



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 20-628/S-034
NDA 21-785/S-011

Drug Name: INVIRASE[®] (saquinavir mesylate)

Indication(s): Treatment of HIV-1 infection (b) (4)

Applicant: Hoffmann-La Roche Inc.

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Key Words: Pediatric Studies, non-randomized trials, descriptive statistics, time window, visit week, Updating INVIRASE[®] Label, (b) (4)

Table of Contents

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES1

FOOD AND DRUG ADMINISTRATION1

STATISTICAL REVIEW AND EVALUATION1

LIST OF TABLES.....3

LIST OF FIGURES.....4

1. EXECUTIVE SUMMARY5

 1.1 CONCLUSIONS AND RECOMMENDATIONS5

 1.2 BIEIF OVERVIEW OF CLINCIAL STUDIES6

 1.3 STATISTICAL ISSUES AND FINDINGS6

2. INTRODUCTION9

 2.1 OVERVIEW.....9

 2.2 DATA SOURCES9

3. STATISTICAL EVALUATION10

 3.1 DATA AND ANALYSIS QUALITY10

 3.2.3.3 CONCLUSIONS22

 3.3 EVALUATION OF SAFETY26

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS27

 4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION27

 4.2 OTHER SPECIAL/SUBGROUP POPULATIONS35

5 SUMMARY AND CONCLUSIONS36

 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE36

 5.2 CONCLUSIONS AND RECOMMENDATIONS37

6. APPENDICES.....39

 6.1 REFERENCES.....39

SIGNATURES/DISTRIBUTION LIST (OPTIONAL).....44

(b) (4)

(b) (4)

LIST OF TABLES

	Page
Table 1. Disposition and Duration of Treatment¹	12
Table 2. Demographic Characteristics¹	13

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LIST OF FIGURES

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[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Figure 6: HIVNAT017: Change from Baseline in CD4% by Age Group 35

1. EXECUTIVE SUMMARY

The sponsor, Hoffmann-La Roche Inc., submitted NDA 20-628/S-34 (NDA 21-785/S-11) to fulfill the Amended Written Request (WR) for Pediatric Studies (Amendment 6) dated December 23, 2009; the completion of the Post Marketing Requirement (PMR) to complete pediatric studies under PREA: [REDACTED] (b) (4)

[REDACTED]. The NDA 20-628/S-34 /NDA 21-785/S-11 include data from three completed pediatric studies, PACTG 397, HIVNAT 017 (ML 19540), and NV20911 for review in order to update the INVIRASE[®] label [REDACTED] (b) (4)

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1.1 CONCLUSIONS AND RECOMMENDATIONS

The element of the WR for Pediatric Studies for evaluating INVIRASE[®] in treatment of HIV-1 infected pediatric patients < 16 years of age has been fulfilled. The PMR to complete pediatric Studies PACTG 397, HIVNAT 017 (ML19540), and NV20911 under the Pediatric Research Equity Act (PREA) remains open [REDACTED] (b) (4)

[REDACTED] (c) (4)

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1.2 BIEEF OVERVIEW OF CLINCIAL STUDIES

The sponsor submitted the following three completed pediatric studies for review.

Study HIVNAT 017 (ML19540) was an open-label, single-arm study conducted at two different centers in Thailand. The HIVNAT 017 evaluated the pharmacokinetics, safety, and activity of lopinavir/ritonavir (230/57.5 mg/m² twice daily) with saquinavir (50 mg/kg twice daily given as 200 mg hard gel capsule) for 96 weeks. The study population consisted of 50 children between the ages of 4 and 15 years of age. The first 20 children enrolled underwent intensive pharmacokinetic sampling at steady state for plasma levels of lopinavir, ritonavir, and saquinavir.

Study NV20911 was an open label, multicenter study, conducted on 18 children 7 months to less than 6 years old in Argentina, Spain and Thailand. The NV20911 evaluated the pharmacokinetics, safety, and activity of saquinavir (50 mg/kg twice daily up to the adult dose of 1000 mg twice daily) and ritonavir oral solution (3 mg/kg twice daily for body weight from 5 to <15 kg, 2.5 mg/kg twice daily for body weight from 15 to 40 kg and 100 mg twice daily for body weight >40 kg plus ≥ 2 background ARVs).

Cohort 1 of Study PACTG 397 was designed to assess the safety, tolerability, bioavailability and efficacy of Saquinavir soft gel capsules alone (Saq, 50 mg/kg po tid to a maximum of 1200 mg po tid) and in combination with Nelfinavir (Nel), in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-1 infected children aged 3 to 16 years old. Please note that SQV soft gel capsules (FORTOVASE®) were taken off the market in 2006. This study was revised to Cohort 1A which allows 14 subjects on the Saq alone arm to switch to combination therapy Saq with ritonavir (RTV, 100 mg/mm² po bid) and eight subjects on the Saq + Nel combination to raise the maximum dose of Saq, plus one or two NRTIs. The randomization for rolling over to Cohort 1A was stratified by age (\leq or $>$ 12 years) and prior protease experience (yes or no). For updating the INVIRASE® label purposes, the safety and antiviral activity and immunologic response in the 14 subjects of the Saq+RTV arm in Cohort 1A were summarized.

The secondary objectives of these studies are for the evaluation the antiviral activity and immunologic response. Hence, this reviewer focuses on the study parameters related to HIV-1 RNA VL, CD4+ and CD4%.

1.3 STATISTICAL ISSUES AND FINDINGS

This reviewer identified three statistical and data issues during the statistical review.

1. The statistical evaluation of antiviral activity and immunologic response in these studies is the secondary objective, and has been descriptive due to the non-comparative nature of the study design. Because of the single-arm design, the contribution of Saq cannot be

isolated, and comparison to historical data can be confounded by differences in design and conduct.

- Studies HIVNAT017 and NV20911 were open-label, single-arm, non-randomized pediatric studies to evaluate the pharmacokinetics of a twice daily regimen of saquinavir in combination with ritonavir either alone or when co-administered with lopinavir (LPV/r, Kaletra), in addition to background antiretrovirals (ARVs). The primary objective for these studies is the evaluation of pharmacokinetics parameters of the underlying saquinavir regimen. The Saq+RTV arm in the Cohort 1A of PACTG 397 was part of a randomized trial but the utility of the data for the updating of INVIRASE[®] label can be considered as a single-arm study.
2. This reviewer used the Snapshot approach¹ to obtain the percentage of patients with non-detectable HIV-1 RNA VL at weeks 48 or 96. This approach is similar to the sponsor's 'missing=failure' approach, if the time window definitions are the same. It appears that the time windows were not appropriately defined according to the standard¹ in HIVNAT 017. Hence, numerical differences were observed between the sponsor's and the reviewer's. The reviewer's results showed numerical improvement in all measures of antiviral activity after 96 weeks treatment for HIVNAT 017. No time window problems were observed for NV20911 and the Saq+RTV arm in the Cohort 1A of PACTG 397.
 3. Ninety-two percent of the subjects in the HIVNAT017, 89% in the NV20911, and 86% in the Saq+RTV arm in the Cohort 1A of PACTG 397 completed the study. Hence, missing values in HIV-1 VL, CD4+ and CD4% were excluded in the evaluation of mean change in baseline to week 48 (96) in HIV-1 VL, CD4+ and CD4%.

This reviewer's findings are as follows.

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2. INTRODUCTION

2.1 Overview

Saquinavir (Ro 31-8959) is a protease inhibitor (PI) of human immunodeficiency virus (HIV-1). Three formulations of saquinavir have been marketed for oral administration: Invirase[®] 200 mg (hard capsule, HC), Invirase[®] 500 mg film-coated tablets and Fortovase[®] 200 mg soft capsule. Ritonavir (Norvir[®]) is a PI with antiviral activity against HIV-1 and HIV-2. Saquinavir is therefore recommended for administration in combination with low dose ritonavir to increase saquinavir exposure. Invirase[®] 500 mg film-coated tablet and the 200 mg HC were approved in the US for the treatment of advanced HIV-1-infected adult patients in combination with nucleoside analogs, respectively, on December 17, 2004 and December 06, 1995, and were approved in the European Union (EU) on May 25, 2005 and October 04, 1996, respectively. The commercialization of Fortovase[®] was discontinued in the EU and the US in 2006. The approved therapeutic dose is saquinavir 1000 mg twice daily (BID) in combination with ritonavir 100 mg BID.

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In this submission, the sponsor provided the data for three completed pediatric studies

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2.2 Data Sources

The supplemental applications under NDA 20,628/S034 (NDA 21-785/S011) contain the clinical study report for Study HIVNAT017, Study NV20911 and Study PACTG 397, including ‘overview.pdf’, ‘nv20911.pdf’, ‘hivnat017.pdf’ and ‘pactg397.pdf’.

SAS *.xpt and define.pdf files for safety and efficacy analyses can be found in the subdirectories of \\FDSWA150\NONECTD\N20628\S_034\2010-07-29\crt or \\FDSWA150\NONECTD\N21785\S_011\2010-07-29\crt

For Study NV20911, there are four analysis datasets and twelve listing datasets (with two define.pdf files) in ~\N20628 sNDA 072910\crt\Datasets\analyses\NV20911\analysis or listing. For Study HIVNAT17, there are fourteen datasets (with one define.pdf file) in ~\N20628 sNDA 072910\crt\Datasets\analyses\ HIV-NAT 017. For Study PACTG397, there are fifty-one datasets in ~\N20628 sNDA 072910\crt\Datasets\analyses\PACTG397 with one define.pdf.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This reviewer found a minor problem regarding the youngest age in study NV20911 at entry. It should be 7.7 months, not 4 months (see SAS list file below).

```
Age<1
10:57 Tuesday, January 4, 2011 4

Obs          PT      TRT1DC      BIRTHDC      AGE      age2      months
1            1302     03DEC2008   13APR2008     0        0.64      7.72
```

The sponsor's results regarding antiviral and immunologic response could be replicated for NV20911 and the Saq/r arm in the Cohort 1A of the PACTG 397 but not the HIVNAT017 due to the time window problems. It appears that the sponsor did not recode the time window in the HIVNAT017 using the standard definition in defining a time window as described in the DAVP's snapshot approach¹. The definitions of the time windows and the discrepancies of the HIV-1 RNA VL between the reviewer's and the sponsor's are summarized in the Appendix.

Per review team's request, the sponsor also submitted four SAS programs in *.txt files in the subdirectory of "~N20628\S_034\2010-10-20\crt\nv20911\analysis\program". These programs demonstrate how analysis datasets were generated from the raw data:

- Createdemoext.txt
- Createefvalall.txt
- Createhivdiag.txt and
- Createvital.txt.

This reviewer evaluated these programs logically.

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[REDACTED]

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Table 1 is a summary of patient disposition and duration of treatment by study. 92% of the patients completed the 96 week study in HIVNAT017, with a median (mean) of 98 (92) weeks treatment. 89% of the patients in NV20911 completed the 48 week treatment, with a median (mean) of 48 (45) weeks. 86% of the patients in the PACTG397-Saq/r completed the 48 week treatment, with a median (mean) of 49 (46) weeks.

Table 1. Disposition and Duration of Treatment¹

	HIVNAT017 (n=50)	NV20911 (n=18)	PACTG397Saq/r (n=14)
Completion ²	46 (92%) ³	16 (89%)	12 (86%)
Discontinue	4 (8%)	2 (11%)	2 (14%)
Died	3 (6%)	0 (0%)	0 (0%)
Other	1 (2%)	2 (11%)	2 (14%)
Duration of Treatment			
Median	97.9	48.0	48.6
Range	0.7,106.7	10.6,54.7	8.1,55.0
Mean (std)	92.2 (24.2)	44.6 (12.3)	45.8 (11.1)

1. Source: Reviewer's analysis.

2. Cutpoint =90 weeks for HIVNAT017, 44 weeks for NV20911 and PACTG397-Saq/r.

3. Pt 117 had a Week 84 HIV RNA data, with a duration of treatment of 45.6 weeks;

Pt 101 had HIV RNA VLs at Week 96 or longer, with a duration of treatment of 28.4 weeks.

Table 2 is a summary of demographics by study. 56% in the HIVNAT017, 61% in the NV20911 and 50% in the PACTG397Saq/r are female pediatric patients. The median age is 9 years old with a range of (4,15) in the HIVNAT017. The median age is 4 years old with a range of (0.6,6) in the NV20911 and the median age is 11 with a range of (5.6,16.5) in the PACTG397. The HIVNAT017 was conducted among 50 pediatric patients in Thailand, and the NV20911 was conducted in 18 pediatric patients in Argentina, Spain and Thailand, and the PACTG397 was conducted in the US.

Table 2. Demographic Characteristics¹

N		HIVNAT017 50	NV20911 18	PACTG397Saq/r 14
Sex	Male	22 (44%)	7 (39%)	7 (50%)
	Female	28 (56%)	11 (61%)	7 (50%)
Race	Caucasian	0 (0%)	8 (44%)	4 (29%)
	Black	0 (0%)	0 (0%)	5 (36%)
	Asian	50 (100%)	10 (56%)	1 (7%)
	Hispanic	0 (0%)	0 (0%)	4 (29%)
Age-Low: range (n,%)		4.5-11.9 (40,80%)	7 mo -<2 (5,28%)	5.6-11.8 (9,64%)
Age-High: range (n,%)		12.2-15.5 (10,20%)	2-<6 (13,72%)	13.3-16.5 (5,36%)
Age	mean (std)	9.3 (2.5)	3.7 (1.8)	11.4 (3.2)
	median (range)	9.3 (4.5,15.5)	4.3 (0.6,5.9)	10.7 (5.6,16.5)
Weight (kg)	mean (std)	22.4 (7.9)	13.6 (3.9)	46.2 (19.6)
	median (range)	20 (10.7,55.0)	14 (6.3,20)	42.9 (24.7,85.5)
Height (cm)	mean (std)	120 (14.2)	91.8 (13.3)	144.3(16.8)
	median (range)	119 (92,159)	91 (62,116)	145 (117,171)

1. Source: Reviewer's analysis.

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3.2.3 Results and Conclusions

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3.3 Evaluation of Safety

Please refer to medical officer's review of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

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HIVNAT017 was conducted in Thailand, where 100% subjects are Asian. The sample size is 50. Hence, we can conduct the underlying subgroup analysis by age and gender.

NV20911 was conducted in Argentina, Spain and Thailand, where 10 (56%) subjects are Asian and the rest (n=8) are Caucasian. The NV20911 consists of 5 subjects under the age of two years, and 13 age 2-<6 years. Due to insufficient information in primary objective (pharmacokinetic data), the antiviral activity and immunologic response for this group was not the main concern. Hence, the subgroup analysis by age may not be needed. Excluding the five subjects under the age of two years, there are five males and eight females, five Caucasian subjects and eight Asian subjects. The subgroup analysis by race and gender seem unnecessary due to small sample size.

The Saq/RTV arm in Cohort 1A of the PACTG 397 was conducted in the US. Hence, no region analysis can be conducted. It consists of 4 Caucasian, 4 Hispanic, 5 Black, and 1 Asian, and 5 subjects age 12 to 16, and 9 age 5 to < 12. Hence, the underlying subgroup analysis by race and gender seem unnecessary due to small sample size.

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The above conclusions regarding the age differences correspond to those of the sponsor.

4.2 Other Special/Subgroup Populations

No other subgroups have been analyzed for this review.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This reviewer identified three statistical and data issues during the statistical review.

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- Studies HIVNAT017 and NV20911 were open-label, single-arm, non-randomized pediatric studies to evaluate the pharmacokinetics of a twice daily regimen of saquinavir in combination with ritonavir either alone or when co-administered with lopinavir (LPV/r, Kaletra), in addition to background antiretrovirals (ARVs). The Saq+RTV arm in the Cohort 1A of PACTG 397 was part of a randomized trial but the utility of the data can be considered as a single-arm study.

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This reviewer provided the following statistical findings to the review team for future updating the INVIRASE[®] label.

Study HIVNAT 017

Treatment with lopinavir/ritonavir 230/57.5 mg/m² and saquinavir 50 mg/kg twice daily in children 4 to 15 years of age for 96 weeks resulted in a substantial viral load suppression. When using the snapshot analysis, 78% and 66% of patients achieved HIV RNA <400 copies/mL and HIV RNA <50 copies/mL, respectively at week 96. At week 96, 82% of patients experienced at least 1 log₁₀ copies/mL decrease from screening. (b) (4)

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NV20911

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Snapshot analysis showed the virologic suppression at week 48, 72% of patients with HIV RNA <400 copies/mL and 61% of patients with HIV RNA <50 copies/mL,

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5.2 Conclusions and Recommendations

The element of the WR for Pediatric Studies for evaluating INVIRASE® in treatment of HIV-1 infected pediatric patients < 16 years of age has been fulfilled.

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6. APPENDICES

6.1 References

1. Snapshot_document_final_032910.doc. DAVP, 2010.
2. Blood differential. <http://www.nlm.nih.gov/medlineplus/ency/artical/003657.2010>.
3. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. MMWR 47 (RR-4); 1-31. April 17, 1998.

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