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 in pediatric patients
Applicant:	Hoffmann-La Roche Inc.
Date(s):	Date of submission: July 29, 2010
	GRMP date January 6, 2011
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Review Priority:	Priority
Biometrics Division:	DBIV
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Concurring Reviewers:	Statistical team leader: Greg Soon, Ph.D.
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Key Words: Pediatric Studies, non-randomized trials, descriptive statistics, time window, visit week, Updating INVIRASE® Label, pediatric dose recommendation

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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; and the determination of pediatric exclusivity extension granted on October 19, 2010. 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 to support a dosing recommendation for saquinavir (Saq) boosted with ritonavir (RTV) in pediatric HIV patients >2 years to 16 years of age.

For this supplement, consideration of approval is based on extrapolation of efficacy from adequate and well-controlled trials in HIV-1 infected adults, and supportive pharmacokinetic (PK) and safety data from completed pediatric studies HIVNAT 017 and NV20911. The statistical review of this supplement requires antiviral activity and immunologic response evaluations, as a secondary objective. Hence, this reviewer focused on surrogate markers related to HIV-1 RNA VL, CD4+ and CD4%.

Roche concluded that saquinavir treatment as part of a HAART regimen in pediatric patients with HIV infection demonstrated a marked improvement in all measures of antiviral activity. These measurements, including change from baseline in HIV RNA viral load, percentage of patients with viral load below lower limit of quantification (BLQ), change from baseline in CD4+ cell count, were consistent with that seen in adult patients receiving similar mg/kg doses and background antiretroviral therapy (ART) regimens. Based on the data in Saq/RTV arm of Cohort 1A of PACTG 397, Roche concluded that pediatric patients who switched the treatment to Saq soft gel capsules in combination with RTV and one or two NRTIs showed numerical similar antiviral activity and immunologic response at rolling over and at week 48.

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 due to multiple deficiencies conveyed by the Division of Scientific Investigations (DSI). The pharmacokinetic (PK) data from the HIVNAT 017 study were considered invalid. As a result, the pediatric PK data on which to bridge adult efficacy trials is lacking, and the Agency is unable to approve this sNDA submission at this time, nor complete the process of product labeling.

Based on the statistical evaluation of data, this reviewer concurs with the sponsor's conclusions regarding surrogate markers related to HIV-1 RNA VL, CD4+ and CD4%. The sponsor

concluded that there were insufficient data for the Saquinavir dose recommendation for those under 2 years. We agree with this conclusion.

1.2 BEIEF 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/m^2 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/mm^2 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 (≤ 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 approach[1] 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 standard[1] 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.
1. Percentage of study subjects achieved virologic response was high in HIVNAT017 at through week 96 and in NV20911 at week 48 and maintained through week 48 in the Cohort 1A of PACTG 397, when using DAVP's Snapshot analysis.

- In HIVNAT017, 78% of the subjects achieved HIV-1 RNA <400 copies/mL; 66% achieved HIV-1 RNA <50 copies/mL at week 96, significantly increased from baseline levels: 4% with HIV-1 RNA <400 copies/mL and 0% with HIV-1 RNA <50 copies/mL. At week 96, 82% achieved at least 1 $\log_{10}$ copies/mL decrease in HIV-1 RNA from screening.
- In NV20911, 72% of patients had HIV-1 RNA <400 copies/mL and 61% of patients had HIV-1 RNA <50 copies/mL at week 48, significantly increased from baseline levels: 33% with HIV-1 RNA <400 copies/mL and 22% with HIV-1 RNA <50 copies/mL.
- In the SAQ+RTV arm in the Cohort 1A of PACTG 397, 6/14 (43%) of the subjects on the Saq+RTV arm had HIV-1 RNA <400 copies/mL at rolling over to Cohort 1A. After 48 weeks of treatment, five subjects (36%) had HIV-1 RNA <400 copies/mL. This includes four subjects maintained the HIV-1 RNA <400 copies/mL, and one achieved HIV-1 RNA <400 copies/mL from HIV-1 RNA >400 copies/mL at entry to Cohort 1A.

2. Study subjects in HIVNAT017 and in the SAQ+RTV arm in the Cohort 1A of PACTG 397 achieved marked reduction in HIV-1 RNA viral load.

- In HIVNAT017, a mean reduction of VL from baseline to week 96 was 2.7 $\log_{10}$ copies/mL. In NV20911, a mean reduction of VL from baseline to week 48 was 1.4 $\log_{10}$ copies/mL. In the SAQ+RTV arm in the Cohort 1A of PACTG 397, a mean reduction of VL from baseline to week 48 was 2.7 $\log_{10}$ copies/mL.

3. Mean CD4+ and mean CD4% were increased or maintained.
   - In HIVNAT017, mean increases from baseline in CD4+ cell counts were 400 cells/mm^3 at week 48 and 566 cells/mm^3 at week 96. In NV20911, mean increase from baseline in CD4+ cell counts was 91 cells/mm^3 at week 48.
   - In HIVNAT017, mean increases from baseline in CD4% were 11% at week 48 and 14% at week 96. In NV20911, mean increase from baseline to week 48 in CD4% was 3%.
   - In the SAQ+RTV arm in the Cohort 1A of PACTG 397, a mean reduction from baseline to week 48 was 41 cells/mm^3 in CD4+ and 1% in CD4%.

4. Due to the limitation of study designs with small sample size, subgroup analysis by age and gender was conducted in HIVNAT017 only. Gender differences in change from baseline in HIV-1 RNA and CD4+ cell counts, but not CD4% were observed numerically (see Figures 1-3). Age differences in change from baseline in HIV-1 RNA and CD4+ cell counts, but not CD4% were observed numerically (see Figures 4-6). The decrease in HIV RNA levels during the 96 weeks was observed in both older age group (≥ 12 to 16 years) and younger age group (≥ 3 to <12 years), and in both male and female groups. The increase in CD4+ or CD4% during the 96 weeks was observed in both older and younger age groups, and in both male and female groups.
   - The male group overall had a similar HIV RNA level and a lesser CD4+ cell counts at screening. The mean difference (male-female) in mean change from baseline in HIV-1 RNA was 0-0.7 copies/mL during the study period; in CD4+ was between 22 to 110 cells/mm^3 after week 12.

   - The older age group overall had a higher HIV RNA level and a lesser CD4+ cell counts at screening and through Week 96 compared with the younger age group. The mean difference (older-young) in mean HIV-1 RNA was 0.3~1.1 copies/mL during the study period; in CD4+ was between 120 to 352 cells/mm^3 during the study period.

   - During the 96 weeks of study, the overall changes from screening in mean CD4 cell percentage were consistent in both younger age group and older age group patients, and in both male and female patients. The gender difference or the age difference of the absolute values of mean change from baseline in CD4% were below 3%.

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.

To date, the development of a palatable age-appropriate saquinavir pediatric formulation that delivers therapeutic exposures of drug has not been successful. The saquinavir pediatric development program has shifted emphasis to explore the use of commercially available adult formulations of saquinavir in combination with ritonavir as a pharmacokinetic booster, and in particular, the use of unopened or opened Invirase® 200 mg HCs.

In this submission, the sponsor provided the data for three completed pediatric studies to support a dosing recommendation for saquinavir boosted with ritonavir in pediatric HIV patients >2 years to 16 years of age.

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 approach[1]. 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. It appears that the time windows are correctly defined for the calculations of longitudinal HIV-1 RNA VL, CD4+, CD4%, CD8+ and CD8%. No problems were identified for the HIV-1 VL data.

As to the calculation of CD4+ (CD8+), a completed CD4+ or CD8+ dataset should consist of three parts. Using CD4+ as an example, the three parts can be obtained as follows:

- directly extraction of the CD4+ cell count from the labp.xpt;
- indirectly calculation of CD4+ using the CD4% and lymphocyte count[2];
- indirectly calculation of CD4+ using the CD4%, and % of lymphocyte and WBC count[2].

The CD4+ or CD8+ results were all matched with this reviewer's results.

3.2 Evaluation of Efficacy

3.2.1 Study Design, Endpoints and Statistical Methodologies

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/m^2 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 in 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. 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/mm^2 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 (≤ 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.

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

The study population for the evaluation of antiviral activity and safety was defined as all patients who received at least one dose of study medication.

Statistical methodologies in evaluation of the antiviral activity was based on summary statistics such as sample size, mean, median, standard deviation, for three parameters: HIV-1 RNA viral load, CD4+ cell count and CD4%. Based on the DAVP policy, snapshot approach[1] was used for the estimations of summary statistics for HIV-1 RNA viral load including percentage of patient with HIV-1 RNA VL <400 copies/mL, <50 copies/mL and percentage of patients with at least 1

$\log_{10}$ drop from baseline. This was similar to the 'missing=failure' analysis reported by the sponsor.

The antiviral activity based on the HIV-1 RNA VL and immunologic response based on CD4+ and CD4% in the HIVNAT017, NV20911 and the study arm of Saq+RTV in Cohort 1A of the PACTG 397 will be summarized in this section. In the text below, we refer to the 'Saq/RTV' arm in the Cohort 1A of the PACTG 397 as 'PACTG397-Saq/r'.

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 Treatment[1]

	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 conduced in 18 pediatric patients in Argentina, Spain and Thailand, and the PACTG397 was conducted in the US.

Table 2. Demographic Characteristics[1]

		HIVNAT017	NV20911	PACTG397Saq/r
N		50	18	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.

Table 3 provides a summary statistics for the five parameters HIV-1 RNA VL, CD4+ cell count and CD4% prior to the treatment with study regimens. In HIVNAT017, the mean HIV-1 RNA VL is 4.8 in $\log_{10}$ (copies/mL), with mean CD4+ cell count of 210 cells/mm^3. In the NV20911, the mean HIV-1 RNA VL is 3.8 in $\log_{10}$ (copies/mL), with a mean CD4+ cell count of 1293 cells/mm^3. In the PACTG397Saq/r at the time of rolling over to Cohort 1A, the mean HIV-1 RNA VL is 2.6 in $\log_{10}$ (copies/mL), with a mean CD4+ cell count of 708 cells/mm^3.

Table 3. Screening HIV-1 RNA, CD4+ and CD4%[1]

	n	median	Min.	Max.	mean	std
HIVNAT017 (n=50)						
HIV RNA	47	4.81	1.76	5.88	4.71	0.75
CD4+	49	160	6	939	210	207
CD4%	49	7.0	0.0	23.0	7.5	5.6
NV20911 (n=18)						
HIV RNA	18	3.81	1.69	5.30	3.50	1.47
CD4+	17	1212	383	2992	1340	754
CD4%	17	29.7	14.5	51.5	28.9	10.6
PACTG397Saq/r (n=14)						
HIV RNA	14	2.23	1.32	4.19	2.57	0.79
CD4+	14	545	196	2008	708	497
CD4%	14	29.0	12.0	45.0	28.5	8.0

1. Source: Reviewer's analysis.

3.2.3 Results and Conclusions

3.2.3.1 Antiviral Results

Tables 4 and 5 provide summary statistics using the snapshot approach[1] for the percentage of patients with HIV-1 RNA VL< 50 copies/mL and < 400 copies/mL, respectively. As mentioned previously, time windows were recoded for HIVNAT017 according to the standard definition of time window[1]. For example, time window for Week 48 ranged from Day 294 to Day 377, and time window for Week 96 ranged from Day 630 to Day 713. The sponsor's results are listed in the last two columns for comparison purposes.

At Week 48, 62% and 61% of the subjects in the NV20911 and HIVNAT017 had HIV-1 RNA VL < 50 copies/mL, respectively. The sponsor's results matched the reviewer's. At Week 96, 66% subjects in the HIVNAT017 had HIV-1 RNA VL < 50 copies/mL, significantly greater than that from the sponsor's (52%). In PACTG397, 36 % (5/14) of the subjects had achieved HIV-1 RNA VL < 50 copies/mL at Week 48.

At Week 48, 72% of the subjects in the NV20911 and HIVNAT017 had HIV-1 RNA VL < 400 copies/mL, respectively. The sponsor's results were similar (74% in the HIVNAT017 and 72% in the NV20911) to the reviewer's. At Week 96, 78% subjects in the HIVNAT017 had HIV-1 RNA VL < 400 copies/mL, significantly greater than that from the sponsor's (56%). In PACTG397, 36 % (5/14) of the subjects had HIV-1 RNA VL < 400 copies/mL at Week 48. There were 43% (6/14) of the subjects had HIV-1 RNA VL < 400 copies/mL at entry to Cohort 1A.

Table 4. Percentage of Patients with HIV RNA VL <50 copies/mL

		Reviewer's[1]		Sponsor's[2]	
Week	**N**	**n<LOQ**	**%**	**n<LOQ**	**%**
HIVNAT017 (n=50)					
Screening	47	0	0	0	0
12	27	9	18	10	20
24	48	27	54	27	54
36	45	27	54	26	52
48	45	31	62	31	62
60	47	29	58	33	66
72	47	34	68	31	62
84	47	33	66	32	64
96	45	33	66	26	52
NV20911 (n=18)					
Screening	18	4	22	4	22
12	17	7	39	7	39
24	17	14	78	13[3]	72
36	16	10	56	10	56
48	16	11	61	11	61
PACTG397Saq/r (n=14)					
Baseline	14	1	7		
4	11	0	0		
8	13	0	0		
12	14	0	0		
24	12	2	14		
36	10	3	21		
48	11	5	36		

[1] Source: Reviewer's analysis: "Missing as Failure" approach.
[2] Sponsor's results (Table 6 for HIVNAT017 and Table 7 for NV20911 (Overview.pdf).
[3] PT (4101) had Week 24 HIV-1 RNA VL=50 copies/mL. Sponsor assigned missing.
[4] LOQ=50 Copies/mL

Table 5. Percentage of Patients with HIV RNA VL <400 copies/mL

		Reviewer's[1]		Sponsor's[2]	
Week	N	n<LOQ	%	n<LOQ	%
HIVNAT017					
Screening	47	2	4	2	4
12	27	19	38	20	40
24	48	35	72	35	70
36	45	39	78	37	74
48	45	36	72	37	74
60	47	36	72	40	80
72	47	42	84	41	82
84	47	41	82	40	80
96	45	39	78	28	56
NV20911					
Screening	18	6	33	6	33
12	17	15	83	15	83
24	17	16	89	15[3]	83
36	16	13	72	12	67
48	16	13	72	13	72
PACTG397Saq/r (n=14)					
baseline	14	6	43		
4	11	6	43		
8	13	5	36		
12	14	5	36		
24	12	5	36		
36	10	4	29		
48	11	5	36		

[1] Source: Reviewer's analysis: "Missing as Failure" approach.
[2] Sponsor's results (Table 6 for HIVNAT017 and Table 7 for NV20911 (Overview.pdf).
[3] PT (4101) had Week 24 HIV-1 RNA VL=50 copies/mL and Week 36 VL=84. Sponsor assigned missing.
[4] LOQ=400 Copies/mL

Tables 6 and 7 provide summary statistics respectively, for HIV-1 RNA VL and change from baseline in HIV-1 RNA VL by weeks. Overall, the mean decreases from baseline to Weeks 48 and Week 96 were 2.66 and 2.73, respectively in the HIVNAT017. The mean decrease from baseline to Week 48 was 1.36 copies/mL in NV20911. As to the PACTG397Saq/r, at entry to Cohort 1A, subjects had a mean CD4+ cell count of 708 cells/mm^3 with a mean CD4% of 28.5%. After 48 weeks of treatment with Saq/RTV, the mean CD4+ was 732 cells/mm^3 with a mean CD4% of 26.5%. It appears that the immunologic response was well maintained.

Table 8 provides summary statistics for the percentage of patients with at least 1 $\log_{10}$ copies/mL drop in HIV-1 RNA VL based on 'missing=failure' principle. At Week 48, 80% and 44% of the subjects in the HIVNAT017 and NV20911 had at least 1 $\log_{10}$ copies/mL drop in HIV-1 RNA VL, respectively. At Week 96, 82% of the subjects in the HIVNAT017 had at least 1 $\log_{10}$ copies/mL drop in HIV-1 RNA VL. The sponsor's results in the HIVNAT017 are significantly lower those from the reviewers. This outcome was not summarized by the sponsor and this reviewer.

Table 6. HIV-1 RNA VL ($\log_{10}$ copies/mL)

		Reviewer's				
Week	**n**	**Med**	**Min**	**Max**	**mean**	**Std**
HIVNAT017 (n=50)						
Baseline	47	4.81	1.76	5.88	4.71	0.75
12	25	2.21	1.70	5.00	2.39	0.84
24	45	1.70	1.70	5.00	2.30	0.98
36	42	1.70	1.70	5.00	2.15	0.92
48	42	1.70	1.70	4.95	2.10	0.84
60	44	1.70	1.70	5.88	2.32	1.01
72	44	1.70	1.70	4.96	1.96	0.66
84	44	1.70	1.70	4.93	2.04	0.78
96	42	1.70	1.70	4.86	2.03	0.79
NV20911 (n=18) – Reviewer's using sponsor's data						
Baseline	18	3.81	1.69	5.30	3.50	1.47
8	16	1.69	1.69	3.27	2.08	0.58
12	17	1.93	1.69	3.05	2.01	0.42
24	16	1.69	1.69	3.87	1.85	0.55
36	15	1.69	1.28	5.00	2.13	0.96
48	16	1.69	1.28	4.92	2.10	0.96
PACTG397Saq/r (n=14)						
Baseline	14	2.23	1.32	4.19	2.57	0.79
4	11	2.58	2.09	5.36	3.31	1.26
8	13	2.69	2.20	4.39	3.01	0.72
12	12	3.04	2.21	4.40	3.18	0.76
24	12	2.93	1.18	5.00	2.92	1.24
36	10	2.88	1.15	4.84	2.85	1.38
48	11	2.68	1.00	4.40	2.61	1.44

Table 7. Change From Baseline in HIV RNA (log_{10} copies/mL)

		Reviewer's					Sponsor's[1]		
Week	**n**	**med**	**Min**	**Max**	**Mean**	**Std**	**N**	**Mean**	**Std**
HIVNAT017 (n=50)									
12	25	-2.55	-3.29	0.19	-2.28	0.93	26	-2.25	0.97
24	45	-2.88	-3.63	-0.06	-2.44	1.02	40	-2.37	1.06
36	42	-2.88	-3.66	0.33	-2.61	0.98			
48	42	-2.97	-3.82	0.14	-2.66	0.94	36	-2.63	0.98
60	44	-2.83	-3.82	0.34	-2.41	1.12			
72	44	-3.04	-3.82	0.15	-2.77	0.89	37	-2.82	0.76
84	44	-2.97	-4.18	0.12	-2.69	0.93			
96	42	-2.93	-3.93	-0.04	-2.73	0.92	24	-2.81	0.89
NV20911 (n=18) – Reviewer's using sponsor's data									
8	16	-1.10	-3.21	0.87	-1.21	1.32			
12	17	-1.01	-3.18	0.37	-1.40	1.35	17	-1.40	1.35
24	16	-1.86	-3.31	0.37	-1.61	1.57	16	-1.61	1.57
36	15	-0.60	-3.55	0.12	-1.23	1.34	15	-1.23	1.34
48	16	-0.98	-3.71	0.13	-1.36	1.42	16	-1.36	1.42
PACTG397Saq/r (n=14)									
4	11	0.17	1.06	0.23	-1.22	2.64			
8	13	-0.07	0.62	-0.04	-0.97	1.17			
12	12	0.00	0.59	0.19	-1.06	0.87			
16	13	0.03	0.57	0.09	-1.39	1.06			
24	12	-0.46	0.95	-0.66	-1.60	1.61			
32	9	-0.06	1.41	-0.32	-2.54	2.64			
40	10	-0.46	0.80	-0.36	-1.69	0.71			
48	11	-0.40	1.31	-0.66	-2.65	2.12			

Sponsor's Table 6 for HIVNAT017 and Table 7 for NV20911 (see Overview.pdf).

Table 8. Subjects with at Least 1 log_{10} Decrease from Baseline in HIV-1 RNA VL

Week	n	r	%	n	r	%
HIVNAT017 (n=50)						
		Reviewer's			Sponsor's[1]	
12	27	24	48	26	22	44
24	48	41	82	40	33	66
36	45	41	82			
48	45	40	80	36	32	64
60	47	40	80			
72	47	43	86	37	35	70
84	47	43	86			
96	45	41	82	24	22	44
NV20911 (n=18)						
		Reviewer's			Sponsor's[1]	
8	16	8	44			
12	17	9	50	17	9	50
24	16	9	50	16	9	50
36	15	7	39	15	7	39
48	16	8	44	16	8	44

1. Sponsor's Table 6 for HIVNAT017 and Table 7 for NV20911 (Overview.pdf).

3.2.3.2 Immunologic Response Results

Table 9 lists summary statistics for the longitudinal CD4+ cell count. In HIVNAT017, the mean CD4+ cell count (cells/mm^3) increased from 439 at Week 24 to 612 at Week 48, to 760 at Week 72 and to 781 at Week 96. In NV20911, the mean CD4+ cell count (cells/mm^3) was 1212 at Week 24 and 1381 at Week 48. In PACTG397Saq/r arm, the mean CD4+ cell count (cells/mm^3) was 716 at Week 24 and 777 at Week 48.

Table 10 lists summary statistics for the mean change from baseline. In HIVNAT017, the mean increases from baseline in CD4+ cell count (cells/mm^3) were 228 at Week 24, 400 at Week 48, 547 at Week 72 and 566 at Week 96. In NV20911, the mean increase from baseline in CD4+ cell count was 91 (cells/mm^3) at Week 48. In PACTG397Saq/r arm, the mean change from baseline in CD4+ cell count (cells/mm^3) was -3 at Week 24 and -41 at Week 48.

Table 9. CD4+ Cell Count (cells/mm^3) through Weeks 48 and 96

		Reviewer's[1]					Sponsor's[2]		
Week	N	med	Min	Max	Mean	Std	n	Mean	Std
HIVNAT017 (n=50)									
Screening	49	160	6	939	210	207			
12	28	397	98	1102	452	252	28	196	192
24	48	396	71	1221	439	231	42	211	191
36	46	526	36	1104	546	231			
48	47	571	61	1177	612	273	46	375	242
60	47	631	26	1580	721	335			
72	47	662	36	1522	760	331	39	521	313
84	47	718	39	1427	756	294			
96	46	691	233	1452	781	313	27	536	404
NV20911 (n=18)									
Screening									
8	17	957	454	2575	1257	647			
12	17	1081	429	2921	1218	607	17	1217	607
24	16	865	519	3648	1212	807	16	1212	807
36	16	984	328	3561	1308	935	16	1308	935
48	16	1288	539	2679	1381	639	16	1381	639
PACTG397Saq/r (n=14)									
Baseline	14	545	196	2008	708	497			
4	13	504	185	1959	657	484			
8	12	561	184	2435	755	633			
12	12	526	165	2402	761	606			
16	13	623	169	2135	719	480			
24	13	553	228	2145	716	511			
32	12	491	246	2645	781	656			
40	12	650	278	2514	820	640			
48	10	648	301	2113	777	519			

1. Reviewer's analysis: Same as Sponsor's for NV20911.
2. Sponsor's Table 8 for HIVNAT017 and Table 9 for NV20911 (Overview.pdf).

Table 10. Change From Baseline in CD4+ Cell Count (cells/mm^3)

		Reviewer's[1]					Sponsor's[2]		
Week	n	median	Min.	Max.	mean	Std	N	Mean	Std
HIVNAT017 (n=50)									
12	28	196	-269	583	202	191	28	196	192
24	48	243	-456	677	228	193	42	211	191
36	46	330	-400	943	337	229			
48	47	359	-333	1155	400	282	46	375	242
60	47	421	-238	1547	508	372			
72	47	445	-284	1489	547	357	39	521	313
84	47	544	-357	1374	543	320			
96	46	556	-253	1285	566	360	27	536	404
NV20911 (n=18)									
8	16	-66	-1235	1075	14	508			
12	16	-70	-1460	864	-56	519			
24	15	-121	-2070	1590	-9	769			
36	15	108	-798	1057	76	546			
48	15	-28	-905	1117	91	609			
4	13	-29	-335	245	-51	153			
8	12	58	-139	318	66	119			
12	12	6	-200	213	16	131			
16	13	-23	-251	265	-5	141			
24	13	5	-149	172	-3	100			
32	12	-1	-181	351	36	168			
40	12	48	-182	350	69	171			
48	10	-19	-432	124	-41	170			

1. Reviewer's analyses. Same as Sponsor's for NV20911.
2. Sponsor's Table 8 for HIVNAT017 and Table 9 for NV20911 (Overview.pdf).

Tables 11 and 12 list summary statistics for the CD4% through Weeks 48 and 96, and the mean change from baseline in CD4%. The patients in the HIVNAT017 had a mean increase of 11% at Week 48, and 14% at Week 96. The patients in the NV20911 had a mean increase from baseline in CD4% of 3.2% and 2.8% at weeks 24 and 48. The patients in the Saq/r arm of Cohort 1A in PACTG 397 had a mean change from baseline in CD4% of 1.4% and -1.1% at weeks 24 and 48.

Table 11. CD4% Through Weeks 48 and 96

	Reviewer's[1]					Sponsor's[2]		
Week	N	median	Min.	Max.	mean	Std	N	Mean	Std
HIVNAT017 (n=50)									
Screening	49	7.0	0.0	23.0	7.5	5.6			
12	28	12.0	5.0	30.0	12.6	6.5	29	12.6	6.4
24	48	13.0	3.0	28.0	13.8	5.6	48	14.2	5.5
36	46	16.5	3.0	35.0	16.2	6.6			
48	47	16.0	1.0	47.0	18.2	8.1	46	19.0	8.1
60	47	21.0	2.0	39.0	20.4	6.8			
72	47	22.0	2.0	38.0	21.3	6.1	45	21.3	5.1
84	47	22.0	2.0	33.0	21.5	5.8			
96	46	22.0	11.0	33.0	22.1	5.1	31	23.6	5.2
NV20911 (n=18)									
Screening	17	29.7	14.5	51.5	28.9	10.6			
8	17	29.8	13.0	54.8	30.0	11.1			
12	17	30.0	15.0	49.7	30.1	9.1			
24	16	33.0	12.0	45.4	31.2	9.3			
36	16	31.0	17.9	47.0	32.0	8.6			
48	16	30.0	17.0	77.0	33.8	14.3			
PACTG397Saq/r (n=14)									
Baseline	14	29.0	12.0	45.0	28.5	8.0			
4	13	28.0	12.0	45.0	27.9	8.7			
8	12	27.5	14.0	49.0	29.0	10.3			
12	12	27.0	14.0	50.0	29.3	9.1			
16	13	29.0	12.0	49.0	29.4	9.1			
24	13	28.0	13.0	52.0	29.2	11.3			
32	12	27.0	20.0	51.0	29.8	8.5			
40	12	29.0	16.0	53.0	32.6	10.8			
48	10	25.5	16.0	42.0	26.6	7.7			

1. Reviewer's analysis: Same as Sponsor's for NV20911.
2. Sponsor's Table 8 for HIVNAT017 and Table 9 for NV20911 (Overview.pdf).

Table 12. Change From Baseline in CD4%

		Reviewer's[1]					Sponsor's[2]		
Week	N	median	Min.	Max.	mean	Std	n	Mean	Std
HIVNAT017 (n=50)									
12	28	4	-5	17	5	4	28	4.2	4.3
24	48	6	-5	22	6	5	42	5.6	3.8
36	46	9	-4	34	9	7			
48	47	10	-7	46	11	9	46	9.6	6.0
60	47	13	-3	38	13	8			
72	47	13	-2	37	14	8	39	12.5	5.8
84	47	14	-4	32	14	7			
96	46	14	-1	32	14	7	27	14.0	7.4
NV20911 (n=18)									
8	16	2.5	-9.8	12.1	1.9	5.6			
12	16	1.0	-6.3	15.1	2.2	5.3			
24	15	3.0	-6.3	18.6	3.2	5.8			
36	15	3.7	-5.0	13.9	3.6	5.3			
48	15	2.0	-5.0	13.6	2.8	5.9			
PACTG397Saq/r (n=14)									
4	13	2.0	-3.0	4.0	1.2	2.0			
8	12	1.5	-3.0	6.0	1.8	2.4			
12	12	2.0	-4.0	7.0	1.6	3.7			
16	13	0.0	-5.0	6.0	0.3	3.6			
24	13	1.0	-6.0	9.0	1.4	5.0			
32	12	3.0	-5.0	8.0	2.1	5.0			
40	12	2.5	-3.0	17.0	3.3	5.6			
48	10	-0.5	-6.0	6.0	-1.1	4.3			

1. Reviewer's analyses: same as Sponsor's for NV20911.
2. Sponsor's Table 8 for HIVNAT017 and Table 9 for NV20911 (Overview.pdf).

3.2.3.3 Conclusions

A. HIVNAT 017

Sponsor's Conclusions

Mean HIV RNA at screening for all patients was 4.70 $\log_{10}$ copies/mL, and decreased to 1.85 $\log_{10}$ copies/mL at week 96. The overall change from screening in mean HIV RNA to week 96 was –2.81 $\log_{10}$ copies/mL. This decrease in HIV RNA levels between screening and Week 96 was observed in both high age group (≥ 12 to 16 years) and low age group (≥ 3 to <12 years). However, it should be noted that the high age group overall had a higher HIV RNA levels at screening through Week 96 compared with the low age group.

When using an analysis that considered missing values equal to 400 copies/mL (ie, missing = failure), the percentage of patients with HIV RNA <400 copies/mL at week 96 was 56%. Based on a missing = failure analysis the percentages of patients with HIV RNA <50 copies/mL at week 96 was 52% and the percentage of patients with an HIV RNA decrease of >1 $\log_{10}$ copies/mL from screening was 44%.

Over the course of the study, there was an increasing trend in absolute CD4 cell count in both the high age group and low age group patients. This increasing trend in absolute cell count was reflected in the mean change from screening values which showed an increase of 211, 375 and 536 cells/mm_3 at weeks 24, 48 and 96, respectively. The increases in mean CD4 cell counts were greater in the low age group patients than the high age group patients.

Expressed as a percentage, the mean CD4 value at screening for all safety population patients was 7.6%, and increased to 13.8%, 18.2%, and 22.1% at Weeks 24, 48, and 96, respectively. The overall changes from screening in mean CD4 cell percentages were 5.6%, 9.6%, and 14.0%, respectively and were consistent in both low age group and high age group patients.

Reviewer's comments

- The sponsor also reported the results among those who were on treatment. This method ignores the dropouts in the denominator and numerator, resulting an over-estimated response. The DAVP has never used this method for labeling purposes.

- The sponsor's results will not be used for updating the Saq label because the data and analysis quality issues for the HIVAT 017 described in Section 3.1.

Reviewer's Conclusions

Mean HIV RNA at screening for all patients was 4.7 $\log_{10}$ copies/mL, and decreased to 2.0 $\log_{10}$ copies/mL at week 96. The overall change from screening in mean HIV RNA to week 96 was –2.7 $\log_{10}$ copies/mL. This decrease in HIV RNA levels between screening and Week 96 was observed in both older age group (≥ 12 to 16 years) and younger age group (≥ 3 to <12 years). However, it should be noted that the older age group overall had a higher HIV RNA levels at screening through Week 96 compared with the younger age group.

When using DAVP's Snapshot analysis, the percentage of patients with HIV RNA <400 copies/mL at week 96 was 78%; the percentages of patients with HIV RNA <50 copies/mL at week 96 was 66%; and 82% if the percentage of patients achieved at least 1 $\log_{10}$ copies/mL decrease in HIV-1 RNA VL from screening.

Over the course of the study, there was an increasing trend in absolute CD4 cell count in both the high age group and low age group patients. This increasing trend in absolute cell count was reflected in the mean change from screening values which showed an increase of 228, 400 and 566 cells/mm^3 at weeks 24, 48 and 96, respectively. The increases in mean CD4 cell counts were greater in the younger age group patients than the older age group patients.

Expressed as a percentage, the mean CD4% value at screening for all safety population

patients was 7.5%, and increased to 14.2%, 19.0%, and 23.6% at Weeks 24, 48, and 96, respectively. The overall changes from screening in mean CD4 cell percentages were 6%, 11%, and 14.0%, respectively and were consistent in both younger age group and older age group patients.

B. NV20911

Sponsor's Conclusions

Over the 48 weeks of study NV20911, treatment with SQV/r plus > 2 background ARVs, resulted in a decrease in mean HIV viral load from 3.50 $\log_{10}$ copies/mL to 2.10 $\log_{10}$ copies/mL; a mean change from baseline of -1.36 $\log_{10}$ copies/mL. The decrease in HIV viral load over time was observed to a similar extent in both the low age group and high age group (mean change -1.39 $\log_{10}$ copies/mL and -1.27 $\log_{10}$ copies/mL, respectively).

The decrease in mean HIV viral load was reflected in an increase in the percentage of patients with a viral load BLQ (< 400 copies/mL, < 50 copies/mL) during the 48 weeks of the study. At baseline, 6 of the 18 patients (33.3%) in the combined population had a viral load <400 copies/mL. By week 48, thirteen of the 16 patients (81.3%) with a week 48 assessment had a viral load <400 copies/mL. Similarly, at baseline 4 patients (22.2%) in the combined all patient population had a viral load <50 copies/mL. By week 48, the percentage of patients with a viral load <50 copies/mL (BLQ) had increased to 68.8% (11/16 patients with a valid assessment).

A total of 8/16 (50.0%) patients with both a baseline and week 48 HIV RNA assessment experienced a >1 log decrease from baseline in their HIV RNA. When using a missing = failure analysis, the percentage of patients with a VL <400 copies/mL at week 48 was 72.2%, the percentage with a VL <50 copies/mL was 61.1% and the percentage of patients who experienced a >1 log decrease from baseline in their HIV RNA was 44.4%.

In study NV20911, the mean CD4 lymphocyte count was maintained through week 48 of the study. At baseline, mean CD4 cell count was 1340 cells/mm^3. At weeks 24 and 48, the mean CD4 cell count was 1212 cells/mm^3 and 1381 cells/mm^3, respectively. Mean change from baseline for the combined patient population was -9 cells/mm^3 and +91 cells/mm^3 at weeks 24 and 48, respectively.

Expressed as a percentage of the total lymphocyte count at baseline the mean CD4 lymphocyte proportion was 28.9% of the total. By week 48, the mean CD4 lymphocyte proportion had increased to 33.8% of the total. The CD4 lymphocyte count as a percentage of the total lymphocyte count increased by a mean of 2.8% by week 48 and the mean increase seen was similar in the low age group (2.2%) and high age group (3.0%).

Reviewer's comments

The sponsor's results can be replicated using the analysis datasets. Hence, the sponsor's conclusions are concurred.

C. **Saq/RTV arm in Cohort 1A of the PACTG 397**

Sponsor's Conclusions

Forty-three percent (6/14) of the subjects on the Saq + RTV arm had HIV-1 RNA values <400 copies/ml at entry to Cohort 1A. Overall, after 48 weeks of study treatment, 5 of the 14 subjects on Saq+ RTV had HIV-1 RNA < 400 copies/ml.

Of the 8 subjects with HIV-1 RNA < 400 copies/ml at entry, 6 continued to have HIV-1 RNA < 400 copies/ml at week 16 and 4 by week 48. Of the 14 subjects with HIV-1 RNA > 400 copies/ml at entry, 4 had achieved HIV-1 RNA levels < 400 copies/ml by week 16 and all of them maintained controlled viral load to week 48.

Summary statistics for CD4 and CD8 counts and percents during Cohort 1A are shown in Table 22 and graphed in Figures 8 to 11. Changes from baseline are shown in Table 23. The last column in this Table shows the significance level for a Wilcoxon signed rank test looking for median changes from baseline significantly different from zero. There were no statistically significant changes within treatment groups in any of the parameters to week 16 or 48.

Reviewer's Comments and Conclusions

The sponsor's summary for the second paragraph refer to the entire Cohort 1A, not the Saq+RTV arm. The sponsor's summary for the third paragraph was vague. This reviewer revised the conclusions in the second and third paragraphs as follows.

Forty-three percent (6/14) of the subjects on the Saq + RTV arm had HIV-1 RNA values <400 copies/ml at entry to Cohort 1A. Overall, after 48 weeks of study treatment, 5 of the 14 subjects on Saq+ RTV had HIV-1 RNA < 400 copies/ml.

- Of the 6 subjects with HIV-1 RNA < 400 copies/ml at entry, 3 continued to have HIV-1 RNA < 400 copies/ml at weeks 16 and 48, 2 had HIV-1 RNA < 400 copies/ml at week 48 but not at week 16, and one had HIV-1 RNA < 400 copies/ml at week 16 but had no outcome at week 48.

- Of the 8 subjects with HIV-1 RNA > 400 copies/ml at entry, 2 had achieved HIV-1 RNA levels < 400 copies/ml by week 16 but not maintained controlled viral load to week 48.

- Subjects' CD4+ and CD4% have been well maintained through 48 weeks. The mean changes from baseline in CD4+ were -3 and -41 cells/mm^3 at weeks 24 and 48, respectively. The mean changes from baseline in CD4% were 1.4% and -1.1% cells/mm^3 at weeks 24 and 48, respectively.

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

Subgroup analysis of the antiviral activity and immunologic response were conducted in gender and age groups, not race and geographic region due to the limitation of study design. A subgroup with sample size of five or less would make the analysis less meaningful, specially with missing data at weeks 48 or 96.

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.

In summary, the subgroup analysis of the antiviral activity and immunologic response can be conducted for age and gender in Study HIVNAT017. The sponsor also reported the antiviral activity and immunologic response by age groups (4-11, 12-16). This reviewer also conducted the longitudinal HIV-1 RNA VL in $\log_{10}$ (copies/mL), CD4+ cell count (cells/mm^3) and CD4% by age groups descriptively, and the mean change from baseline in HIV-1 RNA VL ($\log_{10}$ copies/mL), CD4+ cell count (cells/mm^3) and CD4% by gender. The numerical differences observed in the antiviral and immunologic response for these age groups were reported to the review team.

Table 13 provides the summary statistics of baseline HIV-1 RNA VL, CD4+ and CD4% by gender and age (2-<12, 12-16).

Table 14 is a summary of change from baseline in HIV-1 RNA VL by gender. Tables 15 is a summary of change from baseline in CD4+ and CD4% by gender and age (2-<12, 12-16). Figures 1-3 display the mean change from baseline in HIV-1 RNA VL, CD4+ and CD4% by gender.

- At baseline, the mean VL values are similar for males (4.8) and females (4.7).

Male group had more mean reductions than female groups with a mean difference ranging 0-0.7 copies/mL.

- At baseline, the mean CD4+ is 188 for males and 228 for females. Male group had more mean increase in CD4+ except for week 12, with a mean difference (male-female) ranging 22 to 110 cells/mm^3 after week 12.

- At baseline, the mean CD4% is 6.1% for males and 8.6 for females. Male group had slightly more mean increase in CD4% than female group through 96 weeks with a mean difference (male-female) ranging 0.1%~2.4%.

Tables 16-17 are summaries of key statistics in change from baseline in HIV-1 RNA VL, CD4+ and CD4% by age (2-<12, 12-16). Figures 4-6 display the mean change from baseline in HIV-1 RNA VL, CD4+ and CD4% by age. We have the following findings.

- The mean VLs in the older age group were 5.0 at baseline, 3.0, 2.8 and 2.5 at weeks 24, 48 and 96; these were numerically greater than those in the younger group: 4.7 at baseline, 2.2, 2.0 and 1.9 at weeks 24, 48 and 96.

- The mean CD4+ (cells/mm^3) values in the older age group were 159 at baseline, 314, 484 and 672 at weeks 24, 48 and 96; these were numerically lesser than those in the younger group: 221 at baseline, 472, 647 and 807 at weeks 24, 48 and 96.

- The mean CD4% value was 7.5% at baseline, and increased to 14%, 18%, and 22% at weeks 24, 48 and 96, respectively. No obvious age difference in mean CD4% was observed over the study period.

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

Table 13. Baseline HIV-1 RNA VL, CD4+ and CD4% by Gender and Age*

	N	med	Min	Max	mean	std
Baseline HIV-1 RNA VL (log_{10} copies/mL)						
Total	47	4.8	1.8	5.9	4.7	0.7
Female	26	4.8	1.8	5.9	4.7	0.9
Male	21	4.8	3.8	5.5	4.8	0.5
Age 2-<12	39	4.80	1.76	5.88	4.66	0.78
Age 12-16	8	4.96	4.29	5.63	4.97	0.52
Baseline CD4+ (cells/mm^3)						
Total	49	160	6	939	210	207
Female	27	160	18	939	228	220
Male	22	146	6	754	188	193
Age 2-<12	40	150	6	939	221	221
Age 12-16	9	167	6	411	159	121
Baseline CD4%						
Total	49	7.0	0.0	23.0	7.5	5.6
Female	27	7.0	1.0	23.0	8.6	5.8
Male	22	6.0	0.0	18.0	6.1	5.1
Age 2-<12	40	7.0	1.0	23.0	7.6	5.9
Age 12-16	9	6.0	0.0	15.0	6.8	4.2

*. Source: reviewer's analysis.

Table 14. HIVNAT07: Change from Baseline in HIV-1 VL by Gender

Week	N	Med	Min	Max	Mean	Std
HIV-1 RNA VL (log_{10} copies/mL): Male (n=22)						
12	15	-2.6	-3.3	0.2	-2.3	1.1
24	21	-3.0	-3.6	-0.4	-2.7	0.8
36	19	-2.9	-3.6	0.2	-2.6	1.0
48	19	-3.1	-3.8	0.1	-2.8	1.0
60	21	-2.9	-3.8	0.2	-2.6	1.1
72	21	-3.0	-3.8	0.2	-2.7	1.0
84	21	-2.9	-3.7	0.1	-2.6	1.0
96	19	-3.0	-3.7	-0.4	-2.8	0.9
HIV-1 RNA VL (log_{10} copies/mL): Female (n=28)						
12	12	-2.3	-3.0	0.0	-1.8	1.1
24	27	-2.3	-3.4	0.0	-2.0	1.3
36	26	-2.7	-3.7	0.9	-2.3	1.2
48	26	-2.6	-3.7	1.5	-2.3	1.2
60	26	-2.6	-3.7	1.5	-2.0	1.4
72	26	-3.0	-3.7	1.3	-2.5	1.2
84	26	-2.8	-4.2	-0.1	-2.6	1.0
96	26	-2.8	-3.9	0.0	-2.5	1.0

1. Source: Reviewer's analysis.

Table 15. HIVNAT07: Change from Baseline in CD4+ and CD4% by Gender

Week	N	Med	Min	Max	Mean	Std
CD4+: Male (n=22)						
12	15	185	-49	480	168	137
24	21	267	-73	571	247	164
36	20	331	-4	943	368	227
48	21	436	-54	989	412	270
60	21	445	-13	1547	569	389
72	21	467	-79	1489	582	386
84	21	561	-76	1191	587	332
96	20	583	-72	1285	627	341
CD4+: Female (n=28)						
12	13	247	-269	583	241	239
24	27	210	-456	677	213	214
36	26	330	-400	699	313	232
48	26	355	-333	1155	390	296
60	26	392	-238	1480	459	358
72	26	442	-284	1211	519	336
84	26	516	-357	1374	508	313
96	26	549	-253	1227	519	373
CD4%: Male (n=22)						
12	15	5.0	-5.0	17.0	5.3	4.9
24	21	6.0	1.0	18.0	7.0	3.8
36	20	9.0	-1.0	34.0	9.3	7.1
48	21	10.0	-3.0	39.0	10.8	8.3
60	21	15.0	-1.0	38.0	13.7	8.3
72	21	13.0	-2.0	37.0	14.2	8.1
84	21	14.0	-2.0	32.0	14.9	7.5
96	20	15.9	6.0	30.0	15.9	6.4
CD4%: Female (n=28)						
12	13	4.0	-5.0	12.0	3.7	4.1
24	27	6.0	-5.0	22.0	5.8	5.3
36	26	9.0	-4.0	32.0	8.2	7.3
48	26	9.5	-7.0	46.0	10.6	9.2
60	26	11.5	-3.0	25.0	12.1	7.4
72	26	13.5	-1.0	33.0	13.5	7.9
84	26	12.9	-4.5	28.0	13.2	7.3
96	26	12.5	-1.0	32.0	13.5	8.2

1. Source: Reviewer's analysis.

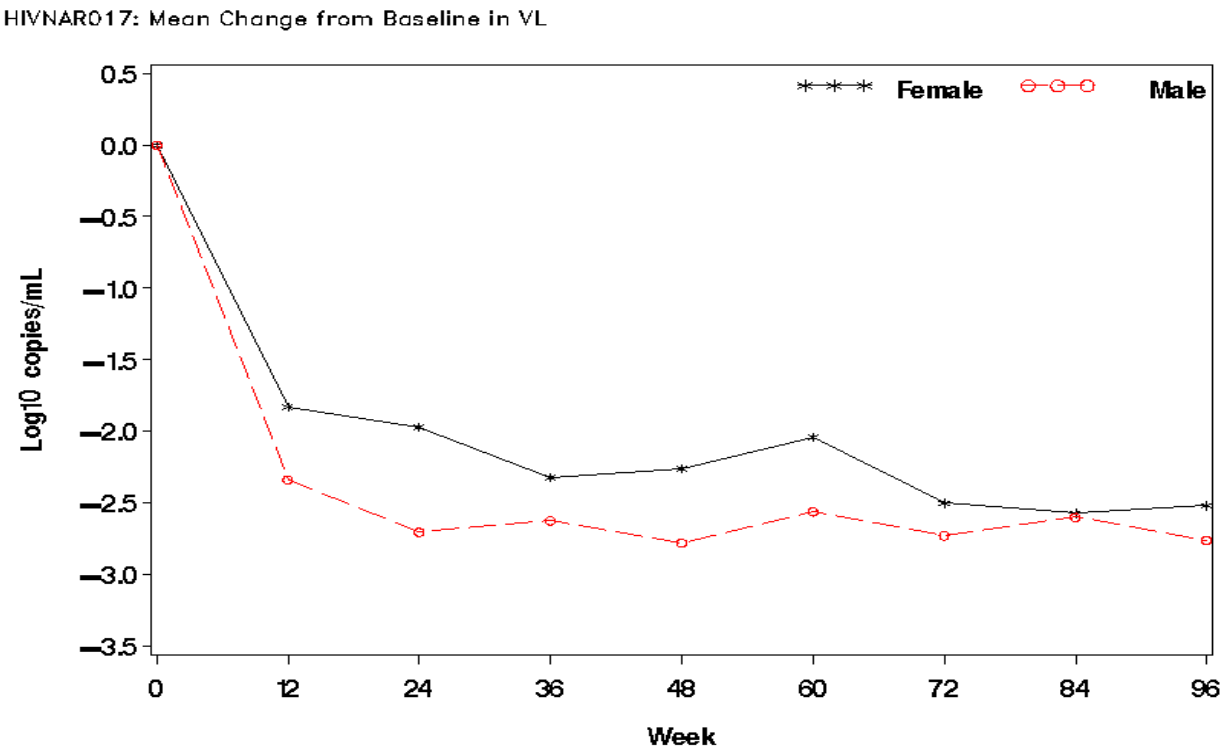

Figure 1: HIVNAT017: Change from Baseline in HIV-1 RNA VL by Gender

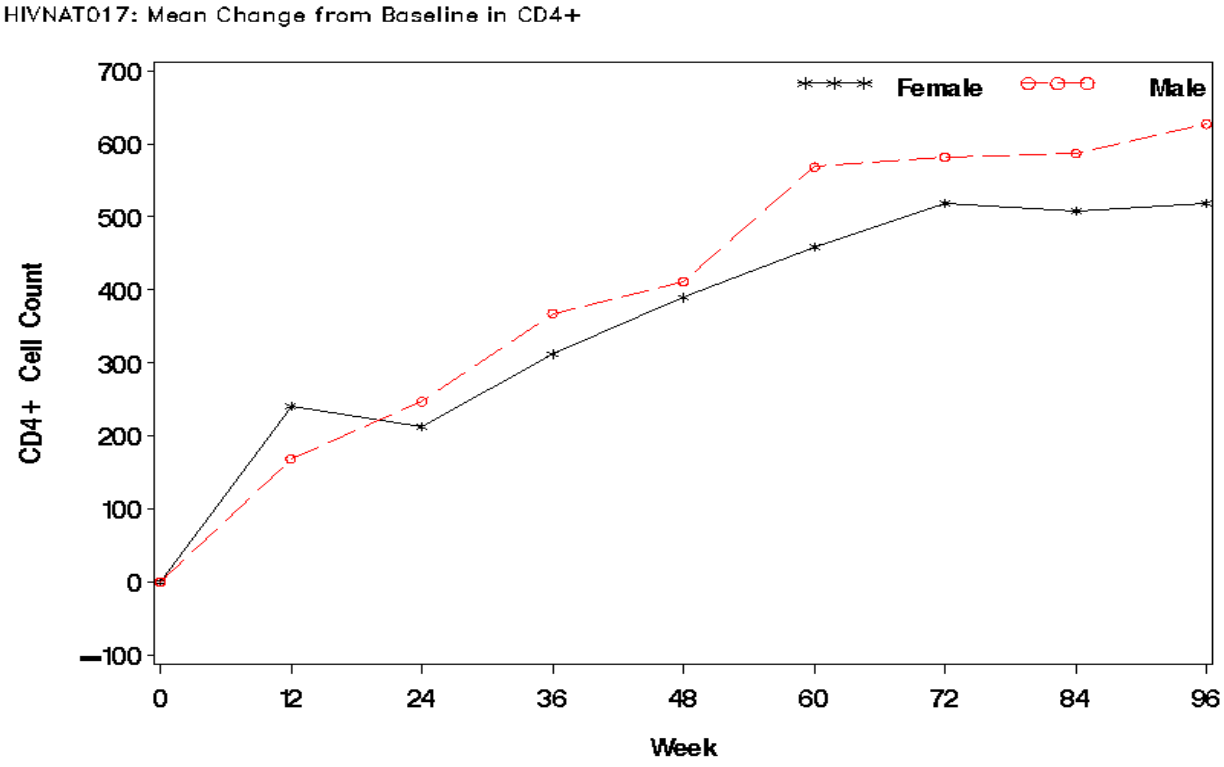

Figure 2: HIVNAT017: Change from Baseline in CD4+ Cell Count (cells/mm^3) by Gender

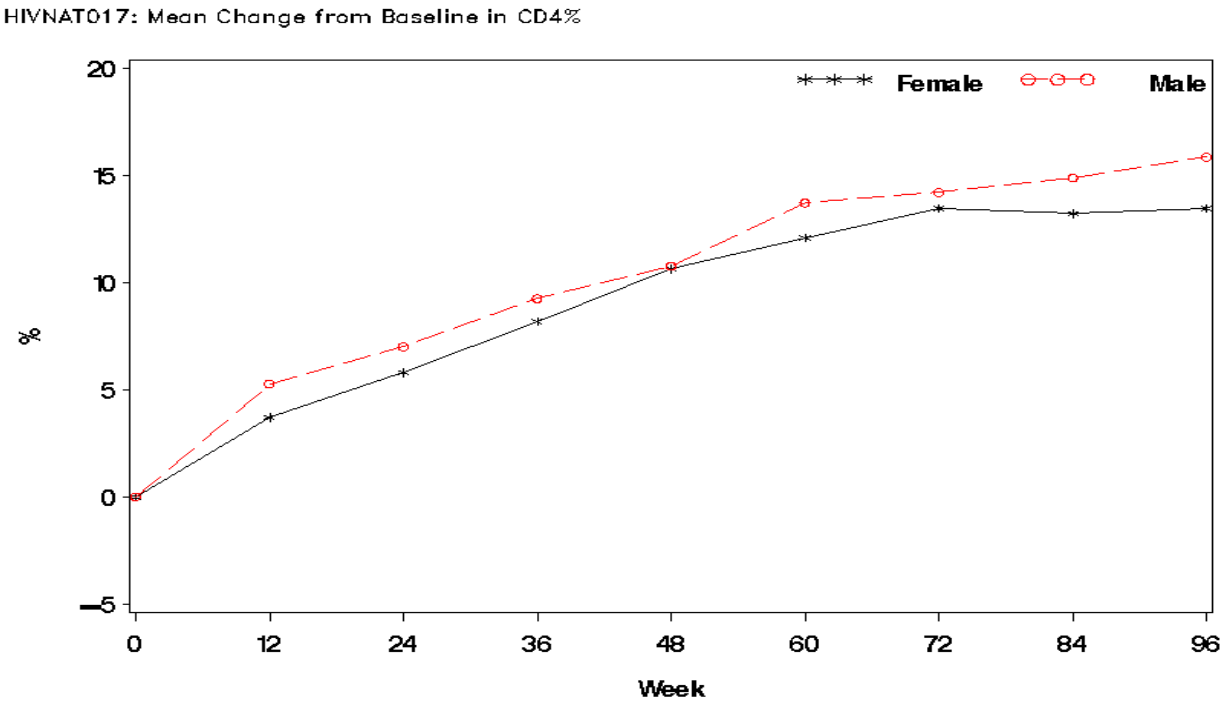

Figure 3: HIVNAT017: Change from Baseline in CD4% by Gender

Table 16. HIVNAT07: HIV-1 RNA VL (log_{10} copies/mL) and Change by Age Groups

							Change from Baseline	
Week	**n**	**Med**	**Min**	**Max**	**mean**	**Std**	**mean**	**Std**
HIVNAT017: Age (4-<12)								
Baseline	39	4.80	1.76	5.88	4.66	0.78		
12	20	2.16	1.70	3.98	2.26	0.64	-2.35	0.85
24	37	1.70	1.70	4.83	2.15	0.84	-2.54	1.00
36	35	1.70	1.70	5.00	1.94	0.62	-2.79	0.85
48	34	1.70	1.70	4.68	1.95	0.67	-2.76	0.89
60	36	1.70	1.70	4.29	2.11	0.73	-2.57	0.97
72	36	1.70	1.70	2.53	1.77	0.21	-2.91	0.76
84	36	1.70	1.70	4.21	1.91	0.57	-2.78	0.86
96	35	1.70	1.70	4.86	1.94	0.62	-2.77	0.88
HIVNAT017: Age (12-16)								
Baseline	8	4.96	4.29	5.63	4.97	0.52		
12	5	2.79	1.70	5.00	2.90	1.37	-2.03	1.26
24	8	2.68	1.70	5.00	3.01	1.28	-1.96	1.07
36	7	2.53	1.70	5.00	3.21	1.45	-1.71	1.14
48	8	2.58	1.70	4.95	2.76	1.16	-2.20	1.09
60	8	2.70	1.70	5.88	3.26	1.54	-1.71	1.53
72	8	2.56	1.70	4.96	2.84	1.18	-2.13	1.21
84	8	1.94	1.70	4.93	2.66	1.27	-2.30	1.19
96	7	1.70	1.70	4.84	2.50	1.32	-2.49	1.13

1. Source: reviewer's analysis.

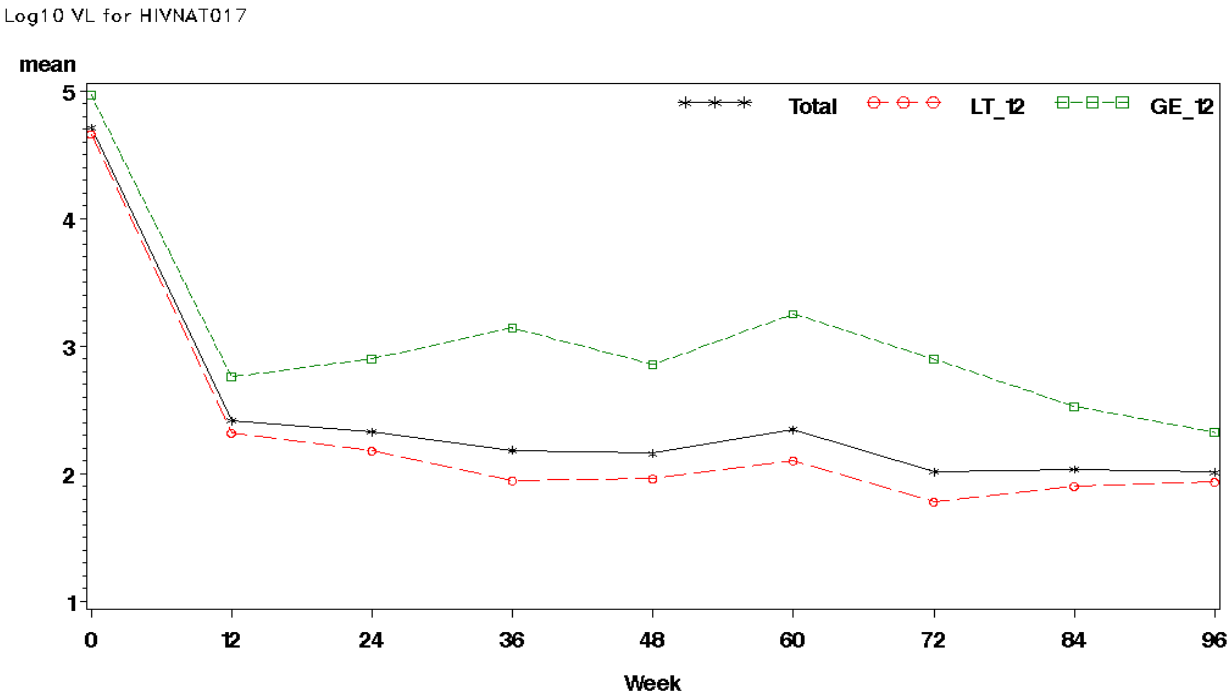

Figure 4: HIVNAT017: HIV-1 RNA VL in log_{10} (copies/mL) by Age Group

Table 17. HIVNAT07: CD4+ Cell Count (cells/mm^3) through Week 48 by Age Groups

Week	N	Med	Min	Max	Mean	Std
Age (4-<12)						
Screening	40	150	6	939	221	221
12	21	421	98	1102	482	273
24	38	415	71	1221	472	243
36	36	556	36	1104	577	231
48	37	606	263	1116	647	257
60	37	716	364	1580	782	319
72	37	721	400	1522	835	314
84	37	799	364	1427	811	283
96	37	702	233	1452	807	318
Age (12-16)						
Screening	9	167	6	411	159	121
12	7	330	180	623	362	158
24	10	355	103	464	314	123
36	10	500	48	644	435	201
48	10	457	61	1177	484	308
60	10	514	26	995	492	301
72	10	495	36	763	483	240
84	10	554	39	902	555	254
96	9	575	366	1193	672	281

1. Reviewer's analysis: Same as Sponsor's for NV20911.
2. Sponsor's Table 8 for HIVNAT017 and Table 9 for NV20911 (Overview.pdf).

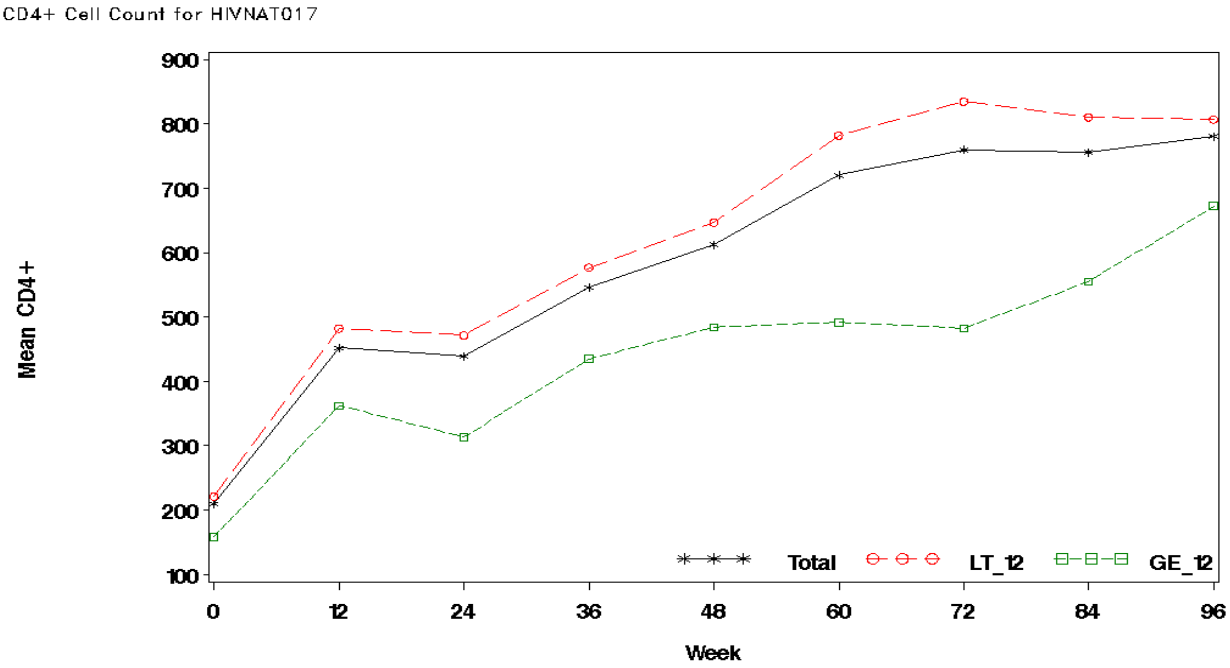

Figure 5: HIVNAT017: CD4+ Cell Count (cells/mm^3) by Age Group

Table 18. HIVNAT07: CD4% through Week 48 and Mean Change by Age Groups

							Change from Baseline	
Week	**n**	**Med**	**Min**	**Max**	**mean**	**Std**	**mean**	**Std**
HIVNAT017: Age (4-<12)								
Baseline	40	7.0	1.0	23.0	7.6	5.9		
12	21	12.0	5.0	30.0	13.2	7.1	4.4	4.4
24	38	14.0	3.0	28.0	14.1	5.8	6.2	4.3
36	36	17.0	3.0	35.0	16.7	6.2	8.8	6.5
48	37	16.0	9.0	40.0	18.2	7.1	10.2	7.2
60	37	22.0	10.0	39.0	21.3	5.9	13.4	7.4
72	37	22.0	14.0	38.0	22.3	5.3	14.3	7.7
84	37	22.0	13.0	33.0	22.0	4.9	14.1	7.2
96	37	22.0	14.0	32.0	22.3	4.5	14.4	7.3
HIVNAT017: Age (12-15)								
Baseline	9	6.0	0.0	15.0	6.8	4.2		
12	7	10.0	6.0	17.0	11.0	4.1	4.9	5.2
24	10	12.0	7.0	23.0	12.8	4.8	6.6	6.1
36	10	14.0	3.0	33.0	14.4	8.2	8.2	9.6
48	10	17.0	1.0	47.0	18.6	11.5	12.4	13.2
60	10	19.5	2.0	26.0	16.8	8.7	10.6	9.2
72	10	18.0	2.0	30.0	18.0	8.0	11.8	8.8
84	10	19.5	2.0	30.0	19.8	8.5	13.6	8.5
96	9	23.0	11.0	33.0	21.3	7.2	14.8	8.6

1. Source: reviewer's analysis.

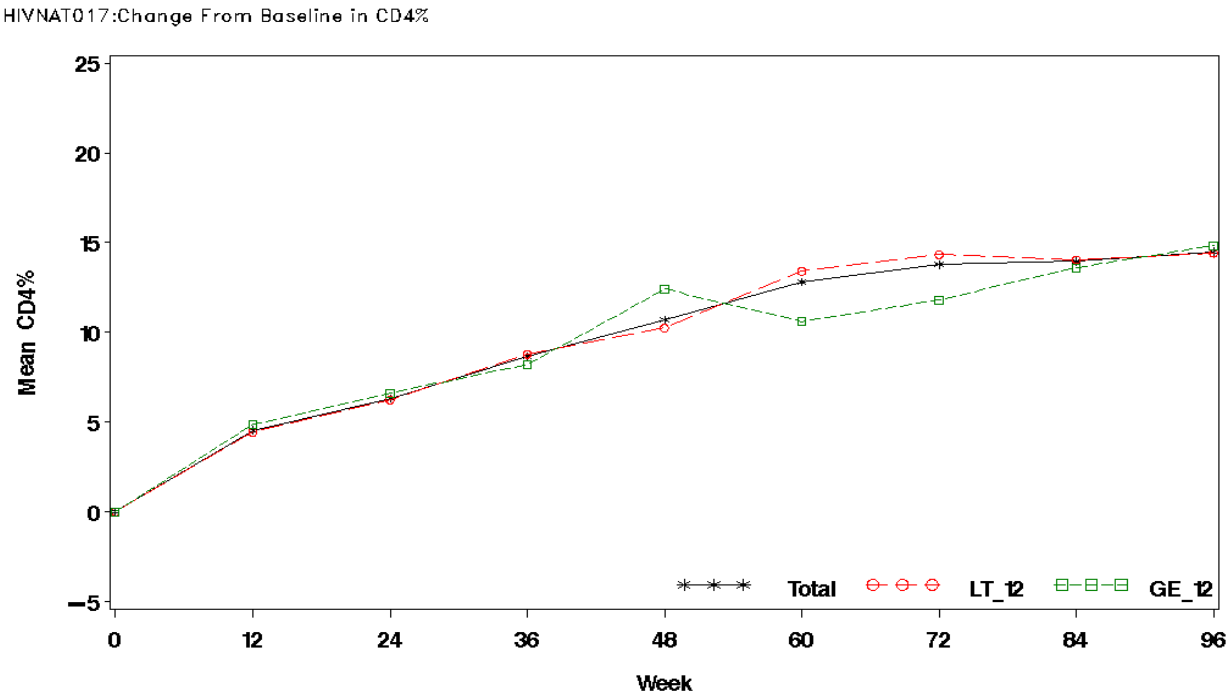

Figure 6: HIVNAT017: Change from Baseline in CD4% by Age Group

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.

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 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.

2. This reviewer used the Snapshot approach[1] to obtain the percentage of patients with non-detective 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 defined according to the standard[1] in HIVNAT 017. Hence, one should use the antiviral and immunologic response at visit weeks including at weeks 48 and 96 based on the standard definitions for time window for future updating label.

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 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/m^2 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 $\log_{10}$ copies/mL decrease from screening. Mean HIV RNA at screening for all patients was 4.71 $\log_{10}$ copies/mL, and this decreased to 2.13 $\log_{10}$ copies/mL at week 96, for a 2.73 $\log_{10}$ copies/mL reduction.

Over the 96 weeks of treatment, there was an increasing trend in absolute CD4+ cell count in both the older age group (12 to 16 years) and the younger age group (<12 years). Overall, mean change from screening in CD4+ cell count had an increment of 228 cells/mm^3 at week 24, followed by 400 cells/mm^3 at week 48 and 566 cells/mm^3 at week 96. The mean CD4% value at screening for all patients was 7.5%, and this increased to 13.8%, 18.2%, and 22.1% at weeks 24, 48, and 96, respectively. The overall changes from screening in mean CD4% were 6%, 11%, and 14% at Weeks 24, 48, and 96, respectively.

- The decreases in HIV RNA levels between screening and week 96 were observed in both the older age group (12 to 16 years) and the younger age group (4 to <12 years). However, the older age group patients overall had a numerically greater HIV RNA at screening through Week 96 when compared with the younger age group patients (see Figure 1). The increases in mean CD4 cell counts were numerically greater in the younger age group than the older age group (see Figure 2). No obvious age difference in mean CD4% was observed over the study period (see Figure 3).

NV20911
After 48 weeks treatment with Saq+RTV+ two or more ARVs, the patients had a mean HIV viral load decrease of 1.36 log_{10} copies/mL, from 3.50 log_{10} copies/mL at screening to 2.10 log_{10} copies/mL at week 48. The decreases in HIV viral load were similar in the age '< 2 years' (-1.39 log_{10} copies/mL) and the age '2-6 years' (-1.27 log_{10} copies/mL). 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, were significantly increased from baseline levels: 33% with HIV RNA <400 copies/mL and 22% with HIV RNA <50 copies/mL. Overall, the mean CD4+ cell count was 1293 cells/mm^3 at baseline, 1212 cells/mm^3 and 1381 cells/mm^3, respectively, at weeks 24 and 48, resulting an increase in CD4+ cell count of 165 cells/mm^3 at week 48 from baseline. The mean CD4% was 28.9% at screening, 31.2% and 33.8% at weeks 24 and 48. The mean increase from baseline in CD4% was 3.2% at week 24 and 2.8% at week 48.

The SAQ+RTV arm in the Cohort 1A of PACTG 397
6/14 (43%) of the subjects on the Saq+RTV arm had HIV-1 RNA <400 copies/mL at rolling over to Cohort 1A. After 48 weeks of treatment with Saq+RTV plus one or two NRTIs, 5/14 (36%) had HIV-1 RNA <400 copies/mL. Among them, four subjects had HIV-1 RNA <400 copies/mL at entry to Cohort 1A. CD4+ cell count and CD4% were well maintained. At entry to Cohort 1A, subjects had a mean CD4+ cell count of 708 cells/mm^3 with a mean CD4% of 28.5%. After 48 weeks of treatment, the mean CD4+ was 732 cells/mm^3 with a mean CD4% of 26.5%.

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. The PMR to complete pediatric

Studies PACTG 397, HIVNAT 017 (ML19540), and NV20911 under the Pediatric Research Equity Act (PREA) remains open due to multiple deficiencies conveyed by the Division of Scientific Investigations (DSI). The pharmacokinetic (PK) data from the HIVNAT 017 study were considered invalid. As a result, the pediatric PK data on which to bridge adult efficacy trials is lacking, and the Agency is unable to approve this sNDA submission at this time, nor complete the process of product labeling.

Roche concluded that saquinavir treatment as part of a HAART regimen in pediatric patients with HIV infection demonstrated a marked improvement in all measures of antiviral activity. These measurements, including change from baseline in HIV RNA viral load, percentage of patients with viral load below lower limit of quantification (BLQ), change from baseline in CD4+ cell count, were consistent with that seen in adult patients receiving similar mg/kg doses and background antiretroviral therapy (ART) regimens. Based on the data in Saq/RTV arm of Cohort 1A of PACTG 397, Roche concluded that pediatric patients who switched the treatment to Saq soft gel capsules in combination with RTV and one or two NRTIs showed numerical similar antiviral activity and immunologic response at rolling over and at week 48.

Based on the statistical evaluation of data, this reviewer concurs with the sponsor's conclusions regarding surrogate markers related to HIV-1 RNA VL, CD4+ and CD4%. The sponsor concluded that there were insufficient data for the Saquinavir dose recommendation for those under 2 years. We agree with this conclusion.

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.

6.2 More Results on Immunologic Response (CD8+ and CD8%)

The analyses of other parameters such as CD8+ cell count and CD8% were conducted by this reviewer. Since the results were not need in the INVIRASE® label, the results will be included in the Appendix.

It appears that the CD8+ and CD8% information in the HIVNAT017 were limited to the first 20 patients (Group 1) enrolled for pharmacokinetic assessment. Hence, the sample sizes are all below 20.

Table 16 provides baseline values for CD8+ and CD8% by studies.

Table 17 lists the summary statistics for mean change from baseline in CD8+ cell count. In HIVNAT017, the mean change from baseline in CD8+ cell count (cells/mm^3) was decreased from 366 at Week 24, to 204 at Week 48, to 49 at Week 96. In NV20911, a mean increase of 14 cells/mm^3 from baseline to Week 48 in CD8+ cell count was obtained. The sponsor did not report the change from baseline in CD8+ cell count for both studies. The patients in the Saq/r arm of Cohort 1A in PACTG 397 had a mean decrease of 3% at week 48.

Table 18 lists summary statistics for the mean change from baseline in CD8%. The patients in the HIVNAT017 had mean decreases from baseline in CD8% of 8%, 11% and 16% at weeks 24, 48 and 96. The mean decrease of CD8% from baseline to week 48 were 2% in the NV20911, and 3% in the Saq/r arm of Cohort 1A in PACTG 397.

Table 19. Screening CD8+ and CD8%[1]

	n	median	Min.	Max.	Mean	std
HIVNAT017 (n=50)						
CD8+	20	1221	320	2719	1191	649
CD8%	20	55.5	22.0	81.0	53.7	16.5
NV20911 (n=18)						
CD8+	17	1541	598	3696	1775	902
CD8%	17	40.7	13.8	76.5	41.4	18.4
PACTG397Saq/r (n=14)						
CD8+	14	869	324	2155	1037	531
CD8%	14	44.0	28.0	64.0	44.0	10.5

1. Source: Reviewer's analysis.

Table 20. Change From Baseline in CD8+ Cell Count (cells/mm^3)

Week	n	med	Min	Max	mean	Std
HIVNAT017: Reviewer's Results using re-coded visit weeks						
12	11	772	-486	3445	1114	1194
24	19	312	-913	2541	366	847
36	17	256	-338	2254	382	686
48	19	265	-1072	1338	204	619
60	19	71	-1311	2252	164	746
72	19	192	-1037	1392	169	553
84	19	88	-1145	1108	60	577
96	19	81	-986	831	49	509
NV20911 (n=18)[1]						
8	16	-162	-1754	1816	-16	1066
12	16	-6	-1443	909	-94	619
24	15	-2	-1837	1570	-43	708
36	15	-177	-1063	930	-163	556
48	15	-30	-1269	1174	14	596
PACTG397Saq/r (n=14)						
4	13	-129	-720	368	-157	301
8	12	-27	-418	384	-8	253
12	12	-203	-467	231	-124	225
16	13	-79	-583	251	-56	247
24	13	18	-784	660	-26	382
32	12	-129	-405	434	-78	255
40	12	-118	-591	339	-135	306
48	10	-80	-479	235	-99	226

1. Reviewer's analyses. Reviewer's and Sponsor's are same for NV20911.

Table 21. Change From Baseline in CD8%

Using revised data recoding time window[1]							Using Sponsor's Data[2]		
Week	N	Median	Min.	Max.	mean	std	N	Mean	Std
HIVNAT017 (n=50)									
12	11	-6	-11	10	-3	7	12	-4.7	6.7
24	19	-10	-19	9	-8	8	16	-8.1	9.1
36	17	-9	-18	7	-9	7	13	-8.4	7.3
48	19	-14	-22	5	-11	8	16	-12.1	8.8
60	19	-16	-25	6	-14	8	16	-12.1	8.8
72	19	-15	-29	3	-14	10	16	-14.2	9.6
84	19	-17	-29	5	-15	9	16	-14.4	9.5
96	19	-18	-31	3	-16	10	16	-15.0	9.4
NV20911 (n=18)[3]									
8	16	-1.7	-16.0	26.4	-0.6	10.0			
12	16	-0.7	-14.0	35.6	0.7	10.8			
24	15	-3.1	-12.1	46.5	1.0	13.5			
36	15	-2.2	-21.0	8.9	-2.7	6.8			
48	15	0.0	-17.6	19.9	-1.7	8.4			
PACTG397Saq/r (n=14)[4]									
4	13	-2.0	-8.0	8.0	-1.8	3.9			
8	12	-2.0	-6.0	4.0	-0.8	3.2			
12	12	-3.0	-7.0	2.0	-2.6	3.0			
16	13	-2.0	-6.0	9.0	-1.0	4.0			
24	13	-1.0	-8.0	34.0	0.8	10.8			
32	12	-1.5	-7.0	7.0	-1.3	4.7			
40	12	-2.5	-8.0	6.0	-2.8	4.0			
48	10	-3.0	-11.0	6.0	-3.2	5.3			

1. Using revised data for HIVNAT017. 2. Using 'efval.xpt'.
3. Reviewer's and Sponsor's are same. 4. Reviewer's analysis.

6.3 Data Problems for HIVNAT017

Time windows appear inappropriately defined to categorize the visit weeks in key parameters such as HIV-1 RNA viral load (VL), CD4+ cell count and CD4% in Study HIVNAT017. Hence, visit weeks were recoded according to the standard[1] for time window definitions. In the recoding process, variable 'trt1dc' and 'trtedc', SAS dates for first dose of study drug and end of the treatment in the 'demoext.xpt'; and variable 'lbdc', a SAS date for laboratory test in the 'labp.xpt'; were used to create visit weeks. Using VL as an example, the new VL dataset consists of 417 data points for VL in labp.xpt, after deleting duplicate records. Among these data points, 11 are outside of the treatment period (trt1dc, trtedc) and 47 can be considered as screening VLs. In comparing the new VL dataset with the HIV-1 RNA VL data in the 'labp.xpt', 158 discordant pairs (37.9%) were found. See a SAS list file attached in Appendix 6.3.1 and comparisons of the visit weeks (Appendix 6.3.2).

6.3.1 List of Discordant Pairs (n=158) Through Week 96 for HIV-1 RNA Data (labp.xpt)

Obs	weeks*	LBCPE	COUNT
1	< Day 1	Screening	47
2	12	Week 12	27
3	24	Week 12	19
4	24	Week 24	28
5	36	Week 24	18
6	36	Week 36	27
7	48	Week 36	19
8	48	Week 48	26
9	60	Week 48	20
10	60	Week 60	27
11	60	Week 72	1
12	72	Week 60	20
13	72	Week 72	26
14	72	Week 84	1
15	84	Week 72	20
16	84	Week 84	26
17	84	Week 96	1
18	96	Week 84	20
19	96	Week 96	25
20	>96	Week 96	19
Total			417

*. Weeks- recoded visit weeks using standard time window definition.

6.3.2 Comparisons of Time Window in HIVNAT 017 (SN270, Nov. 5 2011 Submission)

Table 22. HIVNAT 017: Discrepancies in Time Window Definitions

	Standard (DAVP)		Sponsor's[1]	
Week	From	To	From	To
Screening	>.	1	-28	-1
12	2	126	72	141
24	127	210	142	225
36	211	294	226	295
48	295	378	296	393
60	379	462	394	477
72	463	546	478	561
84	547	630	562	645
96	631	714	646	701
>96	715		702	

1. NDA 20688/SN270, Nov. 5 2011 Submission.

Similar problems for the CD4+, CD4%, and other laboratory variables will be expected due to the misclassification of time windows.

6.3.3 Other Data Problems for HIV-1 RNA Data (SN270, Nov. 5, 2010)

Based on the recoded visit weeks, when selected 10 subjects out of 50 at random from the SN270, submitted on Nov. 5, 2010, two were correct and eight had data problems. Details are as follows.

102 (missing in Week 96 VL)
120 (missing in Week 36 VL)
201 (missing in screening VL)
205 (missing in Week 96 VL, additional VL in Week 12)
207 (missing in screening VL and Week 36 VL)
219 (ok)
110 (missing in Week 96 VL)
111 (missing in Week 60 VL, VLs at Weeks 60, 72, 84 should be switched to the next time window)
113 (ok)
117 (missing VLs at Weeks 60, 72 & 84, missing VL should be assigned to Week 96 and >96)

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