.

### 4.4 Section 5.1: Pharmacodynamic properties

Furthermore, the following proposed wording summarising the results of TQT study NP21249 has been added to Section 5.1:

> ***QT and PR prolongation on electrocardiogram:*** *The effects of therapeutic (1000/100 mg twice daily) and supra-therapeutic (1500/100 mg twice daily) doses of Invirase/ritonavir on the QT interval were evaluated in a 4-way crossover, double blind, placebo- and active-controlled (moxifloxacin 400 mg) study in healthy male and female volunteers aged 18 to 55 years old (N=59). On Day 3 of dosing, ECG measurements were done over a period of 20 hours. The Day 3 timepoint was chosen since the pharmacokinetic exposure was maximum on that day in a previous 14-day multiple dose pharmacokinetic study. On Day 3, mean Cmax values were approximately 3-fold and 4-fold, higher with the therapeutic and supra-therapeutic doses, respectively, relative to the mean Cmax observed at steady with the therapeutic dose administered to HIV patients. On Day 3, the upper 1- sided 95% confidence interval of the maximum mean difference in pre-dose baseline-corrected QTcS (study specific heart rate corrected QT) between the active drug and placebo arms was > 10 msec for the two ritonavir-boosted Invirase treatment groups (see results in Table 3). While the supra-therapeutic dose of Invirase/ritonavir appeared to have a greater effect on the QT interval than the therapeutic dose of Invirase/ritonavir, it is not sure if maximum effect for both doses has been observed. In the therapeutic and the supra-therapeutic arm 11% and 18% of subjects, respectively, had a QTcS between 450 and 480 msec. There was no QT prolongation > 500 msec and no torsade de pointes in the study (see also section 4.4).*

*Table 3: Maximum mean of ddQTcS† (msec) on day 3 for therapeutic dose of Invirase/ritonavir, supra-therapeutic dose of Invirase/ritonavir and active control moxifloxacin in healthy volunteers*

| ***Treatment*** | ***Post Dose Time point*** | ***Mean ddQTcs*** | ***Standard Error*** | ***Upper 95%-CI of ddQTcS*** |
|---|---|---|---|---|
| *Invirase/ritonavir 1000/100 mg BID* | *12 hours* | *18.86* | *1.91* | *22.01* |
| *Invirase/ritonavir 1500/100 mg BID* | *20 hours* | *30.22* | *1.91* | *33.36* |
| *Moxifloxacin* | *4 hours* | *12.18* | *1.93* | *15.36* |

*† Derived difference of pre-dose baseline corrected QTcS between active treatment and placebo arms ^ 400 mg was administered only on Day 3*
*Note: QTcS in this study was QT/RR0.319 for males and QT/RR0.337 for females, which are similar to Fridericia's correction (QTcF=QT/RR0.333).*

> *In this study, PR interval prolongation of > 200 msec was also observed in 40% and 47% of subjects receiving Invirase/ritonavir 1000/100 mg twice daily and 1500/100 mg twice daily, respectively, on Day 3. PR prolongations of > 200 msec were seen in 3% of subjects in the active control group (moxifloxacin) and 5% in the placebo arm. The maximum mean PR interval changes relative to the pre-dose baseline value were 25 msec and 34 msec in the two ritonavir-boosted Invirase treatment groups, 1000/100 mg twice daily and 1500/100 mg twice daily, respectively (also see section 4.4). Events of syncope/presyncope occurred at a higher than expected rate and were seen more frequently under treatment with saquinavir (11 of 13). The clinical relevance of these findings from this study in healthy volunteers to the use of Invirase/ritonavir in HIV-infected patients is unclear, but doses exceeding Invirase/ritonavir 1000/100 mg twice daily should be avoided.*

# 5. Conclusion

On 24 June 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.