



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/Serial Number:** 21-814 / N 000

**Drug Name:** APTIVUS™ (tipranavir, TPV) 500 mg given with  
200 mg ritonavir (RTV)

**Indication(s):** Treatment of HIV infection

**Applicant:** Boehringer Ingelheim Pharmaceuticals

**Dates:** Submitted: December 29, 2004  
Received: December 30, 2004  
User Fee Date: June 29, 2005

**Review Priority:** Priority review

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**Keywords:** 1182\_0012, 1182\_0048, 1182\_0004, 1182\_0051, 1182\_0052,  
Secondary Safety Endpoints, Hematological, Lipids, Liver  
Function Toxicity, DAIDS Grade 3 or 4 Elevation, Change from  
Baseline, Time to Event, Treatment-experienced HIV-infected,  
24-week Safety Data, Baseline PI Mutation analysis

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## 1 EXECUTIVE SUMMARY

### 1.1 Conclusion and Recommendations

This statistical review directly addresses issues requested by medical officers and microbiologic reviewers in support of the priority review of NDA21,814 for the accelerative approval of APTIVUS™ (tipranavir, TPV) 500 mg given with 200 mg ritonavir (RTV, r) as compared with the control group of comparator protease inhibitors boosted with ritonavir.

Collective evidence of laboratory data in two large Phase III trials 1182\_0012 and 1182\_0048 lead the conclusion that the subjects in the TPV/r arm developed excess risk of liver and lipids enzyme abnormalities, in contrast to those in the comparator arms (CPI/r). Data from three Phase II trials, 1182\_0004, 1182\_0051 and 1182\_0052, also partially support the conclusion.

Baseline protease inhibitor (PI) mutation data at 27 selected codons and virologic response data at Week 24 in the TPV/r arm for the two Phase III trials provide evidence that significantly higher proportion of subject with the virologic response at Week 24 were likely associated with the presence of baseline PI mutation at codons I13, M36, I47 and I54 among subjects receiving TPV/r without T-20 at entry. However, the virologic response at Week 24 was not affect by the baseline PI mutations among subjects receiving TPV/r with T-20. Both results were those after adjusting for multiplicity.

### 1.2 Brief Overview of Clinical Studies

The statistical review of NDA21,814 for the accelerative approval of TPV/r was based on laboratory data from two Phase III trials 1182\_0012 and 1182\_0048, and three Phase II trials 1182\_0004, 1182\_0051 and 1182\_0052, and efficacy data from 1182\_0051.

The Phase III trials 1182\_0012 (RESIST 1) and 1182\_0048 (RESIST 2) were of identical design except for regional differences. These studies were multi-center, multi-national, open label, randomized, active controlled 96 week study of safety and efficacy of TPV/RTV + optimized background regimen (OBR) versus comparative protease inhibitor (CPI)/RTV + OBR in subjects with 3 class (NRTI, NNRTI, and PI) antiretroviral (ARV) experience HIV-1 infected subjects.

In RESIST 1, a total of 1406 subjects in 125 study centers located in the US, Canada and Australian were enrolled; 630 were randomized and 620 received at least one study drug dose, of these, 311 subjects received TPV 500 mg/RTV 200 mg and 309 received CPI/r. In RESIST 2, a total of 1903 subjects in 171 study centers located in Europe, South Africa and Mexico were enrolled, 878 were randomized and 863 received at least one dose of study drug, of those 435 subjects received TPV 500 mg/RTV 200 mg and 428 received CPI/r.



At screening, genotype resistance was tested selecting subjects who had at least one per-protocol protease (PI) mutation(s) at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M and with two or less mutations at codons 33, 82, 84 or 90. Qualified subjects were randomized to either TPV/r or CPI/r arm at a ratio of 1:1, and stratified with respect to the pre-selected PI and the use of enfuvirtide (T-20).

Study 1182\_0004 was a Phase II, open-label, randomized, multicenter, parallel trial in single failed PI- experienced HIV subjects. This study was design to evaluate the efficacy and safety of TPV/r 500/100 mg and TPV/r 1250/100 mg + two new NRTI's as compared to standard dual PI combination RTV-boosted Saquinavir (SQV/r) 400/400 mg + two new NRTI's. HIV-1 infected subjects in 23 sites in United States, 2 in France, and 1 in Italy, were randomized in a 1:1:1 ratio to one of three treatment groups. The study duration was initially 24 weeks, but was later modified for up to 96 weeks.

Study 1182\_0051 was a Phase II, open-label, randomized, parallel-group, multicenter, 24 week trial in treatment experienced subjects who failed to meet the entry criteria for one of the Phase III trials of TPV 1182\_0012 or 1182\_0048 due to an HIV isolate containing greater than 2 mutations at codons 33, 82, 84 or 90. Participants in Europe and North America countries were randomized to one of the following four regimens with 1:1:1:1,

- TPV/r 500/200 mg b.i.d. + OBR;
- LPV/r 400/100 mg b.i.d. + OBR;
- APV/r 600/100 mg b.i.d. + OBR; or
- SQV/r 1,000/100 mg b.i.d. + OBR.

The treatments were administered for two weeks. At Week 2, TPV/r 500/100 mg b.i.d. was added to three other PI-containing regimens.

1182\_0052 was a Phase II, double-blind, randomized, dose optimization trial of three doses of tipranavir boosted with low dose ritonavir (TPV/r) in subjects with multiple antiretroviral (ARV) drug-experiences.

All patients were triple ARV class, two PI-based-experienced and had baseline viral isolate with at least one primary protease mutation at codons 30N, 46I/L, 48V, 50V, 82A/L/F/T, 84V and 90M, with no more than two of the 82 L/T, 84V, or 90M mutations. Following genotypic screening at baseline, qualifying subjects were randomized to received TPV/r 500/100 mg, TPV/r 500/200 mg, and TPV/r 750/200 mg. All TPV/r were administered as twice daily with a genotypically OBR that was individually chosen by investigators. The first two weeks of the study were the functional monotherapy phase, in which patients changed the PI they were taking at entry to one of the three TPV/r doses, but maintained the same OBR. After 2 weeks, each patient's background ARV medications were optimized, and the patient remained on blinded TPV/r and optimized ARV therapy for up to 32 weeks.

### 1.3 Statistical Issues and Findings

This statistical review directly addressed several issues in support medical officers and reviewers

from other disciplines in FDA's review of NDA21,814. Different from a typical statistical review of a NDA for the evaluation of primary efficacy endpoints, this statistical review and evaluation was based on (1) the collective laboratory data from two Phase III trials 1182\_0012 and 1182\_0048, and three Phase II studies 1182\_0004, 1182\_0051 and 1182\_0052 for the evaluation of secondary efficacy and safety parameters; (2) the collective efficacy data from Phase II study 1182\_0051 for the evaluation of secondary efficacy parameters; and (3) the collective efficacy and baseline PI mutation data from the TPV/r arms of 1182\_0012 and 1182\_0048 for the evaluation of associations between baseline PI mutation and virologic responses; and (4) the collective secondary efficacy and safety parameters from 1182\_0012 and 1182\_0048 for the evaluation of specific topics requested by the medical officers.

In the following, we summarize several statistical and data issues identified during the review.

1. The risk assessment of secondary safety efficacy endpoints was essentially post-hoc, exploratory and data-driven sensitivity analysis. It was not a comprehensive one.
  - The selections of secondary safety and efficacy parameters to be analyzed were suggested by the medical officers for three Phase II trials during the review process. Two methods were employed in evaluation of laboratory test values (LTV): change from baseline in LTV and in the Division of Acquired Immunodeficiency Syndrome, NIAID, NIH (DAIDS) classification for grading severity of LTV.
2. The analyses of safety endpoints were mainly exploratory to look for safety signals. Hence, the problems of multiplicity in analyses of secondary safety endpoints would not be our concerns.

The type I error had not been adjusted for multiplicity in the summary of secondary safety parameters. However, safety signals concerning the elevations of liver function and lipids enzymes in several studies were very apparent. Even with adjusting for multiplicity, elevated ALT, total bilirubin, Gamma GT, total cholesterol and triglycerides in subjects of the TPV/r arm would also be significantly greater than subjects in the CPI/r arm at  $\alpha=0.05$  level since majority of the p-values were much lower than 0.0001. For instance, adjusting for 60 comparisons via Bonferroni approach, a p-value is less than 0.0083 ( $\alpha'=0.05/60=0.00083$ ) would be considered as statistically significant.

3. One should be cautious when making a conclusion or explanation from the results of secondary efficacy and safety parameters for the five Phase II/III studies reported in this document.
  - The two Phase III trials had an escape clause at Week 8 of the trial, allowing subjects in the control group to discontinue their randomized trial if they lack of initial virologic response. A significantly higher proportion of subjects in the CPI/r arms had discontinued treatment before Week 24 and was mainly contributed to virologic failure. For details please see statistical reviewer Dr. Rafia Bhore's review. Therefore, the significantly higher proportion of subjects in the TPV/r arm developed DAIDS Grade 3 or 4 in liver and lipids elevations may be due to significantly different length

of follow-up in part. However, the escape clause at Week 8 should have limited impact on change from baseline in LTVs, especially for the evaluations at Weeks 2, 4 and 8.

- The Phase II trial 1182\_0051 was designed as a two-phase study: the treatments were administered for two weeks. At Week 2, TPV/r 500/100 mg b.i.d. was added to three other PI-containing regimens. Therefore, the results for the secondary efficacy parameters and change from baseline in LTV at Week 2 may be appropriate to report. Other results for the secondary safety parameters should be exploratory, because the effects of TPV/r compared to those by other CPI/r could not be separated after Week 2.

Based on our evaluation of the collective evidence from the two Phase III and three Phase II studies, we have the following conclusions.

1. Based on available laboratory data through Week 24 from the two Phase III trials, we conclude that the subjects in the TPV/r arm had apparent excess risk of liver and lipids enzyme abnormalities.
  - Compared to subjects in the CPI/r arm, subjects in the TPV/r arm had significantly greater increases in ALT, Gamma GT and total bilirubin, total cholesterol and triglycerides, and greater decreases in creatinine than those in the CPI/r arm. In addition, subjects in the TPV/r regimen had significantly greater reductions in hemoglobin and increases in platelets for most of the Weeks 2-24 studies. For example, one can see in the following graph that median ALT was consistently higher in the TPV/r arm than in the CPI/r arm in RESIST trials. The other parameters mentioned above show similar patterns, as can be seen in the main report.
  - The most common Grade 3 or 4 elevations for the two trials were in triglycerides, Gamma GT, white blood cell count, ALT, AST and total cholesterol.
  - Compared to the CPI/r arms, significantly higher percentages of patients in the TPV/r arm developed Grade 3 / 4 or Grade 4 elevations in ten parameters, and Grade 3 / 4 elevations in four liver enzymes. See the table below.
  - Within each regimen, there were no significant gender differences in development of a Grade 3 or 4 elevations in ten parameters, Grade 4 elevations in ten parameters and Grade 3 or 4 LFTs with one exception. In the TPV/r arm of 1182\_0048, significantly higher percentage of male subjects developed Grade 4 elevations than those in female subjects.

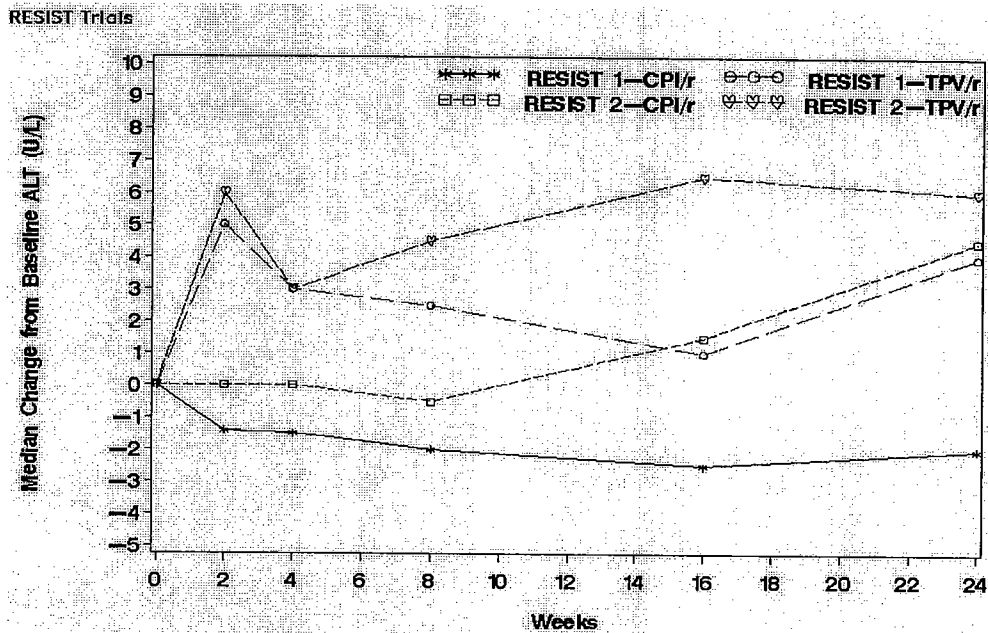


Figure 9: RESIST Trials: Median Change From Baseline ALT (U/L)

Table 67: RESIST Trials: Summary of DAIDS Grade 3 or 4 Elevations

|   |          | CPI/r      |      | TPV/r      |      |
|---|----------|------------|------|------------|------|
|   |          | # subjects | %    | # subjects | %    |
| Grade 3 or 4 elevations <sup>1</sup>                  | RESIST 1 | 62         | 20.3 | 123        | 39.9 |
|   | RESIST 2 | 79         | 18.7 | 151        | 35.1 |
|   | total    | 141        | 19.4 | 274        | 37.1 |
| Grade 3 or 4 elevations in liver enzymes <sup>2</sup> | RESIST 1 | 23         | 7.5  | 68         | 22.1 |
|   | RESIST 2 | 30         | 7.1  | 88         | 20.5 |
|   | total    | 53         | 7.3  | 156        | 21.1 |
| Grade 4 elevations <sup>1</sup>                       | RESIST 1 | 24         | 8.2  | 52         | 16.9 |
|   | RESIST 2 | 25         | 5.7  | 53         | 12.3 |
|   | total    | 47         | 6.5  | 105        | 14.2 |

1. In ten selected lab parameters: platelets, hemoglobin, white blood cell count, AST, ALT, Gamma GT, total bilirubin, total cholesterol, triglycerides and creatinine.
2. AST, ALT, Gamma GT and total bilirubin.

2. Results from the Week 2 data in Phase II trial 1182\_0051 partially support the above findings because of the study design. The subjects in this trial were those who failed the inclusion criterion regarding baseline PI mutation and thus were those who may be in more advance stage of HIV-1 infection at entry.

- At Week 2, subjects in the TPV/r arm had significantly greater increase in total cholesterol, triglycerides, Gamma GT and greater decrease in hemoglobin, compared to subjects in the other CPI/r regimens. Subjects in the TPV/r and SQV/r arms had significantly greater increase in ALT, compared to subjects in the APV/r and LPV/r arms.

3. Based on available laboratory data through Week 24 from the dose-optimization Phase II trial 1182\_0052, we observed significantly greater increases in median AST, ALT and Gamma GT from baseline prior to Week 16. Subjects in the TPV/r 500/100 mg arm had lesser increase in median AST, ALT and Gamma GT, followed by those in the TPV/r 500/200 mg arm, and those in the TPV/r 750/200 mg arm. Significantly dose-response effects were observed for AST and Gamma GT (not ALT), respectively. Significantly dose-response effects were observed for the combination of these four liver enzyme parameters. The combination dose effect of both TPV and RTV is the main concern.

4. Based on available laboratory data through Week 24 from the Phase II trial 1182\_0004, we observed that the subjects in the TPV/r arms had consistently greater increases in Gamma GT, and consistently lower in AST compared to those in the SQV/r arm. There was no consistent pattern in ALT. No clear dose-response effect was observed between the TPV/r 500/100 mg and the TPV/r 1250/100 mg arms.

5. Based on available baseline PI mutation data and virologic response data (percentage of subjects having a confirmed 1 log<sub>10</sub> decrease from baseline at Week 24) in the TPV/r arm for the two Phase III trials, we concluded the following.

Overall, a significantly higher virologic response at Week 24 (VR) was associated with the absence of baseline PI mutation at codons I13, K20, E36, M36, I47 and I54, and the presence of baseline PI mutation at G48. Except for PI mutation at G48, the VR was between 50% and 59% for subjects without any of the other six PI mutations, significantly greater than the VR values ranging between 31% and 43% for those who had at least one of the above baseline PI mutation locations. On the contrary, the VR was 63% for those with baseline PI mutation at G48, significantly greater than 44% for those without mutation at G48.

The association between VR at Week 24 and the baseline PI mutation is significantly, qualitatively and quantitatively interacted with T-20 use prior to entry.

#### TPV/r alone without T-20

Among those receiving TPV/r alone without T-20, absence of ten baseline PI mutation at codons I13, K20, V32, E36, M36, I47, I54, Q58, D60 and I84, or presence of baseline PI mutation at codons D30 and G48 were associated with significantly greater virologic response at Week 24. Adjusting for 27 comparisons, the presence of four baseline PI mutation at codons I13, M36, I47 and I54 were significantly associated with greater virologic response at Week 24.

TPV/r with T-20

Among those receiving TPV/r and T-20, the virologic response at Week 24 was significantly associated with the presence or absence of only one baseline PI mutation at codon L89, p-value=0.0346. The VR rates were 50% and 69%, respectively, for the presence or absence of PI mutation at codon L89. Taking multiple comparison into account, the virologic response at Week 24 was not affected by the baseline PI mutations among subjects using T-20 with TPV/r.

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## 2 INTRODUCTION

### 2.1 Overview

Per review team's requests, the statistical review evaluated secondary efficacy and safety endpoints in two pivotal studies 1182\_0012 & 1182\_0048, three phase II studies 1182\_0004, 1182\_0051 and 1182\_0052. The sensitivity analyses of secondary safety and efficacy endpoints consist of the following aspects:

- 1) Analyses in laboratory toxicity for ten selected hematology (platelets, hemoglobin and white blood cell count), liver enzymes (AST, ALT, Gamma GT and total bilirubin), lipids (total cholesterol and triglycerides) and renal enzyme creatinine, respectively, for 1182\_0012 (RESIST 1) and 1182\_0048 (RESIST 2), and Phase II studies 1182\_0004, 1182\_0051 and 1182\_0052;
- 2) Analyses on selected secondary efficacy endpoints for Studies 1182\_0052, 1182\_0012 and 1182\_0048;
- 3) Additional analyses requested by medical officers to investigate associations between time to first Grade 3 or 4 lab test value abnormality and baseline characteristics for 1182\_0012 and 1182\_0048; and
- 4) Special analyses requested by microbiology reviewer to investigate associations between baseline PI mutations and virologic response for the TPV/r arms in 1182\_0012 and 1182\_0048.

This statistical review document follows the formats of standard template for a statistical reviewer.

### 2.2 Data Sources

The application under NDA 21,814 is comprised of over one hundred volumes in paper submissions that collectively contain the results of many studies.

#### 2.2.1 Databases Used for Analyses

Between Oct. 21, 2004 and December 29, 2004, the applicant submitted electronic datasets for eight or nine studies multiple times as support data or as revised data with friendly formats to ensure the quality of the data. The web addresses of the datasets used for safety and efficacy analyses by this reviewer are

[N21814\N\\_000\2004-12-29\crt\datasets\1182\\_0004,](#)

[N21814\N\\_000\2004-12-29\crt\datasets\1182\\_0012,](#)

[N21814\N\\_000\2004-12-29\crt\datasets\1182\\_0048,](#)

[N21814\N\\_000\2004-12-29\crt\datasets\1182\\_0051,](#) and

N21814\N\_000\2004-12-29\crt\datasets\1182\_0052.

The sponsor submitted data using the CDISC formats. Three types of laboratory databases for each study are applicable in the analyses OTHE, HEMA and CHEM (CDISC names). We have decided to use datasets submitted on December 29, 2004. However, some of the information for triglycerides measurements for Study 1182\_0004 was not completely loaded in the laboratory database CHEM, the datasets in previous submissions were used to create a triglycerides data set for analyses.

For the six datasets in the two Phase III trials, the actual time interval is between January 24, 2003 to April 6, 2004, or 437.73 days for 1182\_0012 and between February 17, 2003 to March 23, 2004, or 400.073 days for 1182\_0048. The time intervals for the laboratory datasets of three Phase II trials appear to be shorter.

## 2.2.2 DAIDS Classification for Grading Severity of Laboratory Test Values

In the analysis of selected laboratory parameters, the severity of laboratory test values abnormalities was assessed using the Division of AIDS (DAIDS) grading, unless DAIDS grading was not available such as white blood cell count, total cholesterol. Table 1 shows DAIDS toxicity grades (Normal, Grade 1-4) for ten selected laboratory parameters, similar to the sponsor's criterion used in Phase II study 1182\_0051. The upper limit normal (ULN) was used to determine DAIDS grade for a specific laboratory parameter.

Table 1: DAIDS Classification for Grading Severity of Laboratory Test Values<sup>1</sup>

|   | Normal    | Grade 1      | Grade 2      | Grade 3      | Grade 4 |
|---|-----------|--------------|--------------|--------------|---------|
| <b>Hemoglobin (g/dL)</b>                              | 9.5+      | 8.0-9.5      | 7.0-7.9      | 6.5-6.9      | <6.5    |
| <b>WBC(10<sup>9</sup> cells/L)</b>                    | 4.0+      | 3.0-3.9      | 2.0-2.9      | 1.0-1.9      | <1.0    |
| <b>Platelets(10<sup>3</sup> cells/mm<sup>3</sup>)</b> | 100+      | 75-99.9      | 50-74.9      | 20-49.9      | <20     |
| <b>Triglycerides (mg/dL)</b>                          |           |              | 400-750      | 751-1200     | >1200   |
| <b>Cholesterol (mg/dL)</b>                            | <=ULN     | >ULN-300     | 300-400      | >400-500     | >500    |
| <b>Gamma GT (U/L)</b>                                 | <1.25 ULN | 1.25-2.5 ULN | >2.5-5.0 ULN | >5.0-10 ULN  | >10 ULN |
| <b>SGPT (U/L)</b>                                     | <1.25 ULN | 1.25-2.5 ULN | >2.5-5.0 ULN | >5.0-10 ULN  | >10 ULN |
| <b>SGOT (U/L)</b>                                     | <1.25 ULN | 1.25-2.5 ULN | >2.5-5.0 ULN | >5.0-10 ULN  | >10 ULN |
| <b>Total Bilirubin (mg/dL)</b>                        | ≤1.0 ULN  | >1.0-1.5 ULN | >1.5-2.5 ULN | >2.5-5.0 ULN | >5 ULN  |
| <b>Creatinine (mg/dL)</b>                             | ≤1.0 ULN  | 1.1-1.5 ULN  | >1.5-3.0 ULN | >3-6 ULN     | >6 ULN  |

1. DAIDS classification for grading severity of laboratory test values, except for total cholesterol by CTC grades and ECOG grades for white cell count.
2. Source: Table 7.1.5:1 Toxicity grades for laboratory tests of special interest. Page 226 of 318, U04-0174. NDA 21,814 submission.



During the review process, this reviewer identified several data issues regarding DAIDS classification for grading severity of laboratory test values.

The toxicity grades of laboratory test values in the databases appeared not to be consistent with those by the DAIDS's classifications. This was evident by the fact that data ranges for different toxicity grades (0-normal, 1-Grade 1, 2- Grade 2, 3 Grade 3, 4- Grade 4) for a parameter of interest were overlapped. Table 2 summarizes data ranges by DAIDS grade for four liver enzyme parameters AST, ALT, total bilirubin and Gamma GT for the five studies.

- The sponsor explained that a maximum grading value was coded for several sub-follow-up visits under a scheduled visit. For example, if the grading values of ALT (SGPT) at Visits 7, 7.1, 7.2 are 1, 2 and 1, then the coded grading values would be 2, 2, 2 for Visits 7, 7.1 and 7.2.

Table 3 summarizes number of distinguish ULN values by ten of laboratory parameters and study. Most of the parameters had one or two ULN values except for total cholesterol and triglycerides where over ten ULN values were obtained. ULN values for some parameters showed gender differences. However, the ULN values showed significantly different between the two treatment arms,  $p < 0.0001$  by the Kruskal-Wallis test.

- The sponsor explained that [redacted] and other data processing companies had used criteria slightly different for grading laboratory toxicity.

As a result, this reviewer recoded some of the toxicity grades according to the DAIDS criteria used for Study 1182\_0051 to report shifts from Normal or Grade 1 or 2 to Grades 3 & 4.

- We have recoded the unit of the original measurement relative to the ULN in four liver enzyme parameters total bilirubin, Gamma GT, AST and ALT as criteria for grading the laboratory test value abnormality in order to summarize change from baseline in DAIDS grading.
- For total cholesterol (mg/dL), the 'Grade 1' based on Common Toxicity Criteria (CTC) was defined as cholesterol measurement from 'ULN' to 300 mg/dL. However, we observed ULN values of greater than 300 mg/dL, which are not comparable with the definition by CTC. In such cases, 'Grade 1' was recoded.
- For fast triglyceride (mg/dL), there were no definitions for 'Normal' and 'Grade 1' by the DAIDS and ACTG toxicity grading systems. We have adopted the use of 0-199 mg/dL for a 'Normal' and 200-399 mg/dL for a 'Grade 1' triglycerides.
  - The American Heart Association's classifications are 0-149 mg/dL and 150-199 mg/dL, respectively for 'Normal' and 'Borderline-high' triglycerides (see <http://www.americanheart.org/presenter.jhtml?identifier=4500>).
- There were no DAIDS grades for a 'Normal' and 'Grade 1' platelets. We have recoded the platelets grades using the range of 75000-99900 for 'Grade 1' and 99901-high for 'Normal' platelets.

Table 2: Data Ranges for the Upper Limit Normal (ULN) Values by Study<sup>1</sup>

|              |                        | 0004     | 0012      | 0048      | 0051      | 0052      |
|--------------|------------------------|----------|-----------|-----------|-----------|-----------|
| <b>Grade</b> | <b>Gamma GT</b>        |          |           |           |           |           |
| 0            | <1.25 ULN              | 7-90     | 6-76      | 6-76      | 8-76      | 11-81     |
| 1            | 1.25-2.5               | 59-182   | 54-152    | 31-152    | 50-152    | 62-162    |
| 2            | >2.5-5.0               | 103-364  | 69-305    | 103-305   | 47-305    | 68-325    |
| 3            | >5.0-10.0              | 195-716  | 109-609   | 112-610   | 64-603    | 112-636   |
| 4            | >10.0                  | 756-1265 | 250-3248  | 403-2921  | 33-2620   | 375-2059  |
|              | <b>ALT</b>             |          |           |           |           |           |
| 0            | <1.25 ULN              | 7-90     | 6-53      | 5-53      | 7-53      | 11-81     |
| 1            | 1.25-2.5               | 41-179   | 20-107    | 20-107    | 35-107    | 62-162    |
| 2            | >2.5-5.0               | 128-347  | 20-208    | 66-213    | 29-208    | 68-325    |
| 3            | >5.0-10.0              | 76-511   | 15-424    | 27-405    | 70-424    | 112-636   |
| 4            | >10.0                  | 79-939   | 80-1582   | 11-1579   | 39-1096   | 375-2059  |
|              | <b>AST</b>             |          |           |           |           |           |
| 0            | <1.25 ULN              | 10-73    | 9-44      | 7-44      | 11-44     | 9-49      |
| 1            | 1.25-2.5               | 41-140   | 24-90     | 19-90     | 22-90     | 17-100    |
| 2            | >2.5-5.0               | 36-255   | 21-175    | 27-179    | 34-178    | 20-200    |
| 3            | >5.0-10.0              | 28-365   | 22-341    | 18-360    | 58-317    | 35-390    |
| 4            | >10.0                  | 25-423   | 65-604    | 377-737   | 25-663    | 24-2830   |
|              | <b>Total Bilirubin</b> |          |           |           |           |           |
| 0            | ≤1.0 ULN               | 0.2-1.3  | 0.08-1.23 | 0.18-1.23 | 0.18-1.23 | 0.06-1.23 |
| 1            | >1.0-1.5               | 1.0-1.8  | 0.6-1.7   | 0.47-1.81 | 1.29-1.81 | 1.23-1.81 |
| 2            | >1.5-2.5               | 2.2-2.8  | 0.9-3.0   | 1.5-2.9   | 1.80-2.80 | 0.4-2.51  |
| 3            | >2.5-5.0               | 3.3-6.1  | 3.2-4.7   | 3.1-6.1   | 3.20-5.20 | 1.29-5.03 |
| 4            | >5.0                   | 12.1     | Na        | 6.4-19.7  | 2.50-6.20 | 1.2-8.9   |

Table 3: Upper Limit Normal (ULN) by Lab Parameter and Study<sup>1</sup>

|              | 0004             | 0012              | 0048              | 0051                | 0052        |
|--------------|------------------|-------------------|-------------------|---------------------|-------------|
| <b>HGB</b>   | 15.6,17.2        | 15.8,16.4,17,18.1 | 15.8,16.4,17,18.1 | 15.8,16.4,17.0,18.1 | 14.99,15,17 |
| <b>WBC</b>   | 10.8             | 10.7              | 10.7,13.2         | 10.7                | 10.5        |
| <b>PLTCT</b> | 400              | 394,400           | 394,400           | 394,400             | 415         |
| <b>SGPT</b>  | 48,52            | 32,34,35,43       | 34,35,43          | 34,35,43            | 40          |
| <b>SGOT</b>  | 36,42,59         | 34,36             | 34,36,40          | 34,36               | 40          |
| <b>GGT</b>   | 45,65,73         | 49,50,61          | 49,50,51,61       | 49,50,61            | 60,65       |
| <b>TBILI</b> | 1.29,1.30        | 1.2,1.23          | 1.2,1.23          | 1.2,1.23            | 1.2,1.23    |
| <b>CHOL</b>  | 199,199.15,200   | 218-352, n=17     | 218-352, n=17     | 235-320, n=16       | 199,199.15  |
| <b>TRIGL</b> | 198.4,199.99,200 | 144-327, n=16     | 124-327, n=22     | 176-327, n=16       | 149,149.20  |
| <b>CRE</b>   | 1.2,1.4,1.5      | 1.1-1.6, n=8      | 1.1-1.6, n=7      | 1.1-1.55, n=7       | 1.5,1.504   |

n - number of distinct ULN values.

### 2.2.3 Time Window

In evaluation of secondary efficacy endpoints using viral load data for Study 1182\_0051, it was found that intervals for the consecutive time windows were over lapped (See Table 4). As the time windows for study visit in the databases do not necessary follow the definitions described in the protocols, the analysis using visit number may not be appropriate. In the following sensitivity analyses, time window for the *i*th Week since date of first treatment of study drugs were modified as interval of the mid-point of the (*i-1*)th Week and the *i*th Week, and the mid-point of the *i*th Week and the (*i+1*)th Week.

Table 4: Study 1182\_0051: Visit Number and Time Window

| Visit | Week since 1st Rx | Day since 1 <sup>st</sup> Rx | Planned Time Window | Time Window <sup>1</sup> in Databases |
|-------|-------------------|------------------------------|---------------------|---------------------------------------|
| 1     | Screen            | -7                           | -14,-1              | -128,0                                |
| 2     | 0                 | 0                            | 0                   | -42,1                                 |
| 3     | 1                 | 7                            | +3                  |                                       |
| 4     | 2                 | 14                           | +/-2                | 7,41                                  |
| 5     | 3                 | 21                           | +3                  |                                       |
| 6     | 4                 | 28                           | +/-2                | 22,55                                 |
| 7     | 8                 | 56                           | +/-4                | 42,88                                 |
| 8     | 16                | 112                          | +/-4 or 7           | 85,148                                |
| 98    | 24                | 168                          |                     | 7,209                                 |

Data from plasma HIV-1 RNA.

Table 5 shows definitions of time window for the evaluation of secondary endpoints. They were consistent to the FDA's evaluation of efficacy endpoints for 1182\_0012 and 1182\_0048, except for the definition of time window for computing baseline values. The same definitions were applied to three Phase II studies since the durations of follow-ups were shorter.

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Table 5: 1182\_0012 and 1182\_0048: Time Window

| Visit | Week | Lower Limit<br>of Visit<br>Window | Day | Upper Limit<br>of Visit<br>Window |
|-------|------|-----------------------------------|-----|-----------------------------------|
| 1     | 0    | 0                                 | 0   | 7                                 |
| 2     | 2    | 8                                 | 14  | 21                                |
| 3     | 4    | 22                                | 28  | 42                                |
| 4     | 8    | 43                                | 56  | 84                                |
| 5     | 16   | 85                                | 112 | 140                               |
| 6     | 24   | 141                               | 168 | 196                               |
| 7     | 32   | 197                               | 224 | 252                               |
| 8     | 40   | 253                               | 280 | 308                               |
| 9     | 48   | 309                               | 336 | 364                               |
| 10    | 56   | 365                               | 392 | 420                               |
| 11    | 64   | 421                               | 448 | 476                               |
| 12    | 72   | 477                               | 504 | 532                               |
| 13    | 80   | 533                               | 560 | 588                               |
| 14    | 88   | 589                               | 616 | 644                               |
| 15    | 96   | 645                               | 672 |                                   |

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## 3 STATISTICAL EVALUATION

### 3.1 Overview

For an accelerative approval of APTIVUS™ (tipranavir), the statistical review of NDA21,814 was requested by the review team and mainly supported medical officers' safety review of the laboratory test values. In addition, statistical analyses for secondary efficacy endpoints and special topics were also asked for. The evaluation of selected secondary safety endpoints were conducted for the two Phase III trials 1182\_0012 and 1182\_0048, and three Phase II trials 1182\_0004, 1182\_0051 and 1182\_0052; the evaluation of secondary efficacy endpoints were conducted for the two Phase III trials and for 1182\_0051; and the special topics were those for the two Phase III trials.

#### 3.1.1 Study Design

For complete discussions of study design, see clinical review by Dr. Andrea Smith and statistical review by Dr. Rafia Bhore for the two Phase III trials, and clinical review by Dr. Neville Gibbs for the Phase II trials. The following is a brief summary of study design for the five trials.

##### 3.1.1.1 1182\_0012 & 1182\_0048

The Phase III trials 1182\_0012 (RESIST 1) and 1182\_0048 (RESIST 2) were identically designed, multi-center, multi-national, open label, randomized, active controlled 96 week study of safety and efficacy of TPV/RTV + optimized background regimen (OBR) versus comparative protease inhibitor (CPI)/RTV + OBR in subjects with 3 class (NRTI, NNRTI, and PI) antiretroviral (ARV) experience HIV-1 infected subjects.

At screening, genotype resistance was tested selecting subjects who had at least one per-protocol protease (PI) mutation(s) at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M and with two or less mutations at codons 33,82,84 or 90. Qualified subjects were randomized to either TPV/r or CPI/r arm at a ratio of 1:1, and stratified with respect to the pre-selected PI and the use of enfuvirtide (T-20).

Other inclusion criterion were:

- 1) HIV-positive males or females of 18 years of age or older;
- 2) Treatment with at least 3 months of NRTIs and NNRTIs;
- 3) Treatment with at least two PIs; and
- 4) A viral load of at least 1,000 copies/mL.

The primary efficacy endpoint was the proportion of patients with a treatment response at 48 weeks ( $\geq 1 \log_{10}$  reduction in two consecutive viral load measurements without prior evidence of treatment failure) and the time to treatment failure through 48 weeks.

Treatment response was defined by confirmed virologic response ( $\geq 1 \log_{10}$  below baseline) without prior treatment failure, i.e., occurrence of any of the following events.

- Death.
- Permanent discontinuation of the study drug.
- Loss to follow-up.
- Introduction of a new ARV drug to the regimen for reasons other than toxicity or intolerance to a background ARV drug.
- Confirmed virologic failure.

Confirmed virologic failure was defined as:

- Viral load of  $< 1 \log_{10}$  below baseline confirmed at two consecutive visits  $> 2$  weeks apart, following a confirmed virologic responses of two consecutive viral load measurements ( $\geq 1 \log_{10}$  below baseline), or
- One viral load of  $< 1 \log_{10}$  below baseline followed by permanent discontinuation of the study drug or loss to follow up, following a confirmed virologic response of two consecutive viral loads  $\geq 1 \log_{10}$  below baseline.

Primary safety endpoints were: 1) the proportions of patients with adverse events (AE); and 2) the proportions of patients with severe AE (SAE)s.

Secondary safety endpoints were AEs by severity and by actions taken with regard to test drug; proportion of patients with laboratory test abnormalities with respect to DAIDS grading; laboratory test value change over time and discontinuation due to AEs.

In 1182\_0012, a total of 1406 subjects in 125 study centers located in the US, Canada and Australian were enrolled; 630 were randomized and 620 received at least one study drug dose, of those 311 subjects received TPV 500 mg/RTV 200 mg and 309 received CPI/r. In 1182\_0048, a total of 1903 subjects in 171 study centers located in Europe, South Africa and Mexico were enrolled, 878 were randomized and 863 received at least one dose of study drug, of those 435 subjects received TPV 500 mg/RTV 200 mg and 428 receiving CPI/r.

### 3.1.1.2 1182\_0004

1182\_0004 was a Phase II, open-label, randomized, multicenter, parallel trial in single failed PI-experienced HIV subjects evaluating the efficacy and safety of two doses of TPV/r as compared to RTV-boosted Saquinavir (SQV/r). HIV-1 infected subjects in 23 sites in United States, 2 in France, and 1 in Italy, were randomized in a 1:1:1 ratio to one of three treatment groups:

- 1) TPV (low dose) – TPV/r 500/100 mg b.i.d. + two new NRTI's;

- 2) TPV (high dose) – TPV/r 1250/100 mg b.i.d. + two new NRTI's; and
- 3) SQV/r 400/400 mg b.i.d. + two new NRTI's.

The TPV Self-Emulsifying Drug Delivery System (SEDDS) and the proposed marketed formulation were used. The study duration was initially 24 weeks, but was later modified for up to 96 weeks.

The overall aim of the trial was to determine whether a low or high dose TPV (with a fixed dose of ritonavir) was safe and effective and to compare this safety and efficacy with that of standard dual PI combination of SQV/r. Additionally, the PK profile of TPV was assessed at 2, 4, 8, 16 and 24 weeks of treatment.

All subjects randomized in the trial were required to be HIV positive, to have failed one PI - containing regimen, and have two new NRTI options available. There was no limit on the CD4 cell count at initial screening, and subject's plasma HIV RNA needed to be greater than 1,000 copies/mL.

Primary efficacy endpoints were defined as follows:

1. Change in baseline HIV-1 RNA through weeks 16, 24/48 weeks;
2. Occurrence of HIV RNA values through below the limit of quantitation (LOQ) < 400 copies/mL and < 50 copies /mL; and
3. Occurrence of HIV-RNA at least 1 log<sub>10</sub> below baseline.

Secondary efficacy endpoints were defined as follows:

1. Change from baseline in CD4+ cell count at Weeks 16, 24 and 48; and
2. Time to virological failure defined as plasma HIV RNA values > 400 copies/mL at 2 consecutive time points 2-4 weeks apart, at 16 weeks or later.

Primary safety endpoints were as follows:

1. Treatment emergent and drug-related AE's
2. Grade 3 and 4 laboratory abnormalities SAE's

Secondary safety endpoints were change from baseline in laboratory values of blood glucose, cholesterol, HDL and triglycerides (lipid profile).

The comparisons of efficacy and safety endpoints were as follows:

- 1) TPV/r 500/100 mg b.i.d. versus SQV/r 400/400 mg b.i.d.;
- 2) TPV/r 1250/100 mg b.i.d. versus SQV/r 400/400 mg b.i.d.;
- 3) TPV/r 1250/100 mg b.i.d. versus TPV/r 500/100 mg b.i.d..

### 3.1.1.3 1182\_0051

Study 1182\_0051 was a Phase II, open-label, randomized, parallel-group, multicenter, 24 week trial in treatment experienced subjects who failed to meet the entry criteria for one of the Phase III

trials of TPV 1182\_0012 or 1182\_0048 due to an HIV isolate containing greater than 2 mutations at codons 33, 82, 84 or 90. Participants in Europe and North America countries were randomized to one of the following four regimens with a ratio of 1:1:1:1,

- TPV/r 500/200 mg b.i.d. + OBR;
- LPV/r 400/100 mg b.i.d. + OBR;
- APV/r 600/100 mg b.i.d. + OBR; or
- SQV/r 1,000/100 mg b.i.d. + OBR.

The treatments were administered for two weeks. At Week 2, TPV/r (500/100 mg b.i.d.) was added to three other PI-containing regimens.

The entry criteria included:

- Highly treatment experienced subjects, with antiretroviral (ARV) experience with 3 ARV classes (NRTI, NNRTI, PI).
- Previous treatment with two different PI-based regimens for a minimum of 3 months each.
- Plasma HIV-1 RNA  $\geq$  1,000 copies/mL.
- At least 3 documented mutations at protease codons 33, 82, 84, or 90 at screening. Because study entry criteria in the 1182\_0012 and 1182\_0048 were limited to mutations at less than 3 protease codons, these subjects were excluded from those trials and eligible for 1182.51).
- Any CD4+ cell count was acceptable.

The objectives of this trial were to determine the change in  $C_{12h}$  from Week 2 to Week 4 regarding the change in PI trough (LPV, APV and SQV) from a boosted PI alone to the trough with TPV added; the effect of these drugs on the  $C_{12h}$  of TPV; and the efficacy of TPV/r alone compared with three dual-boosted PI regimens in treatment experienced HIV-positive patients with extensively mutated, highly resistant virus.

Primary PK endpoint was defined as the change of mean trough levels ( $C_{12h}$ ) of the second PI before (average of Day 7 and Day 14) and after (average of Day 21 and Day 28) addition of TPV/r to the current regimen.

Secondary PK endpoints included the following:

- $C_{12h}$  of TPV at Weeks 1 and 2 and at Weeks 3 and 4;
- $C_{12h}$  of RTV at Weeks 1 and 2 and at Weeks 3 and 4;
- Patient adherences at Weeks 1-4; and
- Change in other intensive PK parameters such as  $AUC_{(0-12h)}$ ,  $C_{max}$  and  $C_{12h}$  for the comparison of 2nd PI, TPV, RTV, at Weeks 2 and 4.

Efficacy endpoints in the protocol and were analyzed by the sponsor included:

- Change from baseline viral load at Weeks 2 and 4;
- Proportion of virologic responders at Weeks 2 and 4;
- Change from baseline in CD4+ and CD8+ cell count at Weeks 2 and 4;
- Virologic response at Week 4 and time to virologic failure;
- Reasons for treatment failure;



- Proportion of patients achieving 1 log<sub>10</sub> or more decline from baseline in viral load nadir, <400 copies/mL; <50 copies/mL;
- Proportion of patients with a new CDC category C progression event or death, and time to such events;
- Proportion of treatment responders at Weeks 2 and 4 was planned but not done;
- Time to treatment failure was planned but not done; and
- Genotypic and phenotypic resistance patterns at Week 0.

Note that five secondary efficacy endpoints were planned in the protocol and 'not done' (see Pages 44-45, Vol. 1.76 of 1263).

Safety endpoints were proportion of patients (1) with laboratory abnormalities including hematology, chemistry, liver functions and lipid levels; (2) proportion of patients who experienced adverse events; and (3) proportion of patients who reported serious adverse events (SAEs).

This study consisted of two phases, a single-boosted PI period (Weeks 1-2) and a dual-boosted PI period (Weeks 3-24). The primary and secondary efficacy endpoints were assessed at the end of Week 4. After Week 4, patients were allowed to change the treatment regimen. Hence, endpoints at Week 24 were considered exploratory. Safety endpoints were analyzed over the entire trial period and were analyzed at Week 4 for interim report.

#### **3.1.1.4 1182\_0052**

1182\_0052 was a Phase II, double-blind, randomized, dose optimization trial of three doses of tipranavir boosted with low dose ritonavir (TPV/r) in subjects with multiple antiretroviral (ARV) drug-experiences.

All patients were triple ARV class, two PI-based-experienced and had baseline viral isolate with at least one primary protease mutation at codons 30N, 46I/L, 48V, 50V, 82A/L/F/T, 84V and 90M, with no more than two of the 82 L/T, 84V, or 90M mutations. Following genotypic screening at baseline, qualifying subjects were randomized to received TPV/r 500/100 mg, TPV/r 500/200 mg, and TPV/r 750/200 mg. All TPV/r were administered as twice daily with a genotypically OBR that was individually chosen by investigators. The first two weeks of the study were the functional monotherapy phase, in which patients changed the PI they were taking at entry to one of the three TPV/r doses, but maintained the same OBR. After 2 weeks, each patient's background ARV medications were optimized, and the patient remained on blinded TPV/r and optimized ARV therapy for up to 32 weeks.

Primary efficacy endpoints were PK parameters such as the PK trough concentrations.

Primary safety endpoints were: 1) proportions of patients with adverse events (AE); and 2) proportions of patients with severe AE (SAE)s.

Secondary safety endpoints were 1) AEs by severity and by actions taken; 2) proportion of patients with laboratory test abnormalities with respect to DAIDS grading; 3) laboratory test value change over time and 4) discontinuation due to AEs.

The study population for the sensitivity analyses consists of 216 subjects who was randomized and received at least one treatment of study drugs, of those 73 received TPV/r 500/100 mg, 72 received TPV/r 500/200 mg, and 71 received TPV/r 750/200 mg.

### 3.1.2 Methodology

The evaluation of selected secondary safety endpoints were conducted on ten hematological, liver, lipids and renal enzyme parameters: white blood cell count (WBC), Hemoglobin (HGB), Platelets (PLTCT), Gamma GT (GGT), ALT(SGPT), AST(SGOT), Triglycerides (TRIGL), total Bilirubin (TBILI), total cholesterol (CHOL) and creatinine (CRE). The names in the parentheses are CDISC standard names.

The efficacy analyses include change from baseline CD4+ cell count for 1182\_0012 and 1182\_0048; change from baseline viral load, percentage of subjects with virologic response, and change from baseline in CD4+ and CD8+ cell count for Study 1182\_0051.

The statistical analyses of the ten selected laboratory parameters are the same for five Phase II/III studies. For each study, the following analyses were performed.

- 1) Change from baseline in laboratory test value by treatment regimen and follow-ups;
- 2) Change in laboratory test abnormalities with respect to DAIDS grading and proportion of subjects who developed a Grade 3 or 4 abnormalities during the trial; and
- 3) Comparing secondary safety endpoints described in 1) - 2) between treatment regimens.

Additional statistical analyses and modeling were specifically conducted according to the requests by medical officers and microbiology reviewer during the review, including the following.

- 1) Assessment of dose-response in selected lab parameters for Study 1182\_0051;
- 2) Analyses of time to first DAIDS Grade 3 or 4 liver function toxicities or other lab test value abnormality for 1182\_0012 and 1182\_0048;
- 3) Identifying baseline risk factors associated with the time course of liver toxicities and abnormality in cholesterol for 1182\_0012 and 1182\_0048; and
- 4) Investigating associations between baseline PI mutation position and virologic response at Week 24 for subjects in the TPV/r arm by the T-20 use in 1182\_0012 and 1182\_0048.

For the comparison of change from baseline in a lab parameter between treatment regimens, Kruskal-Wallis (K-W) tests were used. For the comparison of toxicity DAIDS grade shift and number of lab parameters with toxicity Grade 3 or 4 elevations between treatment regimens, Chi-square test and the K-W test were used. In analyses of time to first Grade 3 or 4 toxicity in ten laboratory parameters, and time to first Grade 3 or 4 in liver function toxicity (LFT), Kaplan-Meier (K-M) method was utilized for estimation, and log-rank test was used for the comparisons of the K-M curves. Cox proportional hazard models were used to investigate the associations between baseline characteristics and the development of a clinical event such as DAIDS Grade 3 or 4 LFT

abnormalities. In analyses of presence/absence of a PI mutation position and virologic response at Week 24, contingency table approach and Chi-square test was used. To explore the associations among PI mutation position pairs, the McNemar test was used.

Laboratory test values at baseline and follow-up weeks since date of initial treatment of study regimens were computed based on definitions listed in Table 1 for evaluation. In sensitivity analyses of selected secondary safety endpoints, all measurements in the designated time window should be used for the evaluations. No imputations were used for missing values in a time window. Different methods were employed with respect to more than one measurement per subject.

In computation of group summary statistics for the change from baseline analyses via a laboratory parameter test value,

- Baseline laboratory parameter test value was determined by the mean value of all available values within 12 weeks prior to Day 1 if a subject had more than one measurements of interest.
- In addition to baseline, the follow-up visits for the present analyses were those at Weeks 0, 2, 4, 8, 16 and 24. This was done because there were just a few laboratory measurements in the Week 32 time window or later. If a follow-up time window consists of more than one measurement for a parameter of interest then mean value for this subject would have been used.

For evaluation of laboratory parameters via change in DAIDS toxicity grade and time to first DAIDS Grades 3 & 4 toxicities, laboratory test values at all distinguish time points were used.

- Baseline laboratory parameter test value grade was determined as the one prior to Day 1 with testing date closest to Day 1.
- All post baseline laboratory test values of interests in the databases were used in evaluation of changes in DAIDS toxicity grading.

The intension-to-treat (ITT) population for the sensitivity analyses of selected secondary safety endpoint is the same as the ITT population for the evaluations of primary efficacy and safety endpoints. For example, the ITT population consists of 620 subjects, 309 for CPI/r arm and 311 for TPV/r arm in 1182\_0012, and 863 subjects, 428 for CPI/r arm and 435 for TPV/r arm in 1182\_0048. Depending on the laboratory test values available in the databases, the actual sample sizes for the sensitivity analyses of selected secondary safety endpoints are 302-306 for the CPI/r arm and 303-308 for the TPV/r arm in 1182\_0012 and 407-422 for the CPI/r arm and 417-430 for the TPV/r arm.

## 3.2 Evaluation of Efficacy

The following reports the evaluation of selected secondary efficacy endpoints requested by the medical officers. Therefore, the findings were not summarized in the executive summary in this review. The complete evaluation of efficacy, see Dr. Rafia Bhore's review.

### 3.2.1 1182\_0012 and 1182\_0048

#### Change from baseline CD4+ cell count

Changes from baseline CD4+ cell count were significantly different between the two regimens:  $p < 0.01$ , at Weeks 4, 8 and 16 for 1182\_0012, and  $p < 0.001$  Weeks 2-24 for 1182\_0048, by the K-W tests. During the 24 weeks of trials, subjects in the TPV/r arms had significant greater median increase of 9-25 cells/mm<sup>3</sup> for 1182\_0012, and 14-24 cells/mm<sup>3</sup> for 1182\_0048, respectively, than those in the CPI/r arms. The temporal patterns in median CD4+ cell count change were similar for the TPV/r arms and CPI/r arms in both trials, except for CPI/r arms at Week 24. See Table 6 and Figure 1.

### 3.2.2 1182\_0051

#### Change from Baseline Plasma HIV-1 RNA

Table 7 lists statistics for the change from baseline by treatment regimen at Weeks 2 and 4. Figure 2 shows median change from baseline viral load through Week 24 by treatment regimen. Median baseline viral load values were between 4.78 and 5.06 log<sub>10</sub> for the four regimens.

The temporal trend in median viral load is significantly different between the TPV/r regimen and the other PI/TPV/r regimens at Weeks 2 and 4.

- At Week 2, subjects in the TPV/r regimen had a significant early drop of more than 1.2 log<sub>10</sub> in median viral load while subjects in other PI/TPV/r regimens had a drop of between 0.2-0.4 log<sub>10</sub>,  $p < 0.0001$  by the K-W test.
- At Week 4, subjects in other PI/TPV/r regimens had a continuous drop of 1.2-1.4 log<sub>10</sub>, while subjects in the TPV/r regimen had slightly bounced back to a median of -1 log<sub>10</sub>. No statistical significant differences were found among the four regimens.
- The median change from baseline in viral load by this reviewer is slightly different from the sponsors'. Figure 2 is slightly different from Figure 11.4.1.2:1 by the sponsors', Last Observation Carry Forward (LOCF) analysis. In addition to the LOCF, differences in defining time windows may also contribute for the differences.

#### Virologic Response

Virologic response was assessed at Weeks 2, 4 and 24 for the following four variables: 1) percentage of subjects with at least 1 log<sub>10</sub> decrease from baseline; 2) percentage of subjects with at least 0.5 log<sub>10</sub> decrease from baseline; 3) percentage of subjects with a viral load below 400 copies/mL; and 4) percentage of subjects with a viral load below 50 copies/mL.

In the sensitivity analyses, the sponsor's Non-completer as Failure (NCF) for virologic response analyses were used. Missing in virologic response due to early discontinuation was also considered as failure. If multiple dichotomous outcomes occurred such as viral load < 400 copies/mL, in a time window, the worst one was used. There were only a few discordant viral load responses in the

databases among those with multiple values in a time window (n=3 for viral load < 400 copies/mL).

Table 8 summarizes virologic response for the four virologic response variables. Note virologic response at Week 2 and 4 were secondary efficacy endpoints.

Percentage of subjects with at least 1 log<sub>10</sub> drop from baseline were 51%, 48% and 24% in the TPV/r regimen and 25%, 50% and 28% in the total PI/TPV/r regimens, respectively at Weeks 2, 4 and 24. At Week 2, a significantly higher proportion of subjects in the TPV/r regimen had viral load decline of 1 log<sub>10</sub> or more, compared to those in any of the other PI/TPV/r regimens, p=0.0006 by the Chi-square test. However, at Week 4 the difference was not significant, p>0.05.

Likewise, percentage of subjects with at least 0.5 log<sub>10</sub> drop from baseline were 62%, 61% and 37% in the TPV/r regimen and 37%, 64% and 39% in the total PI/TPV/r regimens, respectively at Weeks 2, 4 and 24. A significantly higher proportion subjects in the TPV/r regimen had viral load drop of more than 0.5 log<sub>10</sub> at Week 2, compared to those in any of the PI/TPV/r regimens, p=0.0006 by the Chi-square test. However, at Week 4 the difference was not significant, p>0.05.

Percentage of subjects with viral load < 400 copies/mL were 16%, 12% and 16% in the TPV/r regimen and 6%, 14% and 16% in the total PI/TPV/r regimens, respectively at Weeks 2, 4 and 24. More subjects in the TPV/r regimen had viral load reached undetected level by the standard assay at Week 2 than those in any of the PI/TPV/r regimens, p=0.0368 by the Chi-square test. However, at Week 4 the difference was not significant, p>0.05. These results were somewhat different from those by the sponsors: at Week 4, this reviewer obtained 12% in the TPV/r regimen and 14% in the total PI/TPV/r regimen, while the sponsors reported a value of 24% in the TPV/r regimen and 18% in the total PI/TPV/r regimen.

Percentage of subjects with viral load < 50 copies/mL was similar between the TPV/r arm and the other PI/TPV/r arm: 2%, 5% and 15% in the TPV/r regimen and <1%, 2% and 15% in the other PI/TPV/r regimens, respectively at Weeks 2, 4 and 24.

- The percentage of subjects with a viral load decrease of at least 0.5 log<sub>10</sub> from baseline has not been defined in the protocol.
- The estimated virologic responses were similar to the sponsors' except for the percentages of subjects with viral load < 400 copies/mL.

#### **Change from baseline CD4+ and CD8+ cell count**

Change from baseline CD4+ and CD8+ cell count by treatment regimen are summarized in Table 9, Figure 3 and Figure 4.

- At Week 2, subjects in the TPV/r regimen had a median CD4+ increase of 23 cells/mm<sup>3</sup> change from baseline, followed by 17 cells/mm<sup>3</sup> in the LPV/TPV/r regimen, greater than a median increase of 7-8 cells/mm<sup>3</sup> in the SQV/TPV/r and APV/TPV/r regimens,

$p=0.0418$ , by the K-W test. At Week 4, the median increases of 14-26 cells/mm<sup>3</sup> were observed for the four regimens,  $p>0.05$  by the K-W test.

- At Week 24, the median CD4+ increases of 18-56 cells/mm<sup>3</sup> were observed for the four regimens.
- At Week 2, subjects in the TPV/r and SQV/TPV/r regimens had a median CD8+ decreases 16-19 cells/mm<sup>3</sup> from baseline, while subjects in the APV/TPV/r and LPV/TPV/r regimen had a median increase of 33-52 cells/mm<sup>3</sup>. At Week 4, the median increase of 20 cells/mm<sup>3</sup> from baseline was observed for the four regimens. No significant differences were observed,  $p>0.05$  by the K-W test.
- Note Change from baseline in CD8+ cell count at Weeks 2 and 4 were defined as secondary efficacy endpoints. However, the sponsor did not report these results.

Change from baseline in CD4+/CD8+ cell count at Week 24 were similar among the four regimens. Note that they were not secondary efficacy endpoints.

### 3.3 Evaluation of Safety

#### 3.3.1 Change from Baseline for Selected Laboratory Parameters

Basic statistics (n, mean, standard deviation, median and range) of the change from baseline in laboratory test value by treatment regimen and follow-ups, along with the p-value by Kruskal-Wallis (K-W) test were summarized in tables. Tables with negative findings or no significant difference among treatment regimens were deleted in this document.

##### 3.3.1.1 1182\_0012

Figure 5, Figure 6 and Figure 7 show median values for platelets, hemoglobin and WBC by follow-up visit and treatment regimen. The basic statistics of platelets and hemoglobin were summarized in Table 10 and Table 11.

- Changes from baseline white blood cell count were not significantly different between the two regimens,  $p>0.05$ , by the K-W tests.
- Changes from baseline hemoglobin were statistically significantly different between the two regimens at Weeks 2, 4, 16 and 24, p-values are between 0.0006 to 0.0256. The median difference was approximately 0.2 g/dL. Subjects in the TPV/r regimen had median drop of 0.1-0.3 g/dL, while subjects in the CPI/r regimen had median drop 0-0.1 g/dL. The results for the Week 8 were similar for the two arms.
- For the comparison of platelets at Week 2, subjects in the TPV/r had a median increase of 9000 cells/mm<sup>3</sup> and subjects in the CPI/r had a median increase of 15000 cells/mm<sup>3</sup>,

p=0.0648. Change from baseline platelets were statistically significantly different between the two regimens at Weeks 4-24, p-values are between <0.0001 to 0.0131. Subjects in the TPV/r regimen had 3000-9000 cells/mm<sup>3</sup> reduction in median platelet count from baseline, while subjects in the CPI/r regimen had an increase of 2000-8000 cells/mm<sup>3</sup>.

Change from baseline in liver enzymes AST, ALT, Gamma GT and total bilirubin are summarized in Table 12, Table 13, Table 14 and Table 15, and Figure 8, Figure 9, Figure 10 and Figure 11.

- Changes from baseline AST were not statistically significantly different between two arms except for Week 2.
- Changes from baseline ALT were statistically significantly different between two arms for Week 2-16. It appears that the subjects in the TPV/r arm had significantly greater increases in ALT than subjects in the CPI/r arm.
- Changes from baseline total bilirubin were significantly different between two arms for Week 2-24. It appears that the subjects in the TPV/r arm had about 0.1 mg/dL greater decrease than subjects in the CPI/r arm.
- Changes from baseline GGT were significantly different between two arms for Week 2-24. It appears that the subjects in the TPV/r arm had a median increase of 11.5-70 U/L while subjects in the CPI/r arm had a median decrease of 0.5-2.0 U/L.

Changes from baseline in total cholesterol, triglycerides and renal parameter creatinine are summarized in Table 16, Table 17 and Table 18, and Figure 12, Figure 13 and Figure 14.

- Changes from baseline in these lipids parameters were significantly different between the two treatment regimens, p <0.0001. Subjects in the TPV/r regimen had a median increase of 16-29 mg/dL in total cholesterol, significantly greater than a median change of -2.5-1/0 mg/dL for those in the CPI/r regimen. Subjects in the TPV/r regimen had a median increase of 31-59 mg/dL in triglycerides, compared to a median drop of 8-23 mg/dL in the CPI/r regimen.
- Changes from baseline in creatinine were significantly different between the two treatment regimens, p-values are between <0.0001~0.0029, by the K-W tests. It appears that the subjects in the TPV/r regimen had a median decline of 0.01 to 0.03 mg/dL, while the subjects in the CPI/r arm had a median increase of 0.01-0.04 mg/dL during the study. Additionally, significant differences between the two arms were observed for the creatinine measurements, p <0.0001.

### 3.3.1.2 1182\_0048

Table 19, Table 20 and Table 21 list basic statistics, respectively, for platelets, white blood cell count and hemoglobin by follow-up visit and treatment regimen. Figure 5, Figure 6 and Figure 7 illustrate median values for these parameters by follow-up visit and treatment regimen.

- Changes from baseline in HGB were significantly different between the two regimens at Weeks 2, 4 and 16 (p<0.05), not at Weeks 8 and 24 (p>0.05), by the K-W tests. Subjects in the TPV/r arm had a median reduction between 0.4 and 0.6 g/dL, a significant greater drop than those in the CPI/r arm where the median reduction was between 0.1-0.3 g/dL.

- Changes from baseline in platelets were not significantly different between the two regimens for Weeks 4, 8 and 16 and 24,  $p > 0.05$ , by the K-W tests. However, at Week 2, those subjects in the TPV/r arm had a median increase of 26,000 cells/mm<sup>3</sup>. This was significantly greater than a median increase of 8,000 cells/mm<sup>3</sup> for subjects in the CPI/r arm,  $p < 0.0001$ .
- Changes from baseline in WBC at Week 2 were significantly different between the two regimens,  $p < 0.05$ , by the K-W test. Subjects in the TPV/r had a greater median increase of  $0.5 \times 10^9/L$ , compared to a median increase of  $0.5 \times 10^9/L$  in the CPI/r arm.

Figure 8, Figure 9, Figure 10 and Figure 11 show median AST, ALT, Gamma GT and total bilirubin by follow-up visit and treatment regimen.

- Changes from baseline in ALT were significantly different between the two regimens for Weeks 2-24, p values were between  $< 0.0001$  to  $0.0050$ . It appears that the subjects in the TPV/r arm had a median ALT increase between 1-5 U/L, while subjects in the CPI/r arm had a median decrease between 1.4 – 2.5 U/L. Also, significant differences in ALT measurements between the two arms were observed with p values between  $< 0.0001$  ~  $0.0146$ . See Table 21.
- Changes from baseline in Gamma GT were significantly different between the two regimens during the 24 week study,  $p < 0.0001$ . It appears that the subjects in the TPV/r arm had a median Gamma GT increase of 12.8 U/L at Week 2 and continued their increase to 53 U/L at Week 24, while subjects in the CPI/r arm had almost no change. Further more, significant differences in Gamma GT measurements between the two arms were observed,  $p < 0.0001$ . See Table 22.
- Changes from baseline in total bilirubin were significantly different between the two regimens for Weeks 2-24, p values were between  $< 0.0001$  to  $0.0005$ . It appears that the subjects in the TPV/r arm had a median decrease between 0.06 ~ 0.10 U/L while subjects in the CPI/r arm had lesser median drop (or no change) from 0 ~ 0.05 U/L. In addition, significant differences in total bilirubin measurements were observed between the two arms,  $p < 0.0001$ . See Table 23.
- Changes from baseline in AST were not significantly different between the two regimens except for Week 2. At Week 2, subjects in the TPV/r arm had no change in median, while subjects in the CPI/r arm had a slight median reduction of 2.0 U/L,  $p = 0.0113$ .

Change from baseline in lipids total cholesterol and triglycerides, and creatinine (CRE) by follow-up visit and treatment regimen are summarized in and Table 25, Table 26 and Table 27. Figure 12, Figure 13 and Figure 14 show the median values for these enzyme parameters by follow-up visit and treatment regimen.

- Changes from baseline in these lipids parameters were significantly different between the two treatment regimens, p-values are between  $< 0.0001$  to  $0.0067$ . Subjects in the TPV/r regimen had a median increase of 23-30 mg/dL in total cholesterol, significantly greater than a maximum median change of 6 mg/dL for those in the CPI/r regimen. Subjects in the TPV/r regimen had a median increase of 16-43 mg/dL in triglycerides. Conversely, subjects in the CPI/r regimen had a median drop of 11-22 mg/dL.



- Changes from baseline in creatinine were significantly different between the two treatment regimens,  $p < 0.0001$  by the K-W tests. It appears that the subjects in the TPV/r regimen had a median decline of 0.01-0.05 mg/dL, while the subjects in the CPI/r arm had a median increase of 0-0.05 mg/dL during the 24 weeks of study.

### 3.3.1.3 1182\_0004

Change from baseline in platelets, hemoglobin and white blood cell count were not significantly different among three regimens.

The liver enzymes AST, ALT, Gamma GT and total bilirubin were summarized in Table 28, Table 29, Table 30 and Table 31. Figure 15, Figure 16, Figure 17 and Figure 18 show median change from baseline for these liver enzymes.

Changes from baseline in liver enzyme parameters did not differ significantly among treatment regimens, with the following exceptions.

- Changes from baseline in Gamma GT at Weeks 2 and 4 were significantly different among three regimens. The median Gamma GT increase in the TPV/r 1250/100 mg regimen was 18.5 U/L at Week 2 and 22.5 U/L at Week 4, significantly greater than a median increase of 1.8 U/L in the SQV/r arm and 6.0 U/L in the TPV/r 500/100 mg arm at Week 2, and a median increase of 4 U/L in the SQV/r arm at Week 4,  $p < 0.01$ . At Week 4, subjects in the TPV/r 500/100 mg arm had a median increase of 21.5 U/L, similar to those in the TPV/r 1250/100 mg arm.
- Changes from baseline in total bilirubin at Week 2 were significantly different amongst the three regimens. However, the median differences were 0- 0.1 mg/dL.
- Changes from baseline in ALT at Week 16 were significantly different among the three regimens: subjects in the SQV/r arm had an increase of 6.0 U/L, followed by subjects in TPV/r 1250/100 regimen and TPV/r 500/100 mg regimen,  $p < 0.05$ , by the K-W test.
- Changes from baseline in AST were significant different at Weeks 8 and 16, subjects in the SQV/r arm had a median increase of 5-8 U/L, greater than subjects in TPV/r 1250/100 regimen and TPV/r 500/100 mg regimen where slightly median reductions were observed,  $p < 0.01$ , by the K-W test.

No significant differences were found among the treatment regimens for change from baseline in total cholesterol and triglycerides, except for total cholesterol at Week 24.

Change from baseline in creatinine at Weeks 2, 4 and 8 were significantly different between treatment regimens,  $p$ -values = 0.0024-0.05. Subjects in the SQV/r 400/400 mg regimen had greater increase in median creatinine 0.04-0.1 mg/dL, compared to no change for those in the TPV/r regimens during the study period. See Figure 19 and Table 32.

### 3.3.1.4 1182\_0051

Due to the study design in 1182\_0051, change from baseline at Weeks 2 and 4 between the TPV/r arm and other CPI/r regimens may be relevant because TPV/r was added to other CPI regimens after the initial treatment for two weeks.

Figure 20 and Figure 21 show median values for hemoglobin and platelets by follow-up visit and treatment regimen. Table 33 lists basic statistics at Weeks 2 and 4 for hemoglobin and platelets.

- For hemoglobin, the only significant difference among four regimens was at Week 2, where subjects in the TPV/r regimen had a median drop of 0.6 g/dL and subjects in the PI/TPV/r regimens had a median drop between 0 to 0.2 g/dL,  $p < 0.0001$  by the K-W test. During the trial, the median decrease in hemoglobin was 0.2-0.3 g/dL. Note that the median baseline hemoglobin was 14.6g/dL in the TPV/r regimen, significantly greater than a median of 13.6 in the SQV/TPV/r regimen,  $p = 0.0371$  by the K-W test.
- There was no significant difference among four regimens regarding white blood cell count at Week 2 or Week 4. Overall, the median increases in WBC from baseline were 0.2 at Week 2 and 0.4 at Week 4.
- For platelets, the only significant difference among four regimens was those at Week 4, where subjects in the TPV/r regimen had a median drop of 3,800 cells/mm<sup>3</sup>, significantly greater than subjects in the other PI/TPV/r regimens where a median increase between 8,500 to 24,800 was observed,  $p = 0.001$  by the K-W test. Overall, the median increase was 5,000 cells/mm<sup>3</sup> at Week 2 and 11,500 cells/mm<sup>3</sup> at Week 4.

Table 34 and Table 35 summarize basic statistics for ALT, AST, GGT and TBILI by follow-up weeks and treatment regimen. Figure 22, Figure 23, Figure 24 and Figure 25 show median values, respectively, for the four liver enzymes by follow-up visit and treatment regimen.

- At Week 2, subjects in the TPV/r regimen had a median increase of 5.5 U/L in ALT and a median increase of 12.0 U/L in Gamma GT, and a median reduce of 0.1 mg/dL in total bilirubin from baseline, significantly greater than those in some of the PI/TPV/r regimens. Additionally, subjects in the SQV/TPV/r regimen had greater elevated AST, significantly greater than subjects in the LPV/TPV/r regimen. The p-values for the Week 2 comparisons in liver enzymes range from  $< 0.0001$  to 0.03.
- At Week 4, subjects in the TPV/r regimen had a median Gamma GT increase of 32 mg/dL from baseline, significantly greater than median change between 8-10 mg/dL for subjects in other PI/TPV/r regimens,  $p = 0.0002$ . Changes from baseline at Week 4 in liver enzymes AST, ALT and total bilirubin were not significantly different among four regimens.

Basic statistics by follow-up weeks and treatment regimen for lipids total cholesterol and triglycerides, and renal enzyme creatinine were summarized, respectively, in Table 36 and Table 37. Figure 26, Figure 27 and Figure 28 show median values for these enzymes by follow-up visit and treatment regimen.

- At Week 2, subjects in the TPV/r regimen had median increases of 16 mg/dL in total cholesterol and 47 mg/dL in triglycerides, significantly greater than a median reduction between 0.5-5.5 mg/dL in total cholesterol and a median change between -35.0 to 2.7 mg/dL in triglycerides for subjects in other PI/TPV/r regimens,  $p < 0.0001$ .
- At Week 2, subjects in the SQV/TPV/r regimen had a median increase of 0.12 mg/dL in creatinine, significantly greater than a median change between -0.05 to 0.02 mg/dL for subjects in other regimens,  $p < 0.0001$ .
- At Week 4, subjects in the four regimens had no significant differences in lipids parameters and creatinine,  $p > 0.05$ .

### 3.3.1.5 1182\_0052

There was no significant differences among three regimens regarding the change from baseline in WBC, HGB and Platelets,  $p > 0.05$ , by the K-W tests.

- For platelets, it appears that subjects in the TPV/r 500/100 mg regimen had less reduction in platelets, followed by subjects in the TPV/r 500/200 mg and subjects in the 750/200 mg regimen. For example, at Week 8, the median reductions were 4800, 7000 and 10800 cells/mm<sup>3</sup> for subjects in the TPV/r 500/100, 500/200 and 750/200 mg regimens, respectively. However, the dose-response is not statistically significant,  $p > 0.05$ . See Figure 29.

Figure 30, Figure 31 and Figure 32 show median values for AST, ALT and Gamma GT by follow-up visit and treatment regimen. Results with significant differences among treatment regimens were summarized in Table 38, Table 39 and Table 40. There were no significant differences among treatment regimens in change from baseline total bilirubin.

For the Weeks 2 and 4 comparisons, significant differences among treatment regimens were observed for change from baseline in ALT, AST and Gamma GT, not in total bilirubin.

- For the Week 8 comparisons, significant differences among treatment regimens were observed for change from baseline in ALT and Gamma GT, not in AST and total bilirubin.
- For the Weeks 16 and 24 comparisons, changes from baseline in any one of the four liver enzymes were not significantly different among treatment regimens.
- The dose-response effects in change from baseline AST, ALT and Gamma GT were observed: subjects in the TPV/r 500/100 arm had lesser median increases in median ALT, AST, Gamma GT, followed by those in the TPV/r 500/200 arm and those in the TPV/r 750/200 arm.

Figure 33, Figure 34 and Figure 35 show median change from baseline in total cholesterol, triglycerides and creatinine by follow-up visit and treatment regimen.

- Change from baseline in total cholesterol and triglycerides were not significantly different among treatment regimens, except for triglycerides at Week 8. At Week 8, subjects in the

TPV/r 500/200 mg regimen had greatest median increase of 115 mg/dL, compared with 45 and 35 mg/dL in TPV/r 500/100 and 750/200 regimens,  $p=0.0142$ . See Table 41.

- Change from baseline in creatinine was not statistically significantly different among treatment regimens, for the Weeks 2-24 comparisons,  $p>0.05$ .
- The change from baseline in these lipids and renal parameters may not be dose-related.

### 3.3.2 Change in DAIDS Laboratory Toxicity Grade

Changes in DAIDS toxicity grade status during the trial were summarized. Toxicity grades at baseline and during follow-up weeks are paired laboratory data. A method that would capture the highest toxicity grade or worst case scenario was applied. For example, if a subject's platelet count status was 'Normal' at baseline and Grade 1, Grade 1, Normal, Grade 1, respectively at Week 4, 8, 16 and 24 visit window, then the subject will be counted in a Normal to Grade 1 category. **This method provides only one transition state per subject as 'from Grade x at baseline' to 'Grade y during the trial'**. Therefore, the multiple Grade 3 or 4 events per subject will not be elaborated in this analysis.

#### 3.3.2.1 1182\_0012

DAIDS toxicity grade shift in platelets, HGB and WBC during the follow-up visits are summarized in Table 42. Number of subjects with toxicity grade shifts from Normal/Grade 1/Grade 2 at baseline to Grades 3 & 4 during the trial in the CPI/r and TPV/r regimens, respectively, were

- $n1:n2 = 3 : 0$  in platelet count;  $n1:n2 = 2 : 3$  in HGB; and  $n1:n2 = 14 (3.3\%) : 8 (1.8\%)$  in WBC.

Table 43 summarizes DAIDS grade shift in liver function enzymes AST, ALT, Gamma GT and total bilirubin. Number of subjects with toxicity grade shifts from Normal/Grade 1/Grade 2 to Grades 3 & 4 in the CPI/r and TPV/r regimens, respectively, were

- $n1:n2 = 3 (0.7\%) : 12 (2.8\%)$  in AST;
- $n1:n2 = 9 (2.1\%) : 23 (5.3\%)$  in ALT;
- $n1:n2 = 9 (2.1\%) : 104 (23.9\%)$  in Gamma GT;
- $n1:n2 = 6 (1.4\%) : 2(0.5\%)$  in total bilirubin.
- It appears that more subjects in the TPV/r regimen developed Grade 3 or 4 toxicity in AST, ALT, Gamma GT.

Table 44 summarize toxicity grade shift in selected lipids. Number of subjects with DAIDS Grade 3 or 4 elevations in the CPI/r and TPV/r regimens, respectively, were

- $n1:n2 = 2 (\%) : 12(\%)$  in total cholesterol; and

- $n1:n2 = 35$  (%): 84 (%) in triglycerides;
- It appears that more subjects in the TPV/r regimen developed DAIDS Grade 3 or 4 elevations in total cholesterol and triglycerides;

No subject developed Grades 3 and 4 elevations in creatinine during the trail.

The most frequent Grades 3 & 4 elevations in ten lab parameters was that in triglycerides ( $n=108$ ), followed by Gamma GT ( $n=94$ ), ALT ( $n=32$ ), WBC ( $n=21$ ), AST ( $n=15$ ) and total cholesterol ( $n=14$ ). Other parameters hemoglobin, platelets, total bilirubin and creatinine had less than ten DAIDS Grade 3 or 4 events.

Figure 36 shows percentage of subjects developing Grades 3 & 4 elevations in 0-3 laboratory parameters. During the study, 20.3% (62/306) in the CPI/r arm and 39.9% (123/308) in the TPV/r arm developed a total of 247 Grade 3 or 4 laboratory abnormalities, with a maximum of three number of parameters per subject in both arms. More subjects in the TPV/r arm had Grade 3 or 4 elevations in ten laboratory parameters. The mean number of parameters with a Grade 3 or 4 toxicity was 0.24 (std=0.52, total=73) for the CPI/r arm and 0.56 (std=0.81, total=174) for the TPV/r arm, respectively,  $p<0.0001$  by the K-W test.

Figure 37 illustrates the percentage of subjects who developed Grade 3 or 4 liver enzyme toxicities in up to three liver enzymes. Overall, 7.5% (23/306) subjects in the CPI/r arm and 22.1% (68/308) subjects in the TPV/r arm, developed Grade 3 or 4 liver enzyme toxicities,  $p<0.0001$ , by the Chi-square test. The frequencies of subjects who had a Grade 3 or 4 elevations in 0-3 liver parameters were 283:20:2:1 for the CPI/r arm and 240:53:12:3 for the TPV/r arm,  $p<0.0001$  by the Chi-square test.

These findings suggest that study subjects in the TPV/r regimen were more likely to have DAIDS Grade 3 or 4 elevations and Grade 4 elevations in ten selected laboratory parameters and LFTs.

### 3.3.2.2 1182\_0048

Toxicity grade shift in platelets, hemoglobin and white blood cell count during the follow-up visits are summarized in Table 45. Number of subjects with toxicity grade shifts from Normal/Grade 1/Grade 2 to Grades 3 & 4 in the CPI/r and TPV/r regimens, respectively, were

- $n1:n2 = 3 : 2$  in hemoglobin;  $n1:n2 = 1 : 3$  in platelets; and  $n1:n2 = 16 : 15$  in white blood cell count.

No significant differences were found between the two regimens in DAIDS Grade 3 or 4 elevations of these parameters.

Table 46 summarizes DAIDS Grade 3 or 4 elevations in liver function parameters AST, ALT, Gamma GT and total bilirubin. Number of subjects with DAIDS Grades 3 & 4 elevations in the CPI/r and TPV/r regimens, respectively, were

- $n1:n2 = 2$  (0.7%) : 7 (2.3%) for AST;

- n1:n2 = 4 (1.3%) : 22(7.1%) for ALT;
- n1:n2 = 19 (6.1%) : 61(19.6) for Gamma GT; and
- n1:n2 = 4 (1.3%) : 2(0.6%) for total bilirubin.

It appears that significantly higher proportions of subjects in the TPV/r regimen developed Grade 3 or 4 toxicity in AST, ALT or Gamma GT, than those in the CPI/r regimen.

Table 47 summarizes DAIDS toxicity grade shift from Normal/Grades 1 & 2 at baseline to Grades 3 and 4 in two lipids enzymes by treatment regimen. Number of subjects with DAIDS Grades 3 & 4 elevations in the CPI/r and TPV/r regimens, respectively, were n1:n2 = 0 (0%) :13(4.2%) in total cholesterol; and n1:n2 = 31 (10.1%) : 62(19.9%) in triglycerides. It appears that significantly higher proportions of subjects in the TPV/r regimen developed Grade 3 or 4 elevations in lipids in the TPV/r regimen than those in the CPI/r regimen.

There was just one subject in the CPI/r arm who had a Grade 3 elevation from Grade 1 at baseline in creatinine during the trial.

In summary, the most frequent Grades 3 & 4 elevations in ten laboratory parameters was in triglycerides (n=102), followed by Gamma GT (n=80), white blood cell count (n=31) and AST (n=26).

Figure 38 shows percentage of subjects developing Grade 3 or 4 elevations in 0-4 lab parameters. During the trial, 18.7% (79/422) in the CPI/r arm and 35.1% (151/430) in the TPV/r arm developed a total of 298 Grade 3 or 4 laboratory test value abnormalities, with a maximum number of 3 parameters per subject in the CPI/r arm and 4 parameters in the TPV/r arm. More subjects in the TPV/r arm had Grade 3 or 4 elevations in laboratory parameters. The mean number of parameters with a Grade 3 or 4 toxicity per subject was 0.21 (std=0.46) for the CPI/r arm and 0.49 (std=0.77) for the TPV/r arm, respectively,  $p < 0.0001$  by the K-W test. Likewise, more subjects in the TPV/r arm had Grade 4 elevations in ten laboratory parameters: 5.9% (25/422) in the CPI/r arm and 12.3% (53/430) in the TPV/r arm,  $p = 0.0012$ , by the Chi-square test.

Figure 39 shows percentage of subjects developing Grade 3 or 4 LFTs. Overall, 7.1% (30/422) subjects in the CPI/r arm and 20.5% (88/430) subjects in the TPV/r arm, developed a Grade 3 or 4 LFTs, or one or more in ALT, AST, Gamma GT, and total bilirubin,  $p < 0.0001$ , by the Chi-square test. The mean number of parameters with Grades 3 & 4 LFTs was 0.08 (std=0.31, maximum=2) for the CPI/r arm and 0.27 (std=0.59, maximum=3) for the TPV/r arm, respectively,  $p < 0.0001$  by the K-W test. The frequencies of subjects who had Grades 3 & 4 elevation in 0-3 liver parameters were 392: 24:4:0 for the CPI/r arm and 342:68:14:6 for the TPV/r arm,  $p < 0.0001$  by the Chi-square test.

These findings suggest that study subjects in the TPV/r regimen were more likely to have Grade 3 or 4 elevations in overall toxicities including liver function toxicities.

### 3.3.2.3 1182\_0004

The DAIDS toxicity grade shift in platelets, hemoglobin and white blood cell count during the follow-up visits were evaluated. No subject developed Grades 3 and 4 elevations in hemoglobin. There was only one subject in the TPV/r 500/100 mg regimen with platelet count toxicity grade switch from normal to Grade 3 toxicity.

- There were n1:n2:n3 = 3: 2: 2 in the SQV/r 400/400 mg, TPV/r 1250/100 mg, TPV/r 500/100 mg regimens, respectively developed Grade 3 or 4 elevations in white blood cell count.

Table 48 summarizes toxicity grade shift in liver function parameters AST, ALT and Gamma GT. Only one subject in the TPV/r 1250/100 mg had a Grade 3 or 4 elevations in total bilirubin. Number of subjects with Grades 3 & 4 elevations in the SQV/r 400/400, TPV/r 1250/100, and TPV/r 500/100 regimens, respectively, were

- n1:n2:n3 = 1 (3.6%) :2 (8.0%) :2(8.4%) for AST;
- n1:n2:n3 = 2 (7.2%): 2(8.0%) :3(12.5%) for ALT; and
- n1:n2:n3 = 2 (7.2%) : 1(4.0%) :4(16.6%) for Gamma GT.

Toxicity grade shift in lipids during the follow-up visits are summarized in Table 49. Shift to Grades 3 and 4 from Normal/Grades 1 & 2 at baseline in the SQV/r 400/400, TPV/r 1250/100, and TPV/r 500/100 regimens, respectively, were n1:n2:n3 = 1:0:2 in total cholesterol and n1:n2:n3 = 2 :3:4 in triglycerides.

During the trial, none of the study subjects with a shift to Grade 3 or 4 in creatinine.

During the study period, there were 11 subjects (one female, ten male) developed Grade 3 or 4 in ten selected laboratory parameters: n1:n2:n3= 3(11%): 3(12%) :5(21%). Of those, ten subjects has toxicity grade shift to Grade 3 and only one subject in the TPV/r 1250/100 mg regimen had toxicity grade shift to Grade 4. Most of the subjects had more than 8 laboratory parameters with Grade 3 or 4 elevations.

In summary, the DAIDS toxicity shifts to Grade 3 or 4 were rare for platelets, hemoglobin, creatinine, total bilirubin and total cholesterol, but more common for white blood cell count, triglycerides, ALT, AST and Gamma GT. DAIDS Grade 3 or 4 elevations in these laboratory parameters did not show TPV/r dose-response trends.

### 3.3.2.4 1182\_0051

DAIDS toxicity grade shift from Normal/Grades 1 & 2 at baseline to Grade 3 or 4 during the follow-up visits in platelets, hemoglobin and white blood cell count are summarized in Table 50.

Shift from Normal/Grades 1 & 2 at baseline to Grade 3 or 4 during the trial were rare for platelets and hemoglobin, and more common for white blood cell count. Number of patients with shift from Normal/Grades 1 & 2 to Grade 3 or 4 in the APV/TPV/r, LPV/TPV/r, SQV/TPV/r and TPV/r, respectively were:

n1:n2:n3:n4 = 2:1:0:2 for platelets;

n1:n2:n3:n4 = 1:0:1:1 for hemoglobin; and

n1:n2:n3:n4 = 8(9.6%):1(1.2%):3(3.7%):3(4.5%) for white blood cell count, p=0.0751.

DAIDS Grade 3 or 4 elevations in liver enzymes ALT, AST, Gamma GT and total bilirubin are summarized in Table 51 and Table 52. Grade shift from Normal/Grades 1 & 2 at baseline to Grade 3 or 4 during the trial were rare in total bilirubin, and more common in AST, ALT and Gamma GT. Number of patients with shift from Normal/Grades 1 & 2 to Grade 3 or 4 in the APV/TPV/r, LPV/TPV/r, SQV/TPV/r and TPV/r, respectively, were

- n1:n2:n3:n4 = 7:0:2:1 for AST, p=0.0129 by Fisher's test;
- n1:n2:n3:n4 = 11:2:3:7 for ALT, p=0.0197 by the Chi-square test;
- n1:n2:n3:n4 = 1:2:0:0 for total bilirubin; and
- n1:n2:n3:n4 = 20 (24%) : 9(11%) : 14 (16%) : 17 (26%) for Gamma GT, p=0.0714 by the Chi-square test.

The DAIDS toxicity grade shift in lipids total cholesterol, triglycerides and renal enzyme creatinine are summarized in Table 53.

- Shifts to DAIDS Grade 3 or 4 in total cholesterol were rare, n1:n2:n3:n4 = 1:1:1:2 for the APV/TPV/r, LPV/TPV/r, SQV/TPV/r and TPV/r regimens, respectively.
- Shift to DAIDS Grade 3 or 4 in triglycerides were common, n1:n2:n3:n4 = 14(16.9%), 21(25.3%), 11(13.4%) and 10 (14.9%) for the APV/TPV/r, LPV/TPV/r, SQV/TPV/r and TPV/r regimens, respectively, p=0.1950 by the Chi-square test.

The highest grade was Grade 2 severity in 1182\_0051. No subject developed a Grade 3 or 4 elevations in creatinine.

In summary, during the trial, there were n1:n2:n3:n4= 42 (51.9%):32(39.0%):26(32.1%):30(44.8%) subjects in the APV/TPV/r, LPV/TPV/r, SQV/TPV/r and TPV/r regimens developed DAIDS Grade



3 or 4 elevations in at least one of ten laboratory parameters,  $p=0.0719$  by the Chi-square test.

- Among those, more subjects in the APV/TPV/r arm (28.4%,  $n=23$ ) and TPV/r arm (29.9%,  $n=20$ ) developed DAIDS Grade 3 or 4 elevations in liver enzymes AST, ALT, Gamma GT and total bilirubin, significantly greater than those in the LPV/TPV/r arm (12.2%,  $n=10$ ) and SQV/TPV/r (16.1%,  $n=13$ ),  $p=0.0130$ .
- Among those,  $n1:n2:n3:n4= 15 (18.5\%):11(13.4\%):12(14.8\%):7(10.5\%)$  subjects developed Grade 4 elevations, in the four regimes, respectively,  $p>0.05$ .

The most common DAIDS Grade 3 or 4 elevations in ten selected parameters were those in Gamma GT (18%,  $n=56$ ) and triglycerides ( $n=53$ ), followed by ALT ( $n=23$ ), white blood cell count ( $n=15$ ) and AST ( $n=10$ ). Grade 3 or 4 elevations in total cholesterol ( $n=5$ ), platelets ( $n=5$ ), total bilirubin ( $n=3$ ), hemoglobin ( $n=3$ ) and creatinine ( $n=0$ ) were rare.

On average, subjects in the APV/TPV/r arm developed 0.79 Grade 3 or 4 elevations in ten laboratory parameters ( $std=0.93$ ,  $total=64$ ), followed by those in the TPV/r arm ( $mean=0.66$ ,  $std=0.84$ ,  $total=44$ ), LPV/TPV/r arm ( $mean=0.50$ ,  $std=0.71$ ,  $total=41$ ), and SQV/TPV/r arm ( $mean=0.42$ ,  $std=0.70$ ,  $total=34$ ),  $p=0.0313$  by the K-W test.

On average, subjects in the APV/TPV/r arm developed 0.47 ( $std=0.88$ ) Grade 3 or 4 elevations in four liver enzymes, followed by those in the TPV/r arm ( $mean=0.37$ ,  $std=0.65$ ), SQV/TPV/r arm ( $mean=0.21$ ,  $std=0.54$ ), and LPV/TPV/r arm ( $mean=0.15$ ,  $std=0.42$ ),  $p=0.0107$  by the K-W test.

Figure 40 shows the distribution of subjects with no shift, 1, 2 and 3 lab parameter shifts.

### 3.3.2.5 1182\_0052

Changes in DAIDS toxicity grade in platelets, hemoglobin and white blood cell count during the follow-up visits are summarized in Table 53. P-values for testing the significance of linear trend in toxicity shift to Grade 3 or 4 and TPV/r dose were obtained by the two-sided Cochran-Armitage trend test.

There were only a few subjects with platelet count and HGB toxicity grade switch from Normal/Grades 1&2 to Grades 3 & 4. Only one subject in the TPV/r 500/200 mg regimen and one in the TPV/r 750/200 mg regimen had platelet count switch from normal to Grade 3. Only one subject in the TPV/r 500/100 mg regimen had HGB switch from Grade 2 to Grade 4.

- There were  $n1:n2:n3 = 4: 3: 6$  in the TPV/r 500/100 mg, 500/200 mg and 750/200 mg regimens, respectively had DAIDS Grades 3 and 4 elevations in WBC. No association between exposure dose level and occurrence in Grade 3 or 4 elevation was observed,  $p>0.05$  by the Cochran-Armitage test.

Table 55 summarizes DAIDS toxicity grade shift in liver function parameters ALT, AST, Gamma

GT and total bilirubin. Number of subjects with toxicity grade shifts from Normal/Grade 1/Grade 2 to Grades 3 & 4 in the TPV/r 500/100, TPV/r 500/200, and TPV/r 750/200 regimens, respectively, were

- n1:n2:n3 = 1 (1.4%) :4 (5.6%) :5(7.0%), p=0.0028 for AST;
- n1:n2:n3 = 2 (2.7%) : 5(6.9%) :12 (16.8%), p= 0.1046 for ALT;
- n1:n2:n3 = 10 (13.7%) : 20(27.8) :23(32.4%),p=0.0090 for Gamma GT;
- n1:n2:n3 = 0 (0.0%) :1(1.4%) :3(4.2%), p=0.0604 for total bilirubin.

It appears that subjects in the TPV/r 500/100 mg regimen had significantly lesser DAIDS Grade 3 or 4 elevations in AST and Gamma GT than those in the 500/200 and 750/200 mg regimens.

DAIDS grade shift in two lipids and renal enzymes during the follow-up visits are summarized in Table 56. Shift to DAIDS Grade 3 or 4 from Normal/Grades 1 & 2 at baseline in the TPV/r 500/100 mg, 500/200 mg and 750/200 mg regimens, respectively, were as follows.

- n1:n2:n3 = 1 (1.4%) :2(2.8%) :4(5.6%) in total cholesterol, p=0.1492.
- n1:n2:n3 = 12 (16.4%):18(25.0%):17 (23.9%) in triglycerides, p=0.2722.

No subjects had Grade 3 and 4 elevations in creatinine during the trial.

There is no evidence to show the dose-response regarding the DAIDS Grade 3 or 4 elevations in total cholesterol and triglycerides.

DAIDS Grade 3 or 4 elevations in ten selected laboratory parameters and liver function toxicity (LFT) may be TPV/r dose dependent.

During the trial, 121 (56%) subjects developed a Grade 3 or 4 elevations for at least one of the ten parameters.

Table 57 shows the frequencies of subjects who developed Grade 3 or 4 elevations by parameter of interest.

- Figure 41 shows the percentage subjects developed Grade 3 or 4 elevations in a maximum of five lab parameters. Overall, 21(28.8%), 34(47.2%) and 40(56.3%) subjects in the TPV/r 500/100 mg, 500/200 mg and 750/200 mg regimens, respectively, had ever developed a DAIDS Grade 3 or 4 elevations, p=0.0096, by the Chi-square test.
- On average, subjects in the TPV/r 500/100 mg arm developed mean number of 0.38 (std=0.70, total=28) DAIDS Grade 3 or 4 elevations in ten laboratory parameters, significantly lesser than mean of 0.78 (std=1.01, total=56) in the TPV/r 500/200 mg arm and mean of 1.03 (std=1.24, total=73) in the TPV/r 750/200 mg arm, p<0.001 by the K-W test, indicating that subjects developed DAIDS Grade 3 & 4 elevations in ten selected laboratory parameters may be associated with the level of exposure in TPV/r.

- Overall, 12(18.2%), 23(34.9%) and 31(47.0%) subjects in the TPV/r 500/100 mg, 500/200 mg and 750/200 mg regimens, respectively, had ever developed a DAIDS Grade 3 or 4 elevations in four LFTs,  $p=0.0018$ , by the Chi-square test.
- More than half DAIDS Grade 3 or 4 elevations in ten parameters were contributed by Grade 3 or 4 elevations in LFTs (ALT, AST, Gamma GT and total bilirubin). On average, subjects in the TPV/r 500/100 mg arm developed mean of 0.19 (std=0.49, total=14) Grade 3 or 4 elevations in ALT, AST, Gamma GT and total bilirubin, significantly lesser than mean of 0.47 (std=0.82, total=34) in the TPV/r 500/200 mg arm and mean of 0.66 (std=0.91, total=47) in the TPV/r 750/200 mg arm,  $p<0.001$  by the K-W test, indicating that subjects developed DAIDS Grade 3 & 4 elevations in LFT may be associated with the level of exposure in TPV/r.
- The mean numbers of DAIDS Grade 4 elevations were 0.15, 0.28 and 0.35 for subjects in the TPV/r 500/100 mg, 500/200 mg, and 750/200 mg arms, respectively,  $p=0.0891$  by the K-W test.

In addition, gender differences in developing DAIDS Grade 3 or 4 elevations or LFT were not significantly different,  $p>0.05$ .

### 3.4 Additional Analyses for RESIST Trials

#### 3.4.1 Time to First DAIDS Grade 3 or 4 LFTs Elevations

Kaplan-Meier (K-M) analyses of time to first DAIDS Grade 3 or 4 in any of the liver enzymes ALT, AST, Gamma GT and total bilirubin via approach were summarized by 1182\_0012 and 1182\_0048, respectively. The K-M curves show the estimates of Grade 3 or 4 event-free probabilities by treatment regimen, and the log-rank test was used to statistically test of difference in proportion of subjects who developed a Grade 3 or 4 LFTs (liver function toxicities) between treatment regimens.

Table 58 summarizes distributions of developed a Grade 3 or 4 in liver and lipids parameters by treatment arm and study.

In 1182\_0012,

- Time to first Grade 3 or 4 in ALT ( $p=0.0255$ ) and Gamma GT ( $p<0.0001$ ) were significantly shorter for subjects in the TPV/r arm than those in the CPI/r arm.
- Time to first DAIDS Grade 3 or 4 in AST ( $p=0.0914$ ) and total bilirubin ( $p=0.0882$ ) were slightly shorter for subjects in the TPV/r arm than subjects in the CPI/r arm, but the differences were not significantly different between the two arms.

- Figure 42 shows the K-M curves of time to first DAIDS Grade 3 or 4 in any of the four LFTs: AST, ALT, Gamma GT and total bilirubin, by treatment regimens. During the first 12 weeks of trial, subjects in the TPV/r arm developed DAIDS Grade 3 or 4 in LFTs at a significant faster pace than those in the CPI/r arm,  $p < 0.0001$  by the log-rank test. Subjects in the TPV/r arm were more likely to develop Grade 3 or 4 in any of liver toxicity than those in the CPI/r arm, largely contributed by Grade 3 or 4 elevations in Gamma GT and ALT.
- Figure 43 shows the K-M curves of time to first DAIDS Grade 3 or 4 in three LFTs: AST, ALT and total bilirubin, by treatment regimens. Time to first Grade 3 or 4 LFTs in any of three liver enzymes was not significantly different between the two arms,  $p = 0.1077$  by the log-rank test.

In 1182\_0048,

- Time to first DAIDS Grade 3 or 4 in ALT ( $p = 0.0028$ ) and Gamma GT ( $p = 0.0002$ ) was significantly different between the two arms.
- Time to first DAIDS Grade 3 or 4 in AST ( $p = 0.1358$ ) and total bilirubin ( $p = 0.2522$ ) were not significantly different between the two arms.
- Time to first DAIDS Grade 3 or 4 in any of the AST, ALT, Gamma GT and total bilirubin was highly significantly different between the two arms,  $p < 0.0001$  by the log-rank test. See Figure 44.
- Time to first DAIDS Grade 3 or 4 in three LFTs AST, ALT and total bilirubin was also significantly different between the two arms,  $p = 0.0277$  by the log-rank test. See Figure 45.

### 3.4.2 Time to First DAIDS Grade 3 or 4 Elevations in Lipids

The K-M analyses of time to first DAIDS Grade 3 or 4 in total cholesterol and triglycerides were summarized by 1182\_0012 and 1182\_0048, respectively.

Figure 46 shows the K-W curves of time to first Grade 3 or 4 in total cholesterol and triglycerides by treatment regimen for 1182\_0012.

- Time to first Grade 3 or 4 in total cholesterol ( $p = 0.0255$ ) and triglycerides ( $p < 0.0001$ ) was significantly shorter for subjects in the TPV/r arm, compared those for subjects in the CPI/r arm. Subjects in the TPV/r arm were more likely to develop Grade 3 or 4 total cholesterol and triglycerides events.

Figure 47 shows the K-M curves regarding time to first Grade 3 or 4 in total cholesterol and triglycerides by treatment regimen for 1182\_0048.

- Time to first DAIDS Grade 3 or 4 in total cholesterol ( $p = 0.0189$ ) and triglycerides ( $p = 0.0011$ ) were significantly shorter for subjects in the TPV/r arm than those in the CPI/r arm. Subjects in the TPV/r arm were more likely to develop DAIDS Grade 3 or 4 in total cholesterol and triglycerides than those in the CPI/r arm.

### 3.4.3 Time to First DAIDS Grade 3 or 4 ALT/AST

It is of particular clinical interest to find out the baseline risk factors associated with abnormalities of AST (SGOT-Serum Glutamic Oxaloacetic Transaminase) and/or ALT (SGPT-Serum Glutamic Pyruvic Transaminase) occurred during the TPV/r trials.

Cox Proportional Hazard Regression Models were used for the evaluations of associations between time to first Grade 3 or 4 ALT/AST elevations and treatment regimen, baseline HCV/HBV infections, baseline AST, ALT, CD4+, race (Whites versus Non-whites) and gender. Combined data for 1182\_0012 and 1182\_0048 were used for evaluation. In evaluation of statistical significance, type I error of 0.05 level by the Wald t-test was used. Additionally, Cox Proportional Hazard Regression Models were also used for the evaluations of associations between time to first Grade 3 or 4 ALT/AST elevations and baseline characteristics by treatment regimen, respectively.

- The medical history (CDISC name: MH) databases show that 1182\_0012 and 1182\_0048 trials, respectively, had 63 and 35 subjects with history of HBV/HCV infections, after deleting duplicated records.
- Overall, time to first Grade 3 or 4 elevations in ALT/AST was significantly associated with treatment, baseline HBV/HCV status and baseline ALT. The significant terms were: treatment regimen ( $p=0.0017$ ), baseline HBV/HCV infections ( $p=0.0005$ ) and baseline ALT ( $p<0.0001$ ). The estimated hazard ratios were 2.4 (TPV/r versus CPI/r), 3.3 (baseline HBV/HCV infections or not), and 1.03 (per unit increase in baseline ALT).
- For subjects in the TPV/r arm, the significant terms were: baseline HBV/HCV infections ( $p=0.0339$ ), baseline ALT ( $p<0.0001$ ), and baseline AST ( $p=0.0181$ ). In the TPV/r arm, subjects who were infected with HBV/HCV at entry, those with greater value in baseline ALT and lower level in baseline AST were more likely to develop a Grade 3 or 4 ALT/AST elevations with a faster pace than others. The estimated hazard ratios were 2.8 (baseline HBV/HCV infections or not), 0.96 (per unit increase in baseline AST) and 1.04 (per unit increase in baseline ALT).
- For subjects in the CPI/r arm, the significant term was baseline HBV/HCV infections ( $p=0.0103$ ). In the CPI/r arm, subjects who were infected with HBV/HCV at entry were more likely to develop a Grade 3 or 4 ALT/AST elevations with a faster pace than others. The estimated hazard ratios were 3.8 (baseline HBV/HCV infections or not).

Patients with chronic Hepatitis B or Hepatitis C co-infection or elevations in transaminases are at approximately 2.5-fold risk for developing further transaminase elevations or hepatic decompensation. Additionally, Grade 3 and 4 increases in hepatic transaminases were observed in 6% of healthy volunteers in Phase 1 studies and 6% of subjects receiving APTIVUS/ritonavir in Phase 3 studies.

### 3.4.4 Time to First LDL or HDL Abnormality

Until recently, it was assumed that total cholesterol at 200 mg/dL and above were at increased risk for heart disease. Now we know that not the total of high-density lipoprotein (HDL) and low-density lipoprotein (LDL), but other criterion regarding HDL and LDL such as a ratio between them becomes important. In this review, the LDL & HDL abnormality status was defined as the occurrence of either a low HDL of <40 mg/dL or a high LDL of >160 mg/dL, suggested by the medical officer Dr. Andrea James.

- Changes from baseline LDL during the 24 weeks were significantly different between treatment regimen, p values ranging <0.0001 ~ 0.0159, by the K-W tests. The median LDL was consistently higher in the TPV/r arm than in the CPI/I arm in the RESIST trials. For example, in 1182\_0012, subjects in the TPV/r arm had greater median increases between 12.5-22.5 mg/dL in LDL, significantly greater than median increases between 1.0-6.0 mg/dL in the CPI/r arm. See Table 59 and Figure 49.
- Changes from baseline HDL during the 24 weeks were not significantly different between treatment regimen,  $p > 0.05$ , by the K-W tests. See Table 60 and Figure 51.

The analysis of time to first occurrence of either a low HDL of <40 mg/dL or a high LDL of >160 mg/dL for the two Phase III trials was requested by the medical officers. However, we found 16.3% in the CPI/r arm and 30% in the TPV/r arm had missing LDL when HDL values were available (See Table 61). In addition, the quantitative interactions between treatment and time to first low HDL or time to first high LDL were also identified. Hence, time to first LDL/HDL abnormality was replaced by time to LDL abnormality and time to first HDL abnormality respectively.

Time to first LDL of >160 mg/dL was not significantly different between the two regimens,  $p > 0.05$  by the log-rank tests for either trial, respectively. However, it appears that the subjects in the TPV/r arm had slightly better responses than those in the CPI/r arm. Figure 48 shows Kaplan-Meier curves by study and treatment regimen.

Time to a first HDL of <40 mg/dL was significantly different between the two regimens,  $p = 0.0050$  and  $0.0002$  for 1182\_0012 & 1182\_0048, respectively. Subjects in the CPI/r regimen had developed an abnormal HDL at a significantly faster pace than those in the TPV/r regimen. See Figure 50.

We further investigated the association of total cholesterol and LDL/HDL abnormality during the trial. It appears that in the CPI/r regimen, the median total cholesterol was 16 mg/dL greater in the LDL/HDL normal group, than those in the LDL/HDL abnormal group,  $p < 0.0001$ , by the K-W test. In the TPV/r regimen, the median total cholesterol was 5.6 mg/dL greater in the LDL/HDL normal group, than those in the LDL/HDL abnormal group,  $p > 0.05$ . See Table 62.

### 3.4.5 Virologic Response by Baseline PI Mutations

The following reports the analysis of associations between baseline PI mutation and virologic response at Week 24 for subjects in the TPV/r arm of the RESIST Trials Phase III trials. In the analysis, virologic response was defined as a subject having a confirmed 1 log<sub>10</sub> decrease from baseline at Week 24. “VR rate” is used below to refer to percentage of subjects with a virologic response. Baseline PI mutation data at 27 codons were selected by the review team. Contingency table approach and Chi-square statistic were used to test a significance of an estimated association between presence or absence in a PI mutation location and the corresponding VR rate.

Figure 52 shows the VR rates in those subjects by the absence of baseline PI mutation positions. Likewise, Figure 53 and Figure 54 show the VR rates by the absence of baseline PI mutation positions for T-20 use and non-T20 use, respectively.

#### Overall TPV/r arm

Overall, the VR rates were significantly associated with the presence or absence of seven baseline PI mutation at codons I13, K20, E36, M36, I47, G48 and I54, respectively, with p-values ranging from <0.0001 to 0.0349. The absence or presence of other 20 PI mutations did not affect the VR rates. As shown in Table 63, presence of baseline PI mutation at six codons I13, K20, E36, M36, I47 and I54, results in significantly lower VR rates in the TPV/r arm (ranging 31%-43%), compared to when they were absent (50%-59%). On the contrary, presence of baseline PI mutation at codon G48, results in significantly higher VR rate (63%) compared to when it was absent (44%).

#### TPV/r alone without T-20

Among those without T-20 use, the VR rates were significantly associated with the presence or absence of baseline PI mutation at 12 codons I13, K20, D30, V32, E36, M36, I47, G48, I54, Q58, D60 and I84, respectively, with p-values ranging from <0.0001 to 0.0466.

It appears that absence of baseline PI mutations at codons I13, K20, D30, V32, E36, M36, I47, G48, I54, Q58, D60 and I84, and the presence of baseline PI mutation at codons D30 and G48 were associated with significantly greater virologic response at Week 24 among subjects with TPV/r alone without T-20. As shown in Table 64, absence of baseline PI mutation at codons I13, K20, V32, E36, M36, I47, I54, Q58, D60 and I84, results in significantly greater VR rates in the TPV/r arm (ranging 42%-57), compared to when they were present (18%-35%). On the contrary, presence of baseline PI mutation at codons D30 or G48 were associated with significantly lower virologic response at Week 24: 39% for D30 and 27% for G48, compared to when they were absent: 75% (small sample size 6/8) for D30 and 55% for G48.

Adjusting for 27 comparisons, the type I error via the Bonferroni approach would be 0.0019. Thus, the absence of the four baseline PI mutation at codons I13, M36, I47 and I54 were still associated with significantly greater virologic response at Week 24.

#### TPV/r with T-20

Among T-20 users, the VR rate was significantly associated with the presence or absence of only one baseline PI mutation at codon L89,  $p$ -value=0.0346. The VR rates were 50% and 69%, respectively, for the presence or absence of PI mutation at codon L89. See Table 65.

The virologic response at Week 24 was not significantly affected by the baseline PI mutations among subjects using T-20 with TPV/r, adjusting for multiplicity (27 comparisons),  $p > 0.05$ .

#### Correlations between PI mutations

Seven baseline PI mutations at I13, K20, E36, M36, I47, G48 and I54 locations individually showed associations with significantly virologic response at Week 24 for the TPV/r arm. To evaluate correlations among these PI mutations, contingency table analysis and McNemar statistic was used.

Table 66 shows  $p$ -values by the McNemar's statistics to test whether the probability of presence of one baseline PI mutation location such as I13 equals the probability of presence of the other baseline PI mutation location such as G48 (marginal homogeneity). Among 21 baseline PI mutation codon pairs,

- K20 and M36, I47 and G48 are the only two pairs with  $p$ -values  $> 0.05$ . We failed to reject the marginal homogeneity in presence/absence of the two codon pairs, meaning that the presence/absence of K20 (I47) would be expectedly correlated to the presence/absence of M36 (G48).
- Comparisons from the other 19 PI mutation pairs show that the probability of presence/absence of one baseline PI mutation location is significantly different from that in the other baseline PI mutation location,  $p$ -value between  $< 0.0001$  to  $0.0005$ .
- A type I error would be 0.0024 after adjusting for 21 comparisons. We concluded that the 21 baseline PI mutation pairs among I13, K20, E36, M36, I47, G48 and I54 would not be expectedly correlated, except for K20 and M36, I47 and G48.

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## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The statistical analyses in this review focused on the evaluation of secondary efficacy and safety endpoints. Gender and race comparisons of the secondary safety endpoints regarding DAIDS Grade 3 or 4 elevations or time to first DAIDS Grade 3 or 4 elevations in AST/ALT were summarized. Analyses of baseline PI mutation and virologic response at Week 24 in TPV/r arm by T-20 use were also provided.

### 4.1 Gender Comparisons in DAIDS Grade 3 or 4 Elevations

Gender comparisons in frequencies of subjects with DAIDS Grade 3 /4 or Grade 4 elevations in ten parameters, and Grade 3 or 4 elevations in four LFTs by treatment regimens and two Phase III trials were summarized in Table 67.

Within each regimen, there were no significant gender differences in development of a Grade 3 or 4 elevations or Grade 4 elevations in ten laboratory parameters, and Grade 3 or 4 elevations in LFTs with one exception. In the TPV/r arm of 1182\_0048, significantly higher percentage of male subjects (14.1%) developed Grade 4 elevations than in female subjects (4.8%).

In Study 1182\_0052, no significantly gender differences in developing DAIDS Grade 3 or 4 elevations, Grade 4 elevations, or Grade 3 or 4 elevations in LFTs were observed.

### 4.2 Time to First DAIDS Grade 3 or 4 Elevations in AST/ALT

In this review, subgroup analyses were conducted to investigate the associations between baseline risk factors and time to first DAIDS Grade 3 or 4 AST/ALT elevations, respectively, for the TPV/r arm and the CPV/r arm. The baseline risk factors include the history of HBV/HCV infections, race (White versus Non-whites), gender, baseline ALT, and baseline AST measurements. Cox Proportional Hazard Regression Models were used for evaluations. Results by treatment arms appeared to be different.

- In the TPV/r arm, the significant terms were: HBV/HCV infections prior to entry ( $p=0.0339$ ), baseline ALT ( $p<0.0001$ ) and AST ( $p=0.0181$ ). In the TPV/r arm, subjects had a history of HBV/HCV infections at entry, with greater value in baseline ALT and lower level in baseline AST would more likely develop a Grade 3 or 4 ALT/AST elevations with a faster pace than others. The estimated hazard ratios were 2.8 (baseline HBV/HCV infections or not), 0.96 (per unit increase in baseline AST) and 1.04 (per unit increase in baseline ALT).
- In the CPI/r arm, the significant term (predictors) was baseline HBV/HCV infections ( $p=0.0103$ ). In the CPI/r arm, subjects who were infected with HBV/HCV at entry would likely develop a Grade 3 or 4 ALT/AST elevations with a faster pace than others. The estimated hazard ratios were 3.8 (baseline HBV/HCV infections or not).

### 4.3 Virologic Response at Week 24 by Baseline PI Mutations

Per microbiological review Dr. Lisa Neager's requests, virologic response at Week 24 by baseline PI mutations were investigated for subjects in the TPV/r arms of Phase III studies 1182\_0012 and 1182\_0048. Subgroup analyses by enfuvirtide or T-20 use at entry were performed. The virologic response (VR) was defined as percentage of subjects having a confirmed 1 log<sub>10</sub> decrease from baseline at Week 24.

#### TPV/r alone without T-20

Among those receiving TPV/r alone without T-20, the VR rates were significantly associated with the presence or absence of 12 out of 27 baseline PI mutation at codons I13, K20, D30, V32, E36, M36, I47, G48, I54, Q58, D60 and I84, respectively, with p-values ranging from <0.0001 to 0.0466. See Table 64.

It appears that the absence of ten baseline PI mutation at codons I13, K20, D30, V32, E36, M36, I47, G48, I54, Q58, D60 and I84, or the presence of baseline PI mutation at codons D30 and G48 were associated with significantly greater virologic response at Week 24 among non-T-20 users. Adjusting for 27 comparisons, the type I error via the Bonferroni approach would be 0.0019. Thus, the presence of four baseline PI mutations at codons I13, M36, I47 and I54 were significantly associated with greater virologic response at Week 24.

#### TPV/r with T-20

Among those receiving TPV/r and T-20, the virologic response at Week 24 was significantly associated with the presence or absence of only one baseline PI mutation at codon L89, p-value=0.0346. The VR rates were 50% and 69%, respectively, for the presence or absence of PI mutation at codon L89. See Table 65.

Taking multiple comparisons into account, the virologic response at Week 24 was not affect by the baseline PI mutations among subjects using T-20 with TPV/r.

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## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

This statistical review directly addressed several issues in support medical officers and reviewers from other disciplines in FDA's review of NDA21,814.

At the early stage of the NDA21,814 review it was ambiguous what should be done as a second statistical reviewer. After discussing with medical officers, it was clearer that the analyses of seven secondary safety endpoints regarding the laboratory test values for Phase II Studies 1182\_0052, 1182\_0051 and 1182\_0004 were needed, in addition to the analyses of selected secondary efficacy endpoints for Study 1182\_0051. Later, the number of the secondary safety parameters was requested to increase from seven to ten and the safety analyses on the two Phase III studies were also added. Specific topics for some combination of safety endpoints were subsequently added.

Different from a typical statistical review of a NDA for the evaluation of primary efficacy endpoints, this statistical review and evaluation was based on (1) the collective laboratory data from two Phase III trials 1182\_0012 and 1182\_0048, and three Phase II studies 1182\_0004, 1182\_0051 and 1182\_0052 for the evaluation of secondary efficacy and safety parameters; (2) the collective efficacy data from Phase II study 1182\_0051 for the evaluation of secondary efficacy parameters; and (3) the collective efficacy and baseline PI mutation data from the TPV/r arms of 1182\_0012 and 1182\_0048 for the evaluation of associations between baseline PI mutation and virologic responses; and (4) the collective secondary efficacy and safety parameters from 1182\_0012 and 1182\_0048 for the evaluation of specific topics requested by the medical officers.

It was this reviewer's preference to use raw laboratory data and time variables to compute study weeks and summary statistics for each visit. When generating summary tables and plots systematically for five studies, several data issues regarding the DAIDS classification for grading severity of laboratory test values were identified.

In the following, we summarize several statistical and data issues identified during the review.

#### 5.1.1 Statistical Issues

1. The risk assessment of secondary safety efficacy endpoints was essentially post-hoc, exploratory and data-driven sensitivity analysis. It was not a comprehensive one.
  - The selections of secondary safety and efficacy parameters to be analyzed were suggested by the medical officers for three Phase II trials during the review process. Two methods were employed in evaluation of laboratory test values (LTV): change from baseline in LTV and in the Division of Acquired Immunodeficiency Syndrome, NIAID, NIH (DAIDS) classification for grading severity of LTV.
2. The analyses of safety endpoints were mainly exploratory to look for safety signals. Hence, the

problems of multiplicity in analyses of secondary safety endpoints would not be our concerns. For the discussion of multiplicity in safety variables, please see Reference 2.

The type I error had not been adjusted for multiplicity in the summary of secondary safety parameters. However, safety signals concerning the elevations of liver function and lipids enzymes in several studies were very apparent. Even with adjusting for multiplicity, elevated ALT, total bilirubin, Gamma GT, total cholesterol and triglycerides in subjects of the TPV/r arm would also be significantly greater than subjects in the CPI/r arm at  $\alpha=0.05$  level since majority of the p-values were much lower than 0.0001. For instance, adjusting for 60 comparisons via Bonferroni approach, a p-value of 0.0083 ( $\alpha'=0.05/60=0.00083$ ) would be used to quantify significance.

When evaluating the virologic response at Week 24 by 27 selected baseline PI mutations for the two Phase III studies, we adjusted the type I error for 27 comparisons.

To control for false positive findings, conservative test statistics and methods were used throughout the sensitivity analyses. The non-parametric statistics were used for the comparisons of change from baseline in LTV among treatment regimens. When comparing change from baseline in DAIDS grade in LTV among treatment regimens, percentage of subjects with DAIDS normal/Grade 1 or 2 at baseline and later developed Grade 3 or 4 elevations was summarized and compared among treatment regimen, although the data were those of the multi-state transition structure.

3. One should be cautious when making a conclusion or explanation from the results of secondary efficacy and safety parameters for the five Phase II/III studies reported in this document.
  - The two Phase III trials had an escape clause at Week 8 of the trial, allowing subjects in the control group to discontinue their randomized trial if they lack of initial virologic response. A significantly higher proportion of subjects in the CPI/r arms ha discontinued treatment before Week 24 and was mainly contributed to virologic failure. For details please see statistical reviewer Dr. Rafia Bhore's review. Therefore, the significantly higher proportion of subjects in the TPV/r arm developed DAIDS Grade 3 or 4 in liver and lipids elevations may be due to significantly different length of follow-up in part. However, the escape clause at Week 8 should have limited impact on change from baseline in LTVs, especially for the evaluations at Weeks 2, 4 and 8.
  - The Phase II trial 1182\_0051 was designed as a two-phase study: the treatments were administered for two weeks. At Week 2, TPV/r 500/100 mg b.i.d. was added to three other PI-containing regimens. Therefore, the results for the secondary efficacy parameters and change from baseline in LTV at Week 2 may be appropriate to report. Other results for the secondary safety parameters should be exploratory, because the effects of TPV/r compared to those by other CPI/r could not be separated after Week 2.
4. In addition to the duplicated records and missingness commonly found in laboratory databases,

some other data quality problems were also identified in evaluation of ten laboratory parameters for five studies.

- In the laboratory databases, the toxicity grades of laboratory test values coded by the sponsor did not appear to be consistent with those by the DAIDS's classifications.
- The upper limit normal (ULN) has been used to determine DAIDS grade for a specific laboratory parameter. Multiple ULN values were found for some of the laboratory parameters. The distribution of ULN value for a laboratory parameter appears to be significantly different between the TPV/r and the CPI/r arms for a Phase III study.
- Databases for laboratory test values for some trials appear not to be thoroughly scrutinized even though the sponsor submitted data multiple times. Some of the parameters were not completed loaded in the most recent EDR databases for this NDA submissions.

In communication with the sponsor, it became clear that we can not use sponsor's coded toxicity grading data for analyses. As a result, this reviewer recoded some of the toxicity grades according to the DAIDS criteria used by the sponsor for Study 1182\_0051 to report Grade 3 or 4 elevations in these selected lab parameters.

To ensure the quality review of laboratory data, our experiences indicate:

- 1) The reliability of coding DAIDS classification for grading severity and the subsequent evaluation using multiple ULN values is still an issue to be resolved;
  - 2) Sponsors should explore the accuracy of the coding process and provide data without obvious coding mistakes; and
  - 3) In the future, FDA should create a testing system to scan the laboratory data ensuring the quality of data.
5. We have noticed significant differences in length of follow-up period between the TPV/r arm and other CPI/r arms in some of the five studies, even though the same cut-off date was used for the treatment regimen in each study. For example, the mean or median follow-up times for the ALT measurements were significantly longer in the TPV/r arm than those in the other CPI/r arm in Studies 1182\_0004, 1182\_0012 and 1182\_0048, not in Studies 1182\_0051 and 1182\_0052. We found:
- In 1182\_0012, subjects in the CPI/r arm had a mean (median) follow-up time of 132 (134) days and 150 (168) days in the TPV/r arm; and in 1182\_0048, subjects in the CPI/r arm had a mean (median) follow-up time of 122 (115) days and 138 (161) days in the TPV/r arm;  $p < 0.0001$  for both trials, by the K-W test;
  - In 1182\_0004, subjects in the TPV/r 1250/100 mg arm had a median/mean of 388.4/352.8 days, followed by 230.4/299.0 days for those in the TPV/r 500/100 mg arm, and 164.9/206.3 days for those in the SQV/r arm,  $p = 0.0274$  by the F-test, and the significant difference was between two TPV/r regimens: subjects in the TPV/r 1250/100

mg arm had a significantly greater median and mean follow-up time than those in the SQV/r arm,  $p < 0.05$  by the Turkey test; and

- The follow-up time among regimens were within 10 days in 1182\_0051 and 1182\_0052,  $p > 0.05$ . This included 154-162 days in mean and 166-168 days in median in 1182\_0051 and 165-174 days in mean and 174-184 days in median in 1182\_0052.

A longer follow-up of laboratory test values in the TPV/r arm would also contribute to the greater cumulative number of DAIDS Grade 3 or 4 elevations in LFTs.

### 5.1.2 Collective Evidence

Based on our evaluation of the collective evidence from two Phase III and three Phase II studies, we have the following conclusions for the selected lab parameters. The conclusion of selected secondary efficacy endpoints for the RESIST trials and the Phase II Study 1182\_0051 is provided in Section 6 Appendices.

1. Based on available laboratory data through Week 24 from the two Phase III trials, we conclude that the subjects in the TPV/r arm had apparent excess risk of liver and lipids enzyme abnormalities.

- Compared to subjects in the CPI/r arm, subjects in the TPV/r arm had significantly greater increases in ALT, Gamma GT and total bilirubin, total cholesterol and triglycerides, and greater decreases in creatinine than those in the CPI/r arm. In addition, subjects in the TPV/r regimen had significantly greater reductions in hemoglobin and increases in platelets for most of the Weeks 2-24 studies. For example, one can see in Figure 9 that median ALT was consistently higher in the TPV/r arm than in the CPI/r arm in RESIST trials. The other parameters mentioned above show similar patterns, as can be seen in the main report.
- The most common Grade 3 or 4 elevations for the two trials were in triglycerides, Gamma GT, white blood cell count, ALT, AST and total cholesterol.
- Compared to the CPI/r arms, significantly higher percentages of patients in the TPV/r arm developed Grade 3 / 4 or Grade 4 elevations in ten lab parameters, and Grade 3 or 4 elevations in four liver enzymes (Table 67). For example, there were 7.3% subjects in the CPI/r arm developed Grade 3 or 4 elevations in LFTs, significantly lower than 21.1% in the TPV/r arm.
- Within each regimen, there were no significant gender differences in development of a Grade 3 or 4 elevations in ten parameters, Grade 4 elevations in ten parameters and Grade 3 or 4 LFTs with one exception. In the TPV/r arm of 1182\_0048, significantly higher percentage of male subjects developed Grade 4 elevations than those in female subjects.

2. Results from the Week 2 data in Phase II trial 1182\_0051 should partially support the above findings because of the study design. The subjects in this trial were those who failed the inclusion

criterion regarding baseline PI mutation and thus were those who may be in more advance stage of HIV-1 infection at entry.

- At Week 2, subjects in the TPV/r arm had significantly greater increase in total cholesterol, triglycerides, Gamma GT and greater decrease in hemoglobin, compared to subjects in the other CPI/r regimens. Subjects in the TPV/r and SQV/r arms had significantly greater increase in ALT, compared to subjects in the APV/r and LPV/r arms.

3. Based on available laboratory data through Week 24 from the dose-optimization Phase II trial 1182\_0052 suggest significantly greater increases in median AST, ALT and Gamma GT from baseline prior to Week 16. Subjects in the TPV/r 500/100 mg arm had lesser increase in median AST, ALT and Gamma GT, followed by the TPV/r 500/200 mg arm, and the TPV/r 750/200 mg arm. Significantly dose-response effects were observed respectively for AST and Gamma GT but not ALT. Significantly dose-response effect was also observed for the combination of these four liver enzyme parameters.

- More appropriately, the significance in dose-response effects on these parameters should be determined from the plasma TPV/r concentrations data and drug-drug interaction data. Due to the study design, the three regimens had two levels of TPV (500 and 750 mg) and two levels of RTV (100 and 200), the assumption of linear effect from TPV and RTV should be clarified.

4. Based on available laboratory data through Week 24 from the Phase II trial 1182\_0004, we observed significantly differences in median Gamma GT from baseline at Weeks 2 and 4, ALT at Week 16 and AST at Weeks 8 and 16 among the TPV/r 500/100 mg, TPV/r 1250/100 mg and the SQV/r arms. Subjects in the TPV/r arms had greater increases in Gamma GT than those in the SQV/r arm. No clear dose-response effect was observed between the TPV/r 500/100 mg and the TPV/r 1250/100 mg arms.

- The comparisons of change in DAIDS Grade 3 or 4 elevations may not be needed due to small sample sizes. For example, a total of seven subjects developed DAIDS Grade 3 or 4 elevations in Gamma GT.

5. Based on available baseline PI mutation data on 27 selected codons and virologic response data at Week 24 (percentage of subjects having a confirmed 1 log<sub>10</sub> decrease from baseline) in the TPV/r arm for the two Phase III trials, we concluded the following.

Overall, the virologic response at Week 24 were significantly associated with the presence or absence of seven baseline PI mutation at codons I13, K20, E36, M36, I47, G48 and I54, respectively. The absence or presence of other 20 PI mutations did not affect the virologic response rates. As shown in Table 61, presence of baseline PI mutation at the following six codons I13, K20, E36, M36, I47 and I54, results in significantly lower virologic response rates in the TPV/r arm in the ranging 31%-43%, compared to when they were absent (50%-59%) . However, presence of baseline PI mutation at codon G48, results in significantly higher virologic response rate (63%) compared to when it was absent (44%).

The virologic response rates at Week 24 were significantly associated with baseline PI mutation at codons I13, M36, I47 and I54 among subjects using TPV/r without T-20 at entry, but not affected by the baseline PI mutations among subjects using T-20 with TPV/r, after adjusting for multiplicity.

## 5.2 Conclusions and Recommendations

This statistical review directly addresses issues requested by medical officers and microbiologic other reviewers in support of the priority review of NDA21,814 for the accelerative approval of APTIVUS™ (tipranavir) 500 mg given with 200 mg ritonavir (RTV,r) as compared with the control group of comparator protease inhibitors boosted with ritonavir.

Based on collective evidence of laboratory data in two large Phase III trials 1182\_0012 and 1182\_0048, we conclude that the subjects in the TPV/r arm developed excess risk of liver and lipids enzyme abnormalities, in contrast to those in the comparator arms (CPI/r). Data from three Phase II trials 1182\_0004, 1182\_0051 and 1182\_0052, also partially support the conclusion.

Based on available baseline PI mutation at 27 selected codons and virologic response data at Week 24 in the TPV/r arm for the two Phase III trials, we concluded that significantly higher proportion of subject with the virologic response at Week 24 were associated with the presence of baseline PI mutation at codons I13, M36, I47 and I54 among subjects receiving TPV/r without T-20 at entry. The virologic response at Week 24 was not affected by the baseline PI mutations among subjects receiving TPV/r with T-20. Both results were those after adjusting for multiplicity.

A quality review of laboratory data depends on data reliability including a valid coding of the DAIDS classification for grading severity. Evaluation of laboratory data using multiple ULN values is still an issue to be resolved. In the future, FDA should create a testing system to scan the laboratory data in order to ensuring the quality of data to be reviewed.

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## 6 APPENDICES

1. Based on the Weeks 2 and 4 secondary efficacy data for the Phase II Study 1182\_0051, we conclude that subjects in the TPV/r regimen had significantly greater HIV-1 viral load reduction and virologic response at Week 2.

- At Week 2, subjects in the TPV/r regimen had a significantly greater median HIV-1 viral load drop of more than 1.2 log<sub>10</sub>, compared to a drop between 0.2-0.4 log<sub>10</sub> for subjects in other PI/TPV/r regimens.
- At Week 2, subjects in the TPV/r regimen had significantly greater virologic responses compared to those in the other PI/TPV/r regimens. A significantly higher proportions of subjects in the TPV/r regimen had viral load decline of 1 log<sub>10</sub> or more (51%), viral load decline of 0.5 log<sub>10</sub> or more (62%), and with viral load < 400 copies/mL (16%), compared to 25%, 37% and 6%, respectively for these virologic responses, in the other PI/TPV/r regimens.
- At Week 4 no significant differences were found between the TPV/r and other PI/TPV/r regimens regarding the virologic responses. In addition, percentage of subjects with viral load < 50 copies/mL at Weeks 2 and 4 were not significantly different among treatment regimens.

2. Based on available CD4+ cell count data through Week 24 we conclude that changes from baseline CD4+ cell count were significantly different between the two regimens: at Weeks 4, 8 and 16 for 1182\_0012, and at Weeks 2-24 for 1182\_0048. During the 24 weeks of trials, subjects in the TPV/r arms had significant greater median CD4+ cell count increases between 9-25 cells/mm<sup>3</sup> for 1182\_0012, and 14-24 cells/mm<sup>3</sup> for 1182\_0048, respectively, than median increases between 9-29 in the CPI/r arms.

## 7 REFERENCES

1. Clinical Data Interchange Standards Consortium, Inc., 15907 Two Rivers Cove, Austin, Texas, USA 78717.
2. Point to Consider on Multiplicity Issues in Clinical Trials. The European Agency for the Evaluation of Medical Products: Evaluation of Medicine for Human Use. London, 19 September, 2002.

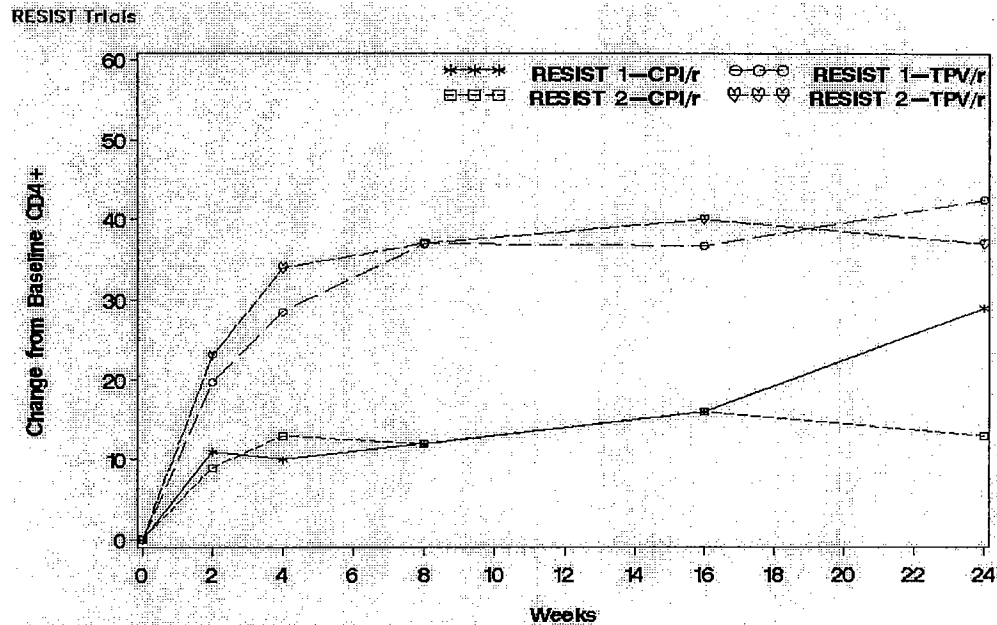


Figure 1: RESIST Trials: Median Change From Baseline CD4+ (cells/mm<sup>3</sup>)

Study 1182\_0051

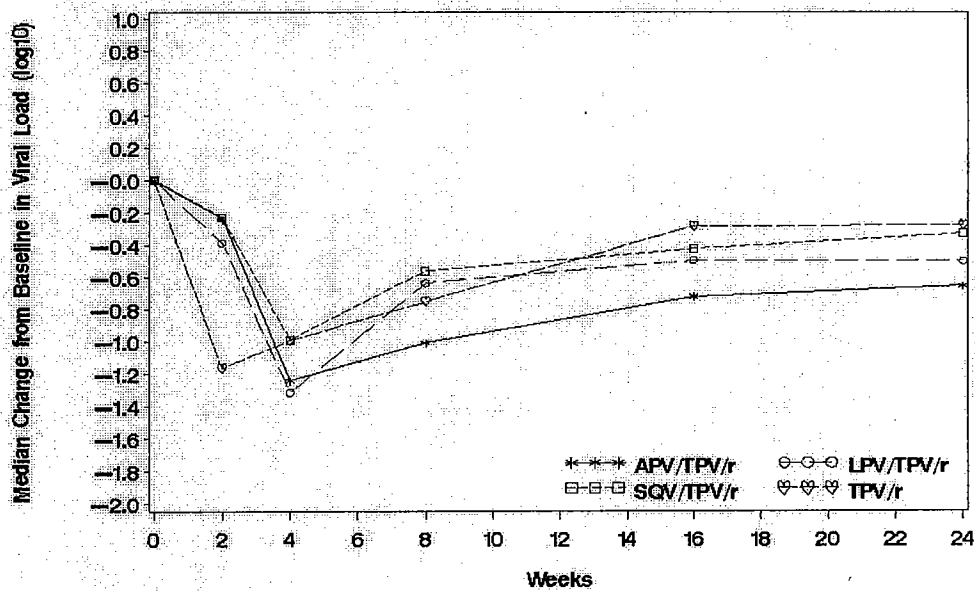


Figure 2: 1182\_0051: Median Change from Baseline Viral Load (Log<sub>10</sub> Copies/mL)

Study 1182\_0051

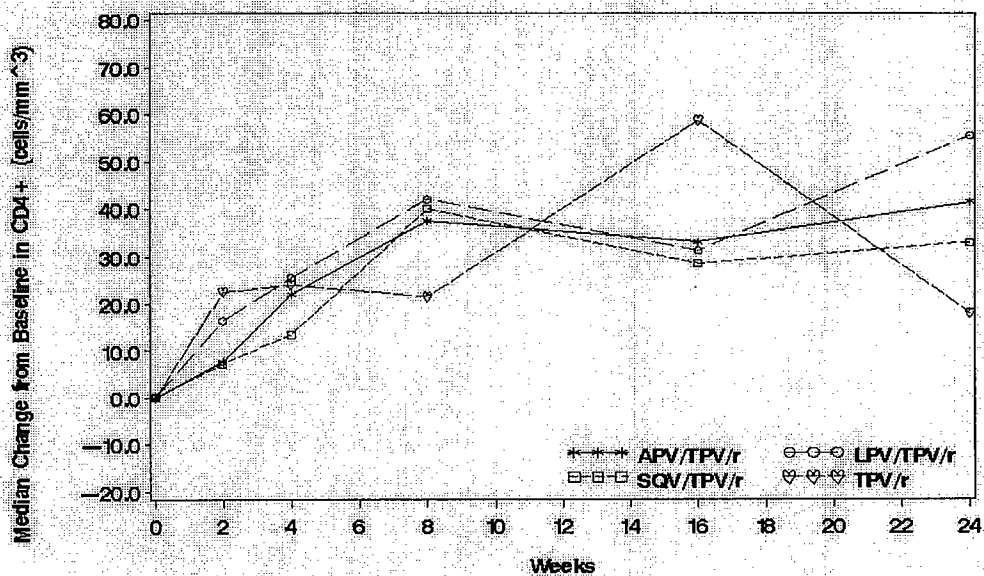


Figure 3: 1182\_0051: Median Change from Baseline CD4+ Cell Count (cells/mm<sup>3</sup>)

Study 1182\_0051

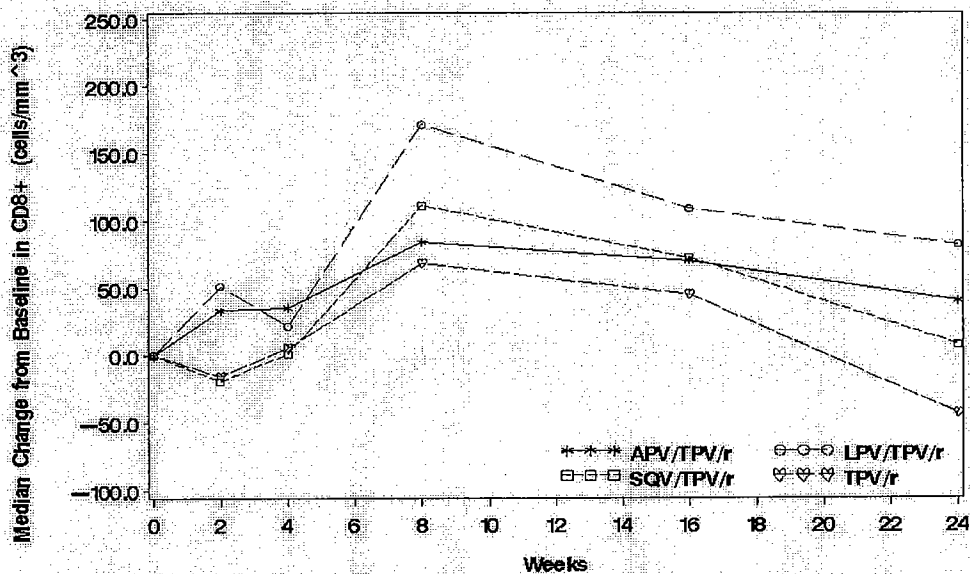


Figure 4: 1182\_0051: Median Change from Baseline CD8+ Cell Count (cells/mm<sup>3</sup>)

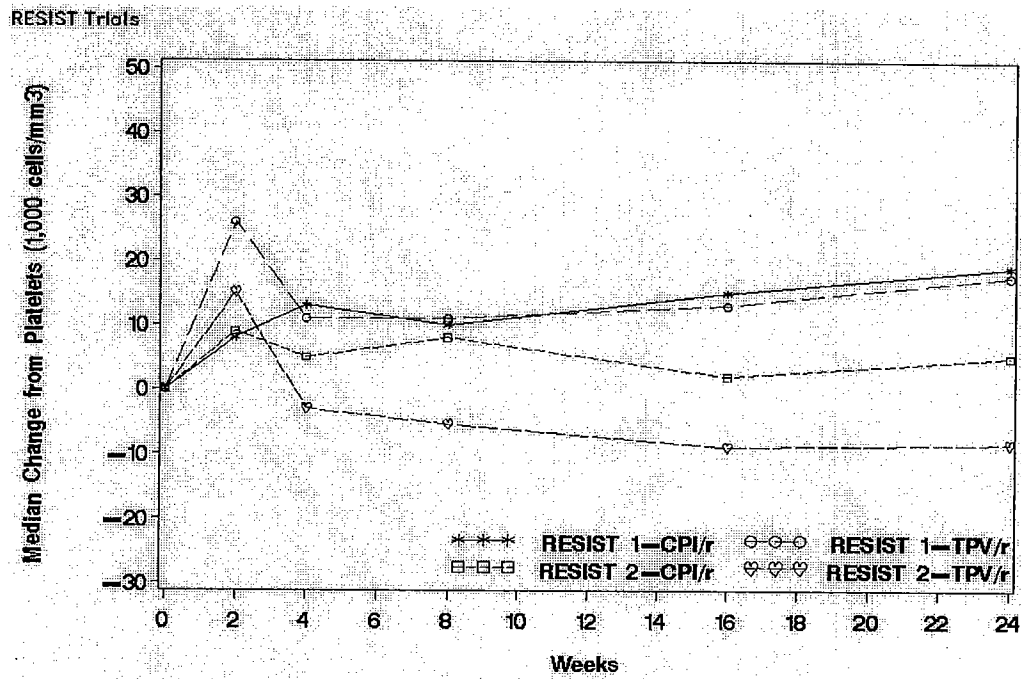


Figure 5: RESIST Trials: Median Change from Baseline Platelet \*1,000 cells/mm<sup>3</sup>

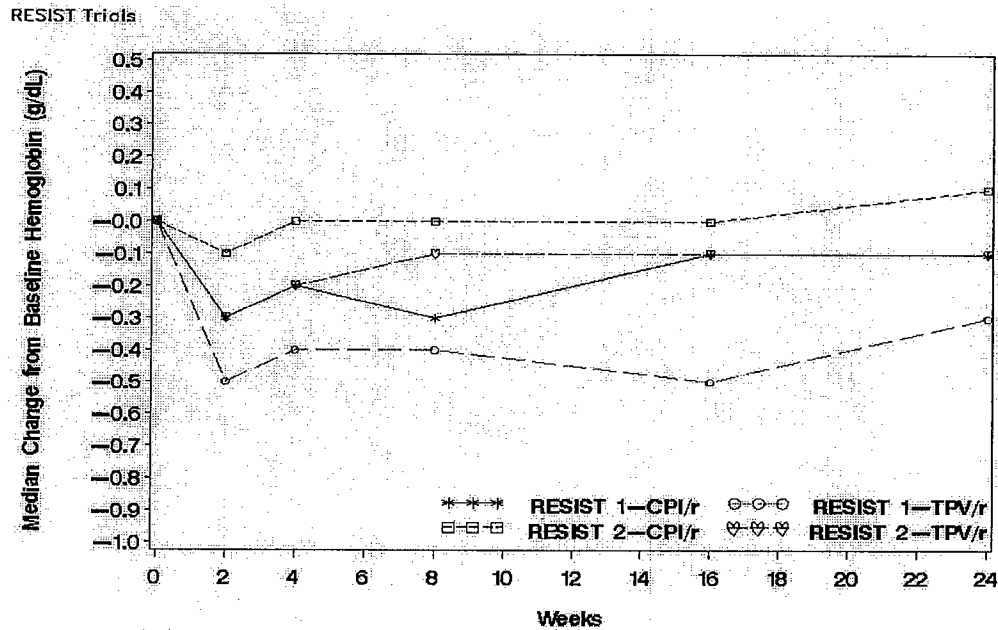


Figure 6: RESIST Trials: Median Change from Baseline Hemoglobin (g/dL)

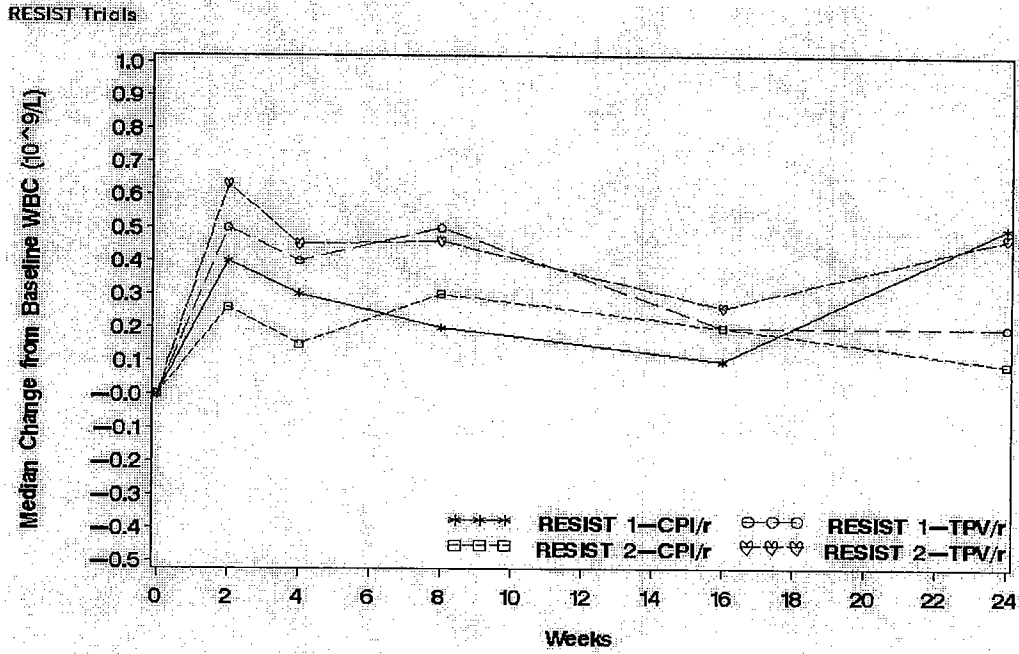


Figure 7: RESIST Trials: Median Change from White Blood Cell Count ( $10^9$  cell/L)

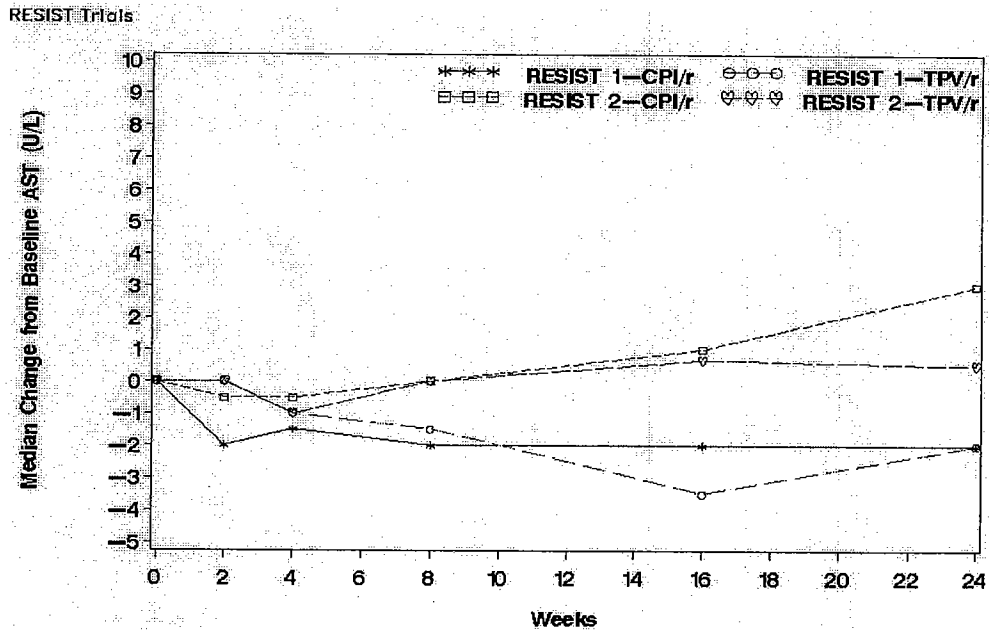


Figure 8: RESIST Trials: Median Change from Baseline AST (SGOT, U/L)

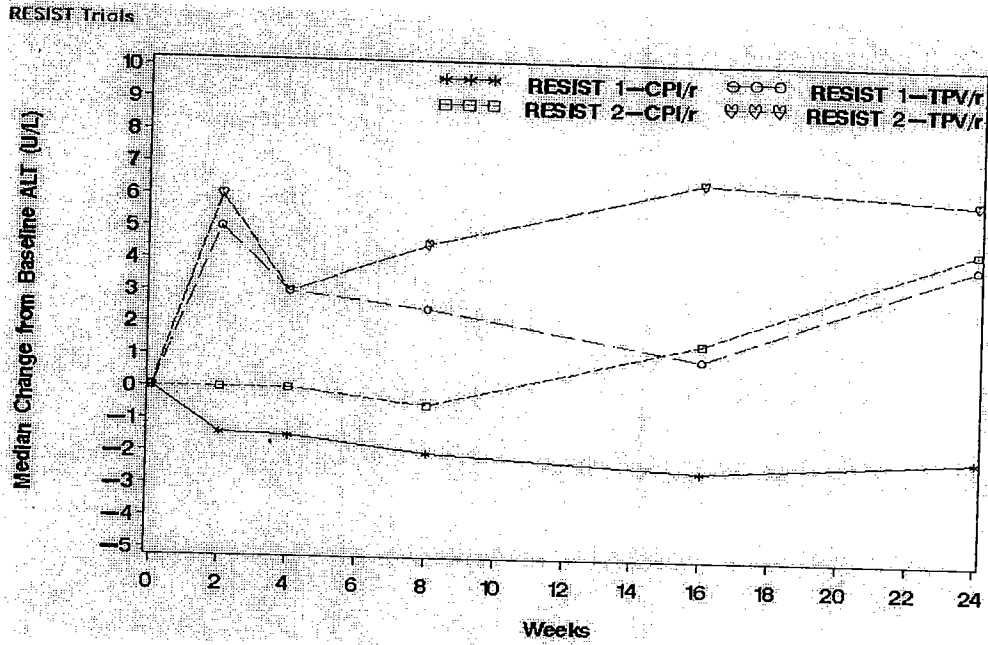


Figure 9: RESIST Trials: Median Change From Baseline ALT (U/L)

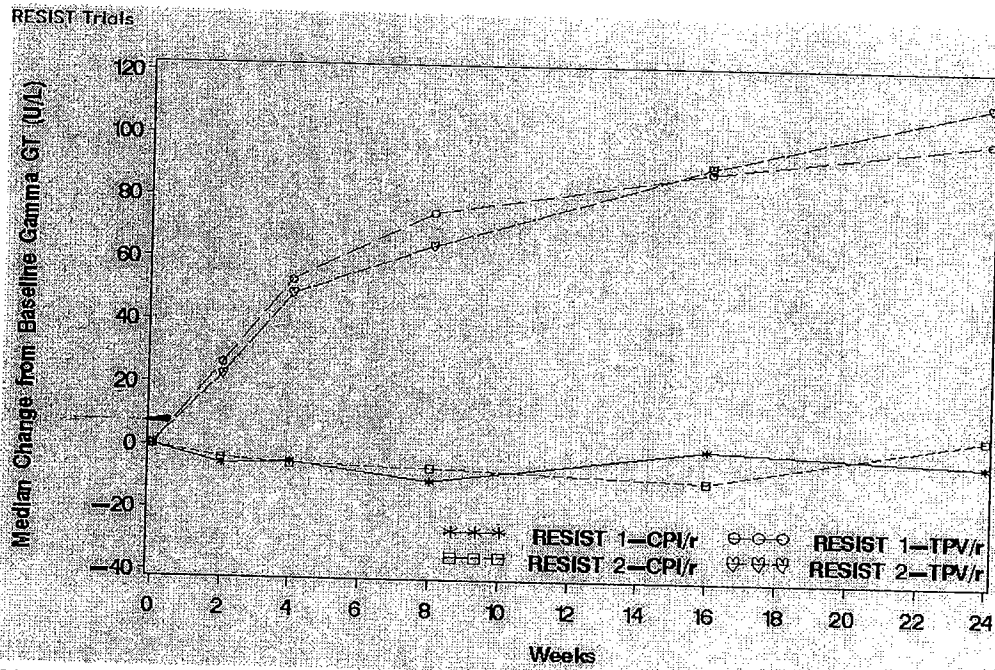


Figure 10: RESIST Trials: Median Change from Baseline Gamma GT (U/L)

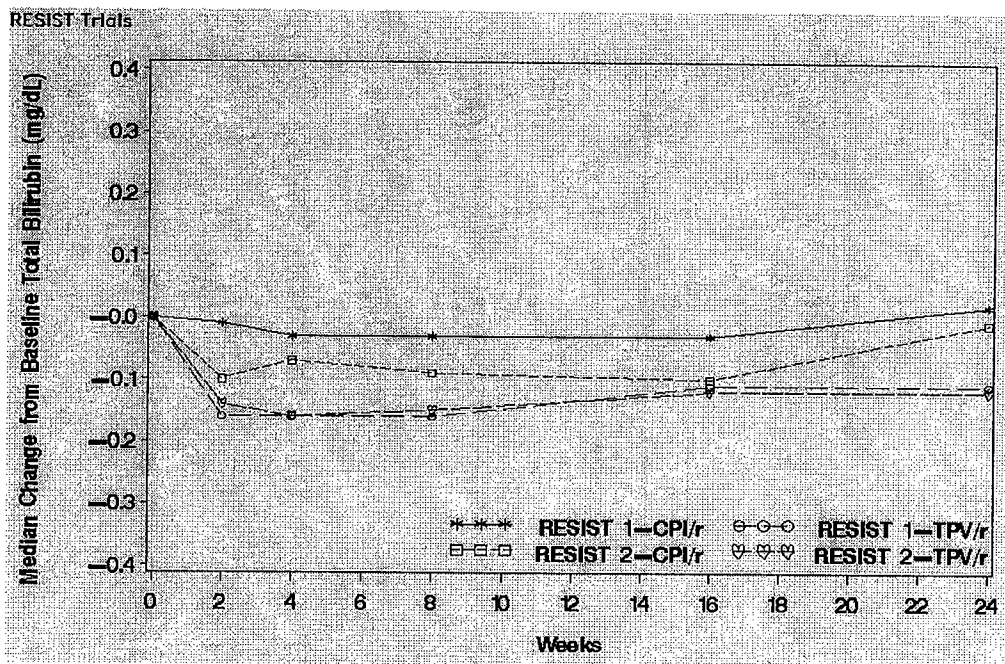


Figure 11: RESIST Trials: Median Change from Baseline Total Bilirubin (mg/dL)

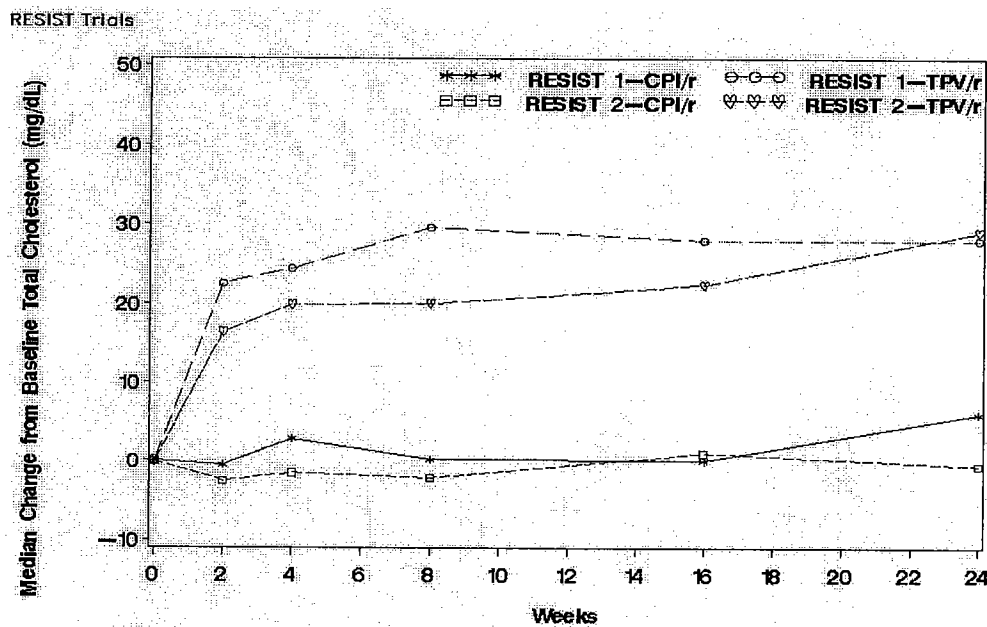


Figure 12: RESIST Trials: Median Change from Baseline Total Cholesterol (mg/dL)

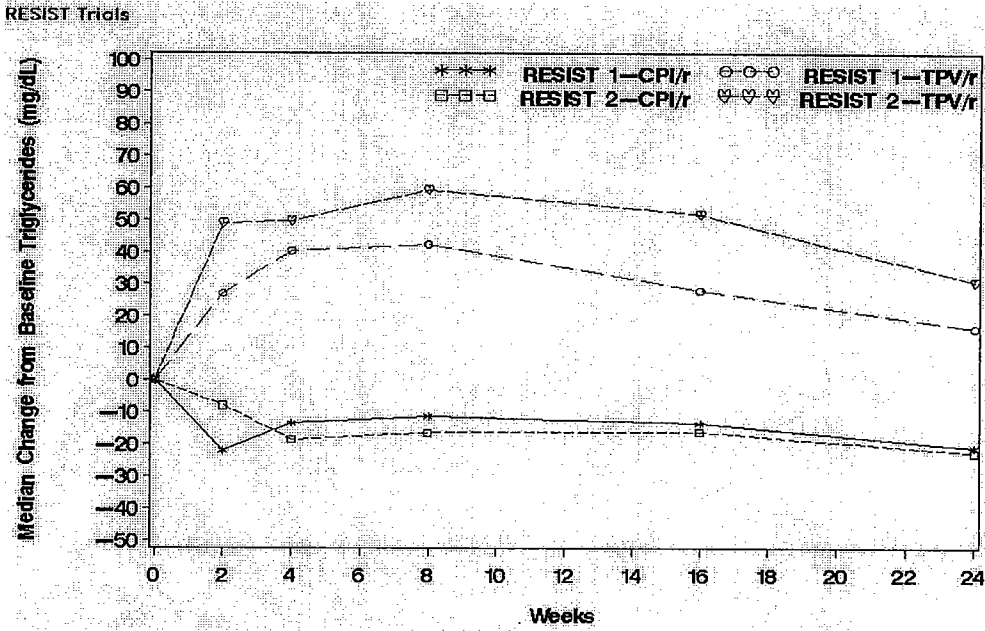


Figure 13: RESIST Trials: Median Change from Baseline Triglycerides (mg/dL)

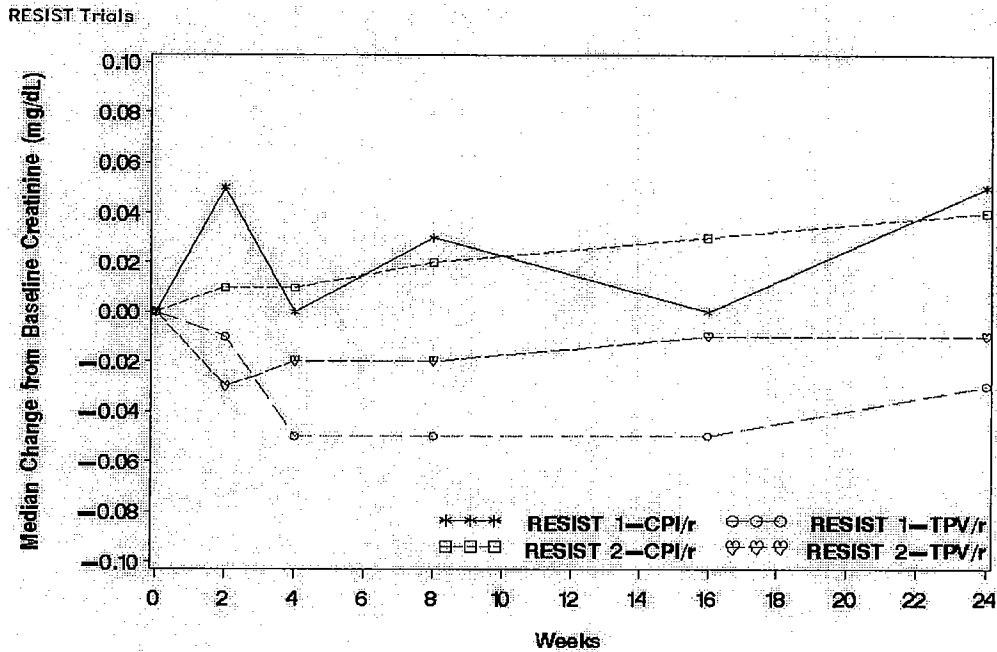


Figure 14: RESIST Trials: Median Change from Baseline Creatinine (mg/dL)



Table 6: RESIST Trials: Change from Baseline CD4+ Cell Count (cells/mm<sup>3</sup>)

| TRTGRP                                      | Week | N   | Min | Max | mean  | Std   | Med   | p25   | p75   | Pvalue |
|---|------|-----|-----|-----|-------|-------|-------|-------|-------|--------|
| <b>1182_0012: Baseline CD4+</b>             |      |     |     |     |       |       |       |       |       |        |
|   | 0    | 615 |     |     | 163.7 | 161.2 | 122.0 | 31.0  | 239.0 | 0.8476 |
| CPI/r                                       | 0    | 307 | /   | /   | 164.7 | 167.5 | 123.0 | 31.0  | 238.0 |        |
| TPV/r                                       | 0    | 308 |     |     | 162.8 | 155.0 | 121.0 | 31.3  | 246.5 |        |
| <b>1182_0012: Change from Baseline CD4+</b> |      |     |     |     |       |       |       |       |       |        |
|   | 2    | 560 |     |     | 24.1  | 61.6  | 14.5  | -3.0  | 50.5  | 0.1460 |
| CPI/r                                       | 2    | 278 |     |     | 22.1  | 67.7  | 11.0  | -5.0  | 51.0  |        |
| TPV/r                                       | 2    | 282 |     |     | 26.1  | 54.9  | 19.8  | -1.0  | 50.0  | 0.0001 |
|   | 4    | 566 |     |     | 33.0  | 72.9  | 18.0  | -2.0  | 66.0  |        |
| CPI/r                                       | 4    | 283 |     |     | 23.2  | 69.0  | 10.0  | -8.0  | 45.0  | 0.0001 |
| TPV/r                                       | 4    | 283 | /   | /   | 42.9  | 75.5  | 28.5  | 1.0   | 80.0  |        |
|   | 8    | 573 |     |     | 39.1  | 75.9  | 24.0  | -1.0  | 79.0  | 0.0001 |
| CPI/r                                       | 8    | 282 |     |     | 25.9  | 70.8  | 12.0  | -7.0  | 56.0  |        |
| TPV/r                                       | 8    | 291 |     |     | 51.8  | 78.7  | 37.0  | 3.0   | 100.0 | 0.0012 |
|   | 16   | 517 |     |     | 48.5  | 95.1  | 31.0  | -1.0  | 88.0  |        |
| CPI/r                                       | 16   | 249 |     |     | 36.3  | 86.1  | 16.0  | -8.0  | 76.0  | 0.1488 |
| TPV/r                                       | 16   | 268 |     |     | 59.9  | 101.6 | 36.8  | 5.3   | 97.5  |        |
|   | 24   | 384 |     |     | 52.8  | 93.9  | 40.5  | 1.0   | 100.0 | 0.1488 |
| CPI/r                                       | 24   | 146 |     |     | 44.0  | 90.5  | 29.0  | -6.0  | 96.0  |        |
| TPV/r                                       | 24   | 238 |     |     | 58.2  | 95.8  | 42.5  | 4.0   | 102.0 |        |
| <b>1182_0048: Baseline CD4+</b>             |      |     |     |     |       |       |       |       |       |        |
|   | 0    | 819 |     |     | 220.7 | 185.9 | 187.0 | 83.0  | 312.0 | 0.9519 |
| CPI/r                                       | 0    | 406 | /   | /   | 217.4 | 171.6 | 192.5 | 80.0  | 312.0 |        |
| TPV/r                                       | 0    | 413 |     |     | 223.9 | 199.2 | 179.0 | 88.0  | 310.0 |        |
| <b>1182_0048: Change from Baseline CD4+</b> |      |     |     |     |       |       |       |       |       |        |
|   | 2    | 694 |     |     | 20.9  | 69.9  | 15.0  | -8.0  | 54.0  | 0.0007 |
| CPI/r                                       | 2    | 342 |     |     | 16.4  | 64.4  | 9.0   | -12.5 | 41.0  |        |
| TPV/r                                       | 2    | 352 |     |     | 25.4  | 74.7  | 23.0  | -2.0  | 63.0  | 0.0001 |
|   | 4    | 714 |     |     | 28.9  | 78.2  | 24.0  | -7.0  | 67.0  |        |
| CPI/r                                       | 4    | 353 |     |     | 20.7  | 70.9  | 13.0  | -14.0 | 55.0  | 0.0001 |
| TPV/r                                       | 4    | 361 |     |     | 37.0  | 84.0  | 34.0  | 1.0   | 77.0  |        |
|   | 8    | 741 |     |     | 35.7  | 83.8  | 26.0  | -4.0  | 72.0  | 0.0001 |
| CPI/r                                       | 8    | 369 |     |     | 22.5  | 75.4  | 12.0  | -13.0 | 54.0  |        |
| TPV/r                                       | 8    | 372 |     |     | 48.8  | 89.5  | 37.0  | 5.5   | 91.5  | 0.0001 |
|   | 16   | 670 |     |     | 41.2  | 85.9  | 29.0  | -8.0  | 86.0  |        |
| CPI/r                                       | 16   | 310 |     |     | 27.2  | 75.9  | 16.0  | -16.0 | 66.0  | 0.0001 |
| TPV/r                                       | 16   | 360 |     |     | 53.3  | 92.1  | 40.0  | 4.0   | 102.0 |        |
|   | 24   | 327 |     |     | 43.0  | 95.2  | 28.0  | -13.0 | 93.5  | 0.0001 |
| CPI/r                                       | 24   | 127 |     |     | 24.5  | 94.2  | 13.0  | -31.0 | 86.0  |        |
| TPV/r                                       | 24   | 200 |     |     | 54.8  | 94.2  | 37.0  | -1.0  | 105.5 |        |

Table 7: Study 1182\_0051: Change From Baseline Viral Load (log<sub>10</sub> Copies/mL)

| TRTGRP                                    | Week | n   | Min | Max | Mean  | Std  | Med   | p25   | p75   | p-value |
|---|------|-----|-----|-----|-------|------|-------|-------|-------|---------|
| Baseline Plasma Viral Load                |      |     |     |     |       |      |       |       |       |         |
|   | 0    | 315 |     |     | 4.87  | 0.63 | 4.97  | 4.46  | 5.32  | 0.2579  |
| APV/TPV/r                                 | 0    | 83  |     |     | 4.91  | 0.67 | 4.97  | 4.52  | 5.46  |         |
| LPV/TPV/r                                 | 0    | 83  |     |     | 4.90  | 0.60 | 4.97  | 4.69  | 5.28  |         |
| SQV/TPV/r                                 | 0    | 82  |     |     | 4.91  | 0.53 | 5.02  | 4.57  | 5.30  |         |
| TPV/r                                     | 0    | 67  |     |     | 4.74  | 0.71 | 4.78  | 4.24  | 5.23  |         |
| Change from Baseline in Plasma Viral Load |      |     |     |     |       |      |       |       |       |         |
|   | 2    | 293 |     |     | -0.64 | 0.82 | -0.41 | -1.32 | 0.03  | <0.0001 |
| APV/TPV/r                                 | 2    | 74  |     |     | -0.48 | 0.79 | -0.23 | -1.05 | 0.10  |         |
| LPV/TPV/r                                 | 2    | 81  |     |     | -0.60 | 0.82 | -0.38 | -1.33 | 0.09  |         |
| SQV/TPV/r                                 | 2    | 77  |     |     | -0.51 | 0.79 | -0.28 | -0.96 | 0.15  |         |
| TPV/r                                     | 2    | 61  |     |     | -1.07 | 0.74 | -1.17 | -1.58 | -0.42 |         |
|   | 4    | 299 |     |     | -1.09 | 0.91 | -1.12 | -1.85 | -0.27 | 0.1986  |
| APV/TPV/r                                 | 4    | 76  |     |     | -1.05 | 0.95 | -1.18 | -1.83 | -0.24 |         |
| LPV/TPV/r                                 | 4    | 80  |     |     | -1.25 | 0.90 | -1.31 | -2.01 | -0.53 |         |
| SQV/TPV/r                                 | 4    | 79  |     |     | -0.94 | 0.87 | -0.99 | -1.74 | -0.07 |         |
| TPV/r                                     | 4    | 64  |     |     | -1.10 | 0.92 | -0.99 | -1.85 | -0.28 |         |
|   | 24   | 269 |     |     | -0.93 | 1.21 | -0.43 | -1.88 | -0.03 | 0.4201  |
| APV/TPV/r                                 | 24   | 64  |     |     | -1.14 | 1.34 | -0.66 | -2.10 | 0.00  |         |
| LPV/TPV/r                                 | 24   | 75  |     |     | -1.02 | 1.28 | -0.50 | -1.97 | -0.02 |         |
| SQV/TPV/r                                 | 24   | 69  |     |     | -0.79 | 1.11 | -0.33 | -1.13 | -0.09 |         |
| TPV/r                                     | 24   | 61  |     |     | -0.76 | 1.07 | -0.28 | -1.24 | -0.08 |         |

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Table 8: Study 1182\_0051: Percentage of Subjects with Virologic Response

| Week<br>N  | TPV/r<br>67 | %    | APV/TPV/r<br>83 | LPV/TPV/r<br>83 | SQV/TPV/r<br>82 | PI/TPV/r<br>248 | %    | P-<br>value <sup>1</sup> |
|--|-------------|------|-----------------|-----------------|-----------------|-----------------|------|--------------------------|
| <b>With at least 1 log<sub>10</sub> copies/mL drop in viral load</b>   |             |      |                 |                 |                 |                 |      |                          |
| 2  | 34          | 50.7 | 19              | 25              | 19              | 63              | 25.4 | 0.0006                   |
| 4  | 32          | 47.8 | 41              | 45              | 39              | 125             | 50.4 | 0.8185                   |
| 8  | 30          | 44.8 | 38              | 33              | 29              | 100             | 40.3 |                          |
| 16   | 17          | 25.4 | 31              | 27              | 22              | 80              | 32.3 |                          |
| 24   | 16          | 23.9 | 26              | 25              | 18              | 69              | 27.8 | 0.4592                   |
| <b>With at least 0.5 log<sub>10</sub> copies/mL drop in viral load</b> |             |      |                 |                 |                 |                 |      |                          |
| 2  | 43          | 64.2 | 27              | 35              | 30              | 92              | 37.1 | 0.0006                   |
| 4  | 41          | 61.2 | 50              | 60              | 48              | 158             | 63.7 | 0.2465                   |
| 8  | 35          | 52.2 | 44              | 44              | 41              | 129             | 52.0 |                          |
| 16   | 26          | 38.8 | 42              | 40              | 34              | 116             | 46.8 |                          |
| 24   | 25          | 37.3 | 34              | 37              | 26              | 97              | 39.1 | 0.3718                   |
| <b>LOQ<sup>2</sup> = 400 log<sub>10</sub> copies/mL</b>                |             |      |                 |                 |                 |                 |      |                          |
| 2  | 11          | 16.4 | 5               | 4               | 5               | 14              | 5.6  | 0.0368                   |
| 4  | 8           | 11.9 | 14              | 15              | 6               | 35              | 14.1 | 0.1350                   |
| 8  | 9           | 13.4 | 15              | 19              | 11              | 45              | 18.1 |                          |
| 16   | 11          | 16.4 | 14              | 15              | 9               | 38              | 15.3 |                          |
| 24   | 11          | 16.4 | 15              | 13              | 11              | 39              | 15.7 | 0.8494                   |
| <b>LOQ<sup>2</sup> = 50 log<sub>10</sub> copies/mL</b>                 |             |      |                 |                 |                 |                 |      |                          |
| 2  | 1           | 1.5  | 1               | 0               | 0               | 1               | 0.4  | 0.5855                   |
| 4  | 3           | 4.5  | 2               | 2               | 0               | 4               | 1.6  | 0.3223                   |
| 8  | 7           | 10.4 | 7               | 10              | 3               | 20              | 8.1  |                          |
| 16   | 8           | 11.9 | 12              | 13              | 8               | 33              | 13.3 |                          |
| 24   | 10          | 14.9 | 14              | 12              | 10              | 36              | 14.5 | 0.8662                   |

1. P-value by Chi-square test or Fisher's exact test for the comparison among four treatment regimens.

2. Assay limit of quantification for viral load.

Table 9: Study 1182\_0051: Change from Baseline in CD4+ & CD8+ Cell Count (cells/mm<sup>3</sup>)

| TRTGRP   | Week | n   | Min | Max | mean   | Std   | Med   | p25    | p75    | p-value |
|--|------|-----|-----|-----|--------|-------|-------|--------|--------|---------|
| <b>Baseline CD4+ Cell Count</b>                |      |     |     |     |        |       |       |        |        |         |
|  | 0    | 310 |     |     | 173.9  | 150.7 | 138.5 | 51.0   | 252.0  | 0.1572  |
| APV/TPV/r                                      | 0    | 81  |     |     | 171.6  | 138.0 | 137.5 | 59.5   | 272.5  |         |
| LPV/TPV/r                                      | 0    | 83  | /   | /   | 165.9  | 142.8 | 126.0 | 45.5   | 247.5  |         |
| SQV/TPV/r                                      | 0    | 81  |     |     | 157.2  | 152.2 | 111.0 | 36.5   | 230.0  |         |
| TPV/r  | 0    | 65  |     |     | 208.1  | 170.8 | 180.5 | 85.0   | 265.0  |         |
| <b>Change from Baseline in CD4+ Cell Count</b> |      |     |     |     |        |       |       |        |        |         |
|  | 2    | 291 |     |     | 25.8   | 58.9  | 11.0  | -2.5   | 51.3   | 0.0418  |
| APV/TPV/r                                      | 2    | 74  |     |     | 11.6   | 56.0  | 7.8   | -7.0   | 37.5   |         |
| LPV/TPV/r                                      | 2    | 81  |     |     | 32.3   | 59.7  | 16.5  | -1.5   | 58.0   | 0.4850  |
| SQV/TPV/r                                      | 2    | 76  |     |     | 22.5   | 49.7  | 7.3   | -4.0   | 39.8   |         |
| TPV/r  | 2    | 60  |     |     | 39.0   | 68.6  | 22.5  | 2.5    | 65.8   |         |
|  | 4    | 288 | /   | /   | 36.2   | 65.7  | 22.0  | -2.0   | 68.0   |         |
| APV/TPV/r                                      | 4    | 75  |     |     | 16.9   | 54.1  | 22.0  | -4.5   | 47.5   |         |
| LPV/TPV/r                                      | 4    | 76  | /   | /   | 41.9   | 63.7  | 25.5  | 0.5    | 88.3   | 0.1508  |
| SQV/TPV/r                                      | 4    | 77  |     |     | 45.0   | 73.0  | 13.5  | -3.0   | 77.5   |         |
| TPV/r  | 4    | 60  |     |     | 41.9   | 68.2  | 24.0  | -4.0   | 60.4   |         |
|  | 24   | 252 |     |     | 56.1   | 88.6  | 36.3  | -1.0   | 103.5  |         |
| APV/TPV/r                                      | 24   | 60  |     |     | 45.5   | 94.7  | 41.5  | -5.5   | 100.5  |         |
| LPV/TPV/r                                      | 24   | 70  |     |     | 74.0   | 91.9  | 55.5  | 7.0    | 117.0  | 0.1508  |
| SQV/TPV/r                                      | 24   | 67  |     |     | 59.9   | 89.1  | 33.0  | -1.5   | 113.0  |         |
| TPV/r  | 24   | 55  |     |     | 40.1   | 73.2  | 18.0  | -6.5   | 80.0   |         |
| <b>Baseline CD8+ Cell Count</b>                |      |     |     |     |        |       |       |        |        |         |
|  | 0    | 310 |     |     | 941.9  | 581.5 | 877.3 | 503.5  | 1270.0 | 0.4663  |
| APV/TPV/r                                      | 0    | 81  |     |     | 1018.8 | 595.0 | 931.5 | 621.0  | 1334.0 |         |
| LPV/TPV/r                                      | 0    | 83  | /   | /   | 895.4  | 534.4 | 801.0 | 482.5  | 1214.5 |         |
| SQV/TPV/r                                      | 0    | 81  |     |     | 910.4  | 648.8 | 705.0 | 379.0  | 1257.5 |         |
| TPV/r  | 0    | 65  |     |     | 944.6  | 535.0 | 889.5 | 634.0  | 1152.0 |         |
| <b>Change from Baseline CD8+ Cell Count</b>    |      |     |     |     |        |       |       |        |        |         |
|  | 2    | 291 |     |     | 63.5   | 309.7 | 10.5  | -77.5  | 168.0  | 0.1341  |
| APV/TPV/r                                      | 2    | 74  |     |     | 73.9   | 297.4 | 33.3  | -64.0  | 178.5  |         |
| LPV/TPV/r                                      | 2    | 81  |     |     | 94.7   | 296.8 | 51.5  | -64.0  | 203.5  | 0.8839  |
| SQV/TPV/r                                      | 2    | 76  |     |     | 58.9   | 364.5 | -19.3 | -73.0  | 86.5   |         |
| TPV/r  | 2    | 60  |     |     | 14.3   | 264.2 | -15.8 | -139.5 | 151.3  |         |
|  | 4    | 288 | /   | /   | 62.9   | 322.4 | 20.3  | -101.0 | 158.8  |         |
| APV/TPV/r                                      | 4    | 75  |     |     | 62.1   | 331.8 | 35.5  | -97.5  | 158.0  |         |
| LPV/TPV/r                                      | 4    | 76  | /   | /   | 82.8   | 393.2 | 21.8  | -129.5 | 169.5  | 0.0815  |
| SQV/TPV/r                                      | 4    | 77  |     |     | 64.9   | 265.8 | 1.0   | -90.5  | 190.5  |         |
| TPV/r  | 4    | 60  |     |     | 35.9   | 280.8 | 5.3   | -146.3 | 121.8  |         |
|  | 24   | 252 |     |     | 62.2   | 381.3 | 19.3  | -144.3 | 248.3  |         |
| APV/TPV/r                                      | 24   | 60  |     |     | 61.5   | 368.0 | 39.8  | -103.0 | 267.3  |         |
| LPV/TPV/r                                      | 24   | 70  |     |     | 149.7  | 418.2 | 82.0  | -49.0  | 340.5  | 0.0815  |
| SQV/TPV/r                                      | 24   | 67  |     |     | 32.0   | 380.7 | 7.5   | -127.0 | 147.5  |         |
| TPV/r  | 24   | 55  |     |     | -11.8  | 332.6 | -44.0 | -226.5 | 135.0  |         |

Table 10: Study 1182\_0012: Change from Baseline in HGB (g/dL)

| TRTGRP                          | Week | N   | Min | Max | mean | Std | Med  | p25  | p75  | p-value |
|---------------------------------|------|-----|-----|-----|------|-----|------|------|------|---------|
| <b>Baseline HGB</b>             |      |     |     |     |      |     |      |      |      |         |
|                                 | 0    | 602 |     |     | 14   | 1.9 | 14   | 12.7 | 15.2 | 0.9082  |
| CPI/r                           | 0    | 303 |     |     | 14   | 1.9 | 13.9 | 12.7 | 15.2 |         |
| TPV/r                           | 0    | 299 |     |     | 13.9 | 1.9 | 14.2 | 12.7 | 15.2 |         |
| <b>Change from Baseline HGB</b> |      |     |     |     |      |     |      |      |      |         |
|                                 | 2    | 547 |     |     | -0.4 | 1.0 | -0.4 | -1.0 | 0.3  | 0.0343  |
| CPI/r                           | 2    | 273 |     |     | -0.3 | 1.0 | -0.3 | -0.9 | 0.4  |         |
| TPV/r                           | 2    | 274 |     |     | -0.5 | 1.1 | -0.5 | -1.1 | 0.2  |         |
|                                 | 4    | 558 |     |     | -0.3 | 1.2 | -0.3 | -1.0 | 0.3  | 0.0070  |
| CPI/r                           | 4    | 281 |     |     | -0.2 | 1.1 | -0.2 | -0.8 | 0.3  |         |
| TPV/r                           | 4    | 277 |     |     | -0.4 | 1.2 | -0.5 | -1.1 | 0.3  |         |
|                                 | 8    | 562 |     |     | -0.3 | 1.4 | -0.3 | -1.0 | 0.5  | 0.0971  |
| CPI/r                           | 8    | 280 |     |     | -0.3 | 1.4 | -0.2 | -0.9 | 0.6  |         |
| TPV/r                           | 8    | 282 |     |     | -0.4 | 1.4 | -0.4 | -1.0 | 0.4  |         |
|                                 | 16   | 507 |     |     | -0.3 | 1.4 | -0.3 | -1.0 | 0.5  | 0.0002  |
| CPI/r                           | 16   | 245 |     |     | -0.1 | 1.3 | -0.2 | -0.9 | 0.7  |         |
| TPV/r                           | 16   | 262 |     |     | -0.5 | 1.4 | -0.6 | -1.2 | 0.3  |         |
|                                 | 24   | 378 |     |     | -0.2 | 1.4 | -0.3 | -0.9 | 0.6  | 0.1262  |
| CPI/r                           | 24   | 143 |     |     | -0.1 | 1.4 | -0.1 | -0.9 | 0.6  |         |
| TPV/r                           | 24   | 235 |     |     | -0.3 | 1.3 | -0.4 | -1.0 | 0.5  |         |

Table 11: Study 1182\_0012: Change from Baseline in Platelets (1,000 cells/mm<sup>3</sup>)

| TRTGRP                                     | Week | N   | Min | Max | mean  | Std  | Med   | p25   | p75   | p-value |
|--|------|-----|-----|-----|-------|------|-------|-------|-------|---------|
| <b>Baseline Platelet Count</b>             |      |     |     |     |       |      |       |       |       |         |
|  | 0    | 591 |     |     | 206.4 | 69.2 | 199.0 | 157.0 | 244.0 | 0.9501  |
| CPI/r                                      | 0    | 298 |     |     | 206.9 | 70.4 | 198.5 | 157.0 | 245.0 |         |
| TPV/r                                      | 0    | 293 |     |     | 205.8 | 68.1 | 200.0 | 158.0 | 239.0 |         |
| <b>Change from Baseline Platelet Count</b> |      |     |     |     |       |      |       |       |       |         |
|  | 2    | 521 |     |     | 22.5  | 54.5 | 19.0  | -7.0  | 54.0  | 0.0001  |
| CPI/r                                      | 2    | 260 |     |     | 13.1  | 56.1 | 8.0   | -17.0 | 44.5  |         |
| TPV/r                                      | 2    | 261 |     |     | 31.9  | 51.1 | 26.0  | -1.0  | 60.0  |         |
|  | 4    | 539 |     |     | 16.9  | 63.2 | 11.0  | -15.0 | 46.0  | 0.9469  |
| CPI/r                                      | 4    | 271 |     |     | 14.7  | 59.5 | 13.0  | -12.0 | 46.0  |         |
| TPV/r                                      | 4    | 268 |     |     | 19.1  | 66.8 | 11.0  | -16.5 | 45.0  |         |
|  | 8    | 539 |     |     | 14.3  | 64.6 | 11.0  | -20.0 | 44.0  | 0.7546  |
| CPI/r                                      | 8    | 265 |     |     | 14.0  | 71.7 | 10.0  | -17.5 | 45.0  |         |
| TPV/r                                      | 8    | 274 |     |     | 14.6  | 57.1 | 11.0  | -22.0 | 39.0  |         |
|  | 16   | 495 |     |     | 17.4  | 64.0 | 14.0  | -18.0 | 46.0  | 0.5879  |
| CPI/r                                      | 16   | 241 |     |     | 19.5  | 70.8 | 15.0  | -13.0 | 47.0  |         |
| TPV/r                                      | 16   | 254 |     |     | 15.5  | 56.9 | 13.0  | -20.0 | 45.0  |         |
|  | 24   | 365 |     |     | 24.8  | 66.5 | 18.0  | -13.0 | 55.0  | 0.1001  |
| CPI/r                                      | 24   | 139 |     |     | 29.9  | 68.7 | 19.0  | -2.0  | 60.0  |         |
| TPV/r                                      | 24   | 226 |     |     | 21.7  | 65.1 | 17.5  | -21.0 | 54.0  |         |

Table 12: Study 1182\_0012: Change from Baseline in AST (SGOT,U/L)

| TRTGRP                    | Week | N   | Min | Max | mean | Std  | Med  | p25   | p75  | p-value |
|---------------------------|------|-----|-----|-----|------|------|------|-------|------|---------|
| Baseline SGOT             |      |     |     |     |      |      |      |       |      |         |
|                           | 0    | 620 |     |     | 37.0 | 15.9 | 33.0 | 26.4  | 43.5 | 0.2322  |
| CPI/r                     | 0    | 309 |     |     | 37.9 | 16.4 | 34.0 | 26.5  | 44.0 |         |
| TPV/r                     | 0    | 311 |     |     | 36.2 | 15.4 | 32.0 | 26.0  | 43.0 |         |
| Change from Baseline SGOT |      |     |     |     |      |      |      |       |      |         |
|                           | 2    | 571 |     |     | 1.6  | 30.2 | -1.0 | -7.0  | 5.5  | 0.0113  |
| CPI/r                     | 2    | 284 |     |     | -1.8 | 14.2 | -2.0 | -7.0  | 3.8  |         |
| TPV/r                     | 2    | 287 |     |     | 5.0  | 39.9 | 0.0  | -7.0  | 8.0  |         |
|                           | 4    | 579 |     |     | 0.5  | 20.9 | -1.5 | -8.0  | 5.0  | 0.4295  |
| CPI/r                     | 4    | 289 |     |     | -0.1 | 19.8 | -1.5 | -8.5  | 4.0  |         |
| TPV/r                     | 4    | 290 |     |     | 1.1  | 21.9 | -1.0 | -7.5  | 5.5  |         |
|                           | 8    | 578 |     |     | 0.4  | 26.0 | -2.0 | -8.5  | 5.0  | 0.9789  |
| CPI/r                     | 8    | 287 |     |     | -0.1 | 25.6 | -2.0 | -7.5  | 4.8  |         |
| TPV/r                     | 8    | 291 |     |     | 0.8  | 26.3 | -1.5 | -10.0 | 5.0  |         |
|                           | 16   | 529 |     |     | 1.1  | 26.0 | -2.5 | -9.5  | 6.0  | 0.3050  |
| CPI/r                     | 16   | 251 |     |     | 0.2  | 21.0 | -2.0 | -9.0  | 6.0  |         |
| TPV/r                     | 16   | 278 |     |     | 1.8  | 29.9 | -3.5 | -9.5  | 6.0  |         |
|                           | 24   | 386 |     |     | 2.2  | 25.8 | -2.0 | -9.0  | 8.5  | 0.6092  |
| CPI/r                     | 24   | 149 |     |     | -0.7 | 16.0 | -2.0 | -8.5  | 5.5  |         |
| TPV/r                     | 24   | 237 |     |     | 4.0  | 30.3 | -2.0 | -9.0  | 10.0 |         |

Table 13: Study 1182\_0012: Change from Baseline in ALT (SGPT,U/L)

| TRTGRP                    | Week | N   | Min | Max | mean | Std  | Med  | p25   | p75  | p-value |
|---------------------------|------|-----|-----|-----|------|------|------|-------|------|---------|
| Baseline SGPT             |      |     |     |     |      |      |      |       |      |         |
|                           | 0    | 620 |     |     | 37.4 | 21.4 | 32.0 | 23.0  | 46.0 | 0.7607  |
| CPI/r                     | 0    | 309 |     |     | 37.8 | 22.0 | 32.0 | 23.0  | 46.0 |         |
| TPV/r                     | 0    | 311 |     |     | 37.0 | 20.7 | 32.0 | 22.5  | 45.5 |         |
| Change from Baseline SGPT |      |     |     |     |      |      |      |       |      |         |
|                           | 2    | 581 |     |     | 8.5  | 69.4 | 1.0  | -6.0  | 11.0 | 0.0001  |
| CPI/r                     | 2    | 290 |     |     | -0.9 | 19.8 | -1.4 | -7.5  | 5.0  |         |
| TPV/r                     | 2    | 291 |     |     | 17.9 | 95.2 | 5.0  | -4.0  | 18.5 |         |
|                           | 4    | 586 |     |     | 5.2  | 31.1 | 0.5  | -7.5  | 10.5 | 0.0004  |
| CPI/r                     | 4    | 290 |     |     | 1.0  | 27.6 | -1.5 | -8.0  | 7.0  |         |
| TPV/r                     | 4    | 296 |     |     | 9.4  | 33.7 | 3.0  | -7.0  | 14.0 |         |
|                           | 8    | 586 |     |     | 6.2  | 47.4 | 0.0  | -9.0  | 11.0 | 0.0001  |
| CPI/r                     | 8    | 291 |     |     | -0.3 | 30.4 | -2.0 | -9.0  | 5.3  |         |
| TPV/r                     | 8    | 295 |     |     | 12.7 | 59.0 | 2.5  | -7.5  | 16.0 |         |
|                           | 16   | 534 |     |     | 6.8  | 42.5 | -0.5 | -10.0 | 12.0 | 0.0050  |
| CPI/r                     | 16   | 254 |     |     | 0.2  | 26.9 | -2.5 | -10.3 | 6.0  |         |
| TPV/r                     | 16   | 280 |     |     | 12.8 | 52.1 | 1.0  | -9.5  | 18.0 |         |
|                           | 24   | 397 |     |     | 10.9 | 56.1 | 0.5  | -7.5  | 14.0 | 0.0014  |
| CPI/r                     | 24   | 149 |     |     | -0.8 | 20.8 | -2.0 | -8.5  | 6.5  |         |
| TPV/r                     | 24   | 248 |     |     | 17.8 | 68.3 | 4.0  | -7.0  | 21.8 |         |

Table 14: Study 1182\_0012: Change from Baseline in Gamma GT (U/L)

| TRTGRP                   | Week | N   | Min | Max | mean  | Std   | Med  | p25   | p75   | p-value |
|--------------------------|------|-----|-----|-----|-------|-------|------|-------|-------|---------|
| Baseline GGT             |      |     |     |     |       |       |      |       |       |         |
|                          | 0    | 620 |     |     | 90.4  | 146.2 | 48.3 | 29.5  | 95.3  | 0.2612  |
| CPI/r                    | 0    | 309 |     |     | 89.7  | 109.2 | 50.0 | 32.0  | 101.0 |         |
| TPV/r                    | 0    | 311 |     |     | 91.1  | 175.5 | 47.0 | 28.5  | 88.0  |         |
| Change from Baseline GGT |      |     |     |     |       |       |      |       |       |         |
|                          | 2    | 582 |     |     | 10.4  | 71.3  | 4.0  | -6.5  | 19.5  | 0.0001  |
| CPI/r                    | 2    | 290 |     |     | -5.7  | 59.0  | -1.5 | -11.5 | 7.0   |         |
| TPV/r                    | 2    | 292 |     |     | 26.3  | 78.6  | 12.8 | 0.5   | 35.3  | 0.0001  |
|                          | 4    | 586 |     |     | 24.2  | 106.2 | 8.8  | -5.3  | 34.5  |         |
| CPI/r                    | 4    | 290 |     |     | -5.0  | 82.8  | -1.3 | -13.0 | 10.5  | 0.0001  |
| TPV/r                    | 4    | 296 |     |     | 52.9  | 118.2 | 23.0 | 6.3   | 64.8  |         |
|                          | 8    | 586 |     |     | 32.3  | 134.4 | 8.0  | -7.5  | 42.5  | 0.0001  |
| CPI/r                    | 8    | 291 |     |     | -10.7 | 81.6  | -3.0 | -18.0 | 9.0   |         |
| TPV/r                    | 8    | 295 |     |     | 74.8  | 160.3 | 31.5 | 7.0   | 94.7  | 0.0001  |
|                          | 16   | 534 |     |     | 46.4  | 159.6 | 14.8 | -4.7  | 71.0  |         |
| CPI/r                    | 16   | 254 |     |     | -0.1  | 104.2 | 0.5  | -18.5 | 16.0  | 0.0001  |
| TPV/r                    | 16   | 280 |     |     | 88.7  | 187.2 | 41.8 | 10.3  | 121.3 |         |
|                          | 24   | 400 |     |     | 61.0  | 182.6 | 25.5 | -1.5  | 93.3  | 0.0001  |
| CPI/r                    | 24   | 149 |     |     | -3.9  | 103.4 | -0.5 | -21.0 | 19.5  |         |
| TPV/r                    | 24   | 251 |     |     | 99.6  | 207.0 | 52.5 | 14.0  | 136.5 |         |

Table 15: Study 1182\_0012: Change from Baseline in Total Bilirubin (mg/dL)

| TRTGRP                               | Week | N   | Min | Max | mean  | Std  | Med   | p25   | p75  | p-value |
|--------------------------------------|------|-----|-----|-----|-------|------|-------|-------|------|---------|
| Baseline Total Bilirubin             |      |     |     |     |       |      |       |       |      |         |
|                                      | 0    | 620 |     |     | 0.55  | 0.34 | 0.45  | 0.35  | 0.60 | 0.9980  |
| CPI/r                                | 0    | 309 |     |     | 0.55  | 0.33 | 0.45  | 0.35  | 0.60 |         |
| TPV/r                                | 0    | 311 |     |     | 0.55  | 0.35 | 0.45  | 0.35  | 0.64 |         |
| Change from Baseline Total Bilirubin |      |     |     |     |       |      |       |       |      |         |
|                                      | 2    | 581 |     |     | -0.09 | 0.34 | -0.05 | -0.20 | 0.05 | 0.0001  |
| CPI/r                                | 2    | 290 |     |     | -0.01 | 0.33 | 0.00  | -0.13 | 0.15 |         |
| TPV/r                                | 2    | 291 |     |     | -0.16 | 0.33 | -0.10 | -0.23 | 0.00 | 0.0001  |
|                                      | 4    | 586 |     |     | -0.10 | 0.35 | -0.05 | -0.20 | 0.05 |         |
| CPI/r                                | 4    | 290 |     |     | -0.03 | 0.36 | 0.00  | -0.15 | 0.10 | 0.0001  |
| TPV/r                                | 4    | 296 |     |     | -0.16 | 0.33 | -0.10 | -0.25 | 0.00 |         |
|                                      | 8    | 586 |     |     | -0.10 | 0.39 | -0.05 | -0.20 | 0.05 | 0.0001  |
| CPI/r                                | 8    | 291 |     |     | -0.03 | 0.44 | 0.00  | -0.15 | 0.10 |         |
| TPV/r                                | 8    | 295 |     |     | -0.16 | 0.33 | -0.10 | -0.20 | 0.00 | 0.0005  |
|                                      | 16   | 534 |     |     | -0.08 | 0.34 | -0.05 | -0.20 | 0.10 |         |
| CPI/r                                | 16   | 254 |     |     | -0.03 | 0.33 | 0.00  | -0.15 | 0.12 | 0.0001  |
| TPV/r                                | 16   | 280 |     |     | -0.11 | 0.35 | -0.07 | -0.22 | 0.05 |         |
|                                      | 24   | 400 |     |     | -0.06 | 0.36 | -0.03 | -0.15 | 0.10 | 0.0001  |
| CPI/r                                | 24   | 150 |     |     | 0.02  | 0.31 | 0.05  | -0.09 | 0.20 |         |
| TPV/r                                | 24   | 250 |     |     | -0.11 | 0.37 | -0.06 | -0.20 | 0.05 |         |

Table 16: Study 1182\_0012: Change from Baseline in Total Cholesterol (mg/dL)

| TRTGRP                                 | Week | N   | Min | Max | mean  | Std   | Med   | p25   | p75   | p-value |
|--|------|-----|-----|-----|-------|-------|-------|-------|-------|---------|
| Baseline Total Cholesterol             |      |     |     |     |       |       |       |       |       |         |
|  | 0    | 619 |     |     | 181.7 | 182.5 | 172.0 | 144.7 | 201.5 | 0.2781  |
| CPI/r                                  | 0    | 308 |     |     | 187.1 | 255.3 | 170.8 | 144.8 | 195.5 |         |
| TPV/r                                  | 0    | 311 |     |     | 176.3 | 42.7  | 174.5 | 144.7 | 203.7 |         |
| Change from Baseline Total Cholesterol |      |     |     |     |       |       |       |       |       |         |
|  | 2    | 580 |     |     | 5.0   | 182.0 | 9.4   | -11.4 | 33.0  | 0.0001  |
| CPI/r                                  | 2    | 289 |     |     | -14.5 | 254.2 | -0.5  | -18.0 | 20.0  |         |
| TPV/r                                  | 2    | 291 |     |     | 24.3  | 35.3  | 22.5  | 2.5   | 46.5  |         |
|  | 4    | 583 |     |     | 9.7   | 182.6 | 13.0  | -10.0 | 38.5  | 0.0001  |
| CPI/r                                  | 4    | 288 |     |     | -11.9 | 254.0 | 2.8   | -17.5 | 23.2  |         |
| TPV/r                                  | 4    | 295 |     |     | 30.9  | 45.6  | 24.4  | 3.5   | 53.5  |         |
|  | 8    | 585 |     |     | 12.2  | 185.8 | 13.5  | -9.5  | 41.4  | 0.0001  |
| CPI/r                                  | 8    | 290 |     |     | -11.4 | 256.1 | 0.2   | -23.5 | 21.5  |         |
| TPV/r                                  | 8    | 295 |     |     | 35.3  | 55.1  | 29.6  | 5.5   | 56.0  |         |
|  | 16   | 533 |     |     | 12.9  | 195.5 | 12.5  | -12.0 | 43.5  | 0.0001  |
| CPI/r                                  | 16   | 253 |     |     | -10.9 | 273.8 | 0.0   | -18.5 | 23.5  |         |
| TPV/r                                  | 16   | 280 |     |     | 34.4  | 64.7  | 28.0  | -1.3  | 59.5  |         |
|  | 24   | 399 |     |     | 15.6  | 223.7 | 19.0  | -4.5  | 49.5  | 0.0001  |
| CPI/r                                  | 24   | 149 |     |     | -19.0 | 357.5 | 6.0   | -14.5 | 32.5  |         |
| TPV/r                                  | 24   | 250 |     |     | 36.2  | 53.6  | 28.0  | 4.5   | 58.5  |         |

Table 17: Study 1182\_0012: Change from Baseline in Triglycerides (mg/dL)

| TRTGRP                             | Week | N   | Min | Max | mean  | Std   | Med   | p25   | p75   | p-value |
|------------------------------------|------|-----|-----|-----|-------|-------|-------|-------|-------|---------|
| Baseline Triglycerides             |      |     |     |     |       |       |       |       |       |         |
|                                    | 0    | 619 |     |     | 322.8 | 294.6 | 260.5 | 172.7 | 399.0 | 0.0715  |
| CPI/r                              | 0    | 308 |     |     | 320.2 | 368.7 | 242.3 | 169.6 | 366.2 |         |
| TPV/r                              | 0    | 311 |     |     | 325.3 | 195.8 | 276.4 | 182.0 | 428.3 |         |
| Change from Baseline Triglycerides |      |     |     |     |       |       |       |       |       |         |
|                                    | 2    | 580 |     |     | 7.8   | 309.8 | 3.5   | -61.8 | 95.0  | 0.0001  |
| CPI/r                              | 2    | 289 |     |     | -37.5 | 367.4 | -22.0 | -74.0 | 52.7  |         |
| TPV/r                              | 2    | 291 |     |     | 52.8  | 231.4 | 27.0  | -40.0 | 134.0 |         |
|                                    | 4    | 583 |     |     | 21.5  | 330.7 | 10.0  | -75.7 | 95.0  | 0.0001  |
| CPI/r                              | 4    | 288 |     |     | -36.7 | 372.7 | -13.5 | -94.6 | 47.0  |         |
| TPV/r                              | 4    | 295 |     |     | 78.2  | 272.7 | 40.5  | -50.0 | 152.5 |         |
|                                    | 8    | 585 |     |     | 35.6  | 347.7 | 12.5  | -70.9 | 113.5 | 0.0001  |
| CPI/r                              | 8    | 290 |     |     | -20.4 | 383.8 | -11.3 | -82.7 | 66.0  |         |
| TPV/r                              | 8    | 295 |     |     | 90.8  | 298.7 | 42.5  | -52.0 | 179.5 |         |
|                                    | 16   | 533 |     |     | 36.9  | 467.2 | 7.0   | -79.7 | 114.5 | 0.0003  |
| CPI/r                              | 16   | 253 |     |     | -25.3 | 406.1 | -13.5 | -85.0 | 69.5  |         |
| TPV/r                              | 16   | 280 |     |     | 93.1  | 510.4 | 28.0  | -67.3 | 157.0 |         |
|                                    | 24   | 399 |     |     | 11.0  | 372.3 | 8.0   | -81.0 | 89.5  | 0.0067  |
| CPI/r                              | 24   | 149 |     |     | -51.2 | 497.2 | -21.0 | -92.0 | 57.3  |         |
| TPV/r                              | 24   | 250 |     |     | 48.2  | 266.3 | 16.2  | -71.7 | 119.5 |         |



Table 18: Study 1182\_0012: Change from Baseline in Creatinine (mg/dL)

| TRTGRP                                 | Week | N   | Min | Max | mean  | Std  | Med   | p25   | p75  | p-value |
|--|------|-----|-----|-----|-------|------|-------|-------|------|---------|
| <b>Baseline Creatinine</b>             |      |     |     |     |       |      |       |       |      |         |
|  | 0    | 620 |     |     | 0.93  | 0.31 | 0.90  | 0.75  | 1.05 | 0.2550  |
| CPI/r                                  | 0    | 309 |     |     | 0.94  | 0.35 | 0.90  | 0.80  | 1.05 |         |
| TPV/r                                  | 0    | 311 |     |     | 0.92  | 0.26 | 0.87  | 0.75  | 1.03 |         |
| <b>Change from Baseline Creatinine</b> |      |     |     |     |       |      |       |       |      |         |
|  | 2    | 582 |     |     | 0.00  | 0.14 | 0.00  | -0.10 | 0.07 | 0.0001  |
| CPI/r                                  | 2    | 290 |     |     | 0.03  | 0.14 | 0.05  | -0.05 | 0.10 |         |
| TPV/r                                  | 2    | 292 |     |     | -0.03 | 0.14 | -0.01 | -0.10 | 0.05 |         |
|  | 4    | 586 |     |     | -0.01 | 0.15 | 0.00  | -0.10 | 0.07 | 0.0001  |
| CPI/r                                  | 4    | 290 |     |     | 0.02  | 0.15 | 0.00  | -0.05 | 0.10 |         |
| TPV/r                                  | 4    | 296 |     |     | -0.04 | 0.15 | -0.05 | -0.10 | 0.05 |         |
|  | 8    | 586 |     |     | 0.01  | 0.22 | 0.00  | -0.10 | 0.10 | 0.0001  |
| CPI/r                                  | 8    | 291 |     |     | 0.03  | 0.21 | 0.03  | -0.05 | 0.10 |         |
| TPV/r                                  | 8    | 295 |     |     | -0.02 | 0.23 | -0.05 | -0.10 | 0.05 |         |
|  | 16   | 534 |     |     | 0.00  | 0.19 | 0.00  | -0.10 | 0.10 | 0.0001  |
| CPI/r                                  | 16   | 254 |     |     | 0.04  | 0.20 | 0.00  | -0.05 | 0.14 |         |
| TPV/r                                  | 16   | 280 |     |     | -0.03 | 0.17 | -0.05 | -0.10 | 0.05 |         |
|  | 24   | 401 |     |     | 0.01  | 0.21 | 0.00  | -0.10 | 0.10 | 0.0001  |
| CPI/r                                  | 24   | 150 |     |     | 0.06  | 0.17 | 0.05  | -0.05 | 0.15 |         |
| TPV/r                                  | 24   | 251 |     |     | -0.01 | 0.23 | -0.03 | -0.10 | 0.05 |         |

Table 19: Study 1182\_0048: Change from Baseline HGB (g/dL)

| TRTGRP                          | Week | N   | Min | Max | mean | Std | Med  | p25  | p75  | P <sub>value</sub> |
|---------------------------------|------|-----|-----|-----|------|-----|------|------|------|--------------------|
| <b>Baseline HGB</b>             |      |     |     |     |      |     |      |      |      |                    |
|                                 | 0    | 820 |     |     | 14.1 | 1.8 | 14.3 | 13.0 | 15.3 | 0.2538             |
| CPI/r                           | 0    | 411 |     |     | 14.2 | 1.8 | 14.3 | 13.0 | 15.4 |                    |
| TPV/r                           | 0    | 409 |     |     | 14.0 | 1.7 | 14.2 | 13.0 | 15.3 |                    |
| <b>Change from Baseline HGB</b> |      |     |     |     |      |     |      |      |      |                    |
|                                 | 2    | 691 |     |     | -0.2 | 0.9 | -0.2 | -0.8 | 0.4  | 0.0006             |
| CPI/r                           | 2    | 341 |     |     | -0.1 | 1.0 | -0.1 | -0.7 | 0.5  |                    |
| TPV/r                           | 2    | 350 |     |     | -0.3 | 0.9 | -0.3 | -0.8 | 0.2  |                    |
|                                 | 4    | 718 |     |     | -0.1 | 1.0 | -0.1 | -0.7 | 0.4  | 0.0129             |
| CPI/r                           | 4    | 359 |     |     | 0.0  | 1.0 | 0.0  | -0.6 | 0.5  |                    |
| TPV/r                           | 4    | 359 |     |     | -0.2 | 0.9 | -0.2 | -0.8 | 0.3  |                    |
|                                 | 8    | 741 |     |     | 0.0  | 1.2 | -0.1 | -0.7 | 0.6  | 0.2074             |
| CPI/r                           | 8    | 373 |     |     | 0.0  | 1.2 | 0.0  | -0.7 | 0.7  |                    |
| TPV/r                           | 8    | 368 |     |     | -0.1 | 1.2 | -0.1 | -0.8 | 0.6  |                    |
|                                 | 16   | 668 |     |     | -0.1 | 1.3 | -0.1 | -0.8 | 0.6  | 0.0258             |
| CPI/r                           | 16   | 311 |     |     | 0.0  | 1.3 | 0.0  | -0.6 | 0.7  |                    |
| TPV/r                           | 16   | 357 |     |     | -0.1 | 1.3 | -0.2 | -0.9 | 0.5  |                    |
|                                 | 24   | 335 |     |     | 0.0  | 1.1 | -0.1 | -0.7 | 0.6  | 0.0245             |
| CPI/r                           | 24   | 132 |     |     | 0.1  | 1.0 | 0.1  | -0.5 | 0.7  |                    |
| TPV/r                           | 24   | 203 |     |     | -0.1 | 1.2 | -0.1 | -0.8 | 0.5  |                    |

Table 20: Study 1182\_0048: Change from Baseline Platelets (1,000 cells/mm<sup>3</sup>)

| TRTGRP                                | Week | N   | Min | Max | mean  | Std  | Med   | p25   | p75   | P <sub>value</sub> |
|---------------------------------------|------|-----|-----|-----|-------|------|-------|-------|-------|--------------------|
| <b>Baseline Platelets</b>             |      |     |     |     |       |      |       |       |       |                    |
|                                       | 0    | 806 |     |     | 207.8 | 69.9 | 203.0 | 161.0 | 251.0 | 0.1362             |
| CPI/r                                 | 0    | 404 |     |     | 205.0 | 70.4 | 201.0 | 157.0 | 248.5 |                    |
| TPV/r                                 | 0    | 402 |     |     | 210.5 | 69.3 | 206.0 | 164.0 | 252.0 |                    |
| <b>Change from Baseline Platelets</b> |      |     |     |     |       |      |       |       |       |                    |
|                                       | 2    | 669 |     |     | 15.5  | 47.6 | 11.0  | -11.0 | 42.0  | 0.0648             |
| CPI/r                                 | 2    | 330 |     |     | 12.2  | 44.7 | 9.0   | -13.0 | 38.0  |                    |
| TPV/r                                 | 2    | 339 |     |     | 18.8  | 50.1 | 15.0  | -9.0  | 46.0  |                    |
|                                       | 4    | 689 |     |     | 5.8   | 50.5 | 1.0   | -22.0 | 27.0  | 0.0131             |
| CPI/r                                 | 4    | 346 |     |     | 8.2   | 43.1 | 5.0   | -18.0 | 30.0  |                    |
| TPV/r                                 | 4    | 343 |     |     | 3.4   | 56.9 | -3.0  | -24.0 | 23.0  |                    |
|                                       | 8    | 714 |     |     | 6.1   | 55.8 | 2.0   | -25.5 | 33.0  | 0.0001             |
| CPI/r                                 | 8    | 360 |     |     | 12.4  | 54.8 | 8.0   | -18.0 | 39.0  |                    |
| TPV/r                                 | 8    | 354 |     |     | -0.4  | 56.2 | -5.5  | -32.0 | 22.0  |                    |
|                                       | 16   | 640 |     |     | 3.5   | 60.7 | -3.0  | -27.0 | 28.0  | 0.0004             |
| CPI/r                                 | 16   | 297 |     |     | 12.3  | 64.7 | 2.0   | -21.0 | 33.0  |                    |
| TPV/r                                 | 16   | 343 |     |     | -4.1  | 56.0 | -9.0  | -34.0 | 23.0  |                    |
|                                       | 24   | 327 |     |     | -0.6  | 55.4 | -3.0  | -32.0 | 29.0  | 0.0039             |
| CPI/r                                 | 24   | 129 |     |     | 8.6   | 55.2 | 5.0   | -22.0 | 39.0  |                    |
| TPV/r                                 | 24   | 198 |     |     | -6.6  | 54.9 | -8.5  | -38.0 | 19.0  |                    |

Table 21: Study 1182\_0048: Change from Baseline WBC (10<sup>9</sup>/L)

| TRTGRP                          | Week | N   | Min | Max | mean | Std | Med | p25  | p75 | P <sub>value</sub> |
|---------------------------------|------|-----|-----|-----|------|-----|-----|------|-----|--------------------|
| <b>Baseline WBC</b>             |      |     |     |     |      |     |     |      |     |                    |
|                                 | 0    | 819 |     |     | 5.4  | 2.5 | 5.1 | 3.9  | 6.4 | 0.2617             |
| CPI/r                           | 0    | 411 |     |     | 5.4  | 2.1 | 5.1 | 3.9  | 6.6 |                    |
| TPV/r                           | 0    | 408 |     |     | 5.3  | 2.8 | 5.0 | 3.9  | 6.2 |                    |
| <b>Change from Baseline WBC</b> |      |     |     |     |      |     |     |      |     |                    |
|                                 | 2    | 690 |     |     | 0.4  | 1.8 | 0.4 | -0.5 | 1.3 | 0.0059             |
| CPI/r                           | 2    | 341 |     |     | 0.3  | 1.6 | 0.3 | -0.6 | 1.0 |                    |
| TPV/r                           | 2    | 349 |     |     | 0.6  | 1.9 | 0.5 | -0.4 | 1.6 |                    |
|                                 | 4    | 714 |     |     | 0.3  | 1.7 | 0.2 | -0.7 | 1.1 | 0.0607             |
| CPI/r                           | 4    | 358 |     |     | 0.1  | 1.7 | 0.2 | -0.7 | 0.9 |                    |
| TPV/r                           | 4    | 356 |     |     | 0.4  | 1.8 | 0.3 | -0.6 | 1.2 |                    |
|                                 | 8    | 740 |     |     | 0.4  | 1.8 | 0.3 | -0.6 | 1.3 | 0.4420             |
| CPI/r                           | 8    | 373 |     |     | 0.3  | 1.8 | 0.2 | -0.7 | 1.3 |                    |
| TPV/r                           | 8    | 367 |     |     | 0.5  | 1.9 | 0.3 | -0.6 | 1.4 |                    |
|                                 | 16   | 667 |     |     | 0.2  | 2.1 | 0.1 | -0.8 | 1.1 | 0.5927             |
| CPI/r                           | 16   | 311 |     |     | 0.2  | 2.2 | 0.1 | -0.8 | 1.1 |                    |
| TPV/r                           | 16   | 356 |     |     | 0.3  | 1.9 | 0.1 | -0.8 | 1.2 |                    |
|                                 | 24   | 335 |     |     | 0.3  | 4.1 | 0.1 | -1.0 | 1.1 | 0.4845             |
| CPI/r                           | 24   | 132 |     |     | 0.1  | 1.9 | 0.2 | -1.0 | 1.1 |                    |
| TPV/r                           | 24   | 203 |     |     | 0.5  | 5.0 | 0.1 | -1.1 | 1.0 |                    |

Table 22: Study 1182\_0048: Change from Baseline ALT (SGPT,U/L)

| TRTGRP                           | Week | N   | Min | Max | mean | Std  | Med  | p25  | p75  | P <sub>value</sub> |
|----------------------------------|------|-----|-----|-----|------|------|------|------|------|--------------------|
| <b>Baseline SGPT</b>             |      |     |     |     |      |      |      |      |      |                    |
|                                  | 0    | 860 |     |     | 33.8 | 19.9 | 28.0 | 20.5 | 41.5 | 0.6606             |
| CPI/r                            | 0    | 427 |     |     | 34.5 | 20.5 | 28.0 | 20.5 | 42.5 |                    |
| TPV/r                            | 0    | 433 |     |     | 33.1 | 19.3 | 28.0 | 20.0 | 40.5 |                    |
| <b>Change from Baseline SGPT</b> |      |     |     |     |      |      |      |      |      |                    |
|                                  | 2    | 796 |     |     | 11.1 | 67.6 | 2.0  | -4.5 | 11.8 | 0.0001             |
| CPI/r                            | 2    | 390 |     |     | 4.0  | 37.6 | 0.0  | -6.0 | 6.5  |                    |
| TPV/r                            | 2    | 406 |     |     | 17.9 | 86.7 | 6.0  | -1.5 | 19.0 | 0.0002             |
|                                  | 4    | 799 |     |     | 6.6  | 35.6 | 1.5  | -5.5 | 10.0 |                    |
| CPI/r                            | 4    | 396 |     |     | 1.6  | 21.4 | 0.0  | -5.8 | 7.0  | 0.0001             |
| TPV/r                            | 4    | 403 |     |     | 11.5 | 44.8 | 3.0  | -5.0 | 14.5 |                    |
|                                  | 8    | 814 |     |     | 6.9  | 39.6 | 2.0  | -6.0 | 11.5 | 0.0001             |
| CPI/r                            | 8    | 401 |     |     | 1.4  | 23.3 | -0.5 | -7.5 | 7.5  |                    |
| TPV/r                            | 8    | 413 |     |     | 12.3 | 50.1 | 4.5  | -4.5 | 15.5 | 0.0001             |
|                                  | 16   | 733 |     |     | 13.7 | 58.4 | 4.0  | -5.0 | 15.5 |                    |
| CPI/r                            | 16   | 339 |     |     | 3.9  | 32.3 | 1.5  | -7.5 | 10.0 | 0.0744             |
| TPV/r                            | 16   | 394 |     |     | 22.1 | 72.8 | 6.5  | -2.5 | 24.0 |                    |
|                                  | 24   | 362 |     |     | 16.5 | 51.2 | 5.4  | -3.5 | 24.0 | 0.0744             |
| CPI/r                            | 24   | 137 |     |     | 10.0 | 35.9 | 4.5  | -6.5 | 18.0 |                    |
| TPV/r                            | 24   | 225 |     |     | 20.5 | 58.2 | 6.0  | -2.0 | 27.0 |                    |

Table 23: Study 1182\_0048: Change from Baseline Gamma GT (U/L)

| TRTGRP                          | Week | N   | Min | Max | mean  | Std   | Med  | p25   | p75   | P <sub>value</sub> |
|---------------------------------|------|-----|-----|-----|-------|-------|------|-------|-------|--------------------|
| <b>Baseline GGT</b>             |      |     |     |     |       |       |      |       |       |                    |
|                                 | 0    | 860 |     |     | 81.8  | 117.2 | 50.5 | 30.0  | 91.5  | 0.3991             |
| CPI/r                           | 0    | 427 |     |     | 80.5  | 136.4 | 51.0 | 29.5  | 82.5  |                    |
| TPV/r                           | 0    | 433 |     |     | 83.0  | 94.7  | 49.0 | 30.5  | 98.0  |                    |
| <b>Change from Baseline GGT</b> |      |     |     |     |       |       |      |       |       |                    |
|                                 | 2    | 800 |     |     | 9.5   | 74.9  | 4.0  | -6.0  | 19.0  | 0.0001             |
| CPI/r                           | 2    | 391 |     |     | -4.0  | 83.5  | -1.0 | -11.0 | 6.5   |                    |
| TPV/r                           | 2    | 409 |     |     | 22.4  | 63.1  | 11.5 | 1.0   | 32.0  | 0.0001             |
|                                 | 4    | 804 |     |     | 21.7  | 114.4 | 6.6  | -8.0  | 33.0  |                    |
| CPI/r                           | 4    | 398 |     |     | -5.6  | 115.3 | -2.0 | -16.0 | 9.5   | 0.0001             |
| TPV/r                           | 4    | 406 |     |     | 48.4  | 107.1 | 23.0 | 4.0   | 58.0  |                    |
|                                 | 8    | 817 |     |     | 29.1  | 128.5 | 10.0 | -7.7  | 48.5  | 0.0001             |
| CPI/r                           | 8    | 403 |     |     | -6.7  | 122.4 | -2.0 | -17.5 | 10.5  |                    |
| TPV/r                           | 8    | 414 |     |     | 64.0  | 124.7 | 33.5 | 9.0   | 87.0  | 0.0001             |
|                                 | 16   | 739 |     |     | 43.8  | 138.9 | 15.5 | -5.0  | 70.3  |                    |
| CPI/r                           | 16   | 342 |     |     | -10.1 | 127.3 | -1.0 | -18.0 | 11.5  | 0.0001             |
| TPV/r                           | 16   | 397 |     |     | 90.2  | 131.8 | 46.0 | 14.5  | 132.5 |                    |
|                                 | 24   | 367 |     |     | 70.9  | 142.7 | 29.0 | -1.0  | 113.5 | 0.0001             |
| CPI/r                           | 24   | 139 |     |     | 4.6   | 62.3  | -0.5 | -20.5 | 21.0  |                    |
| TPV/r                           | 24   | 228 |     |     | 111.3 | 161.7 | 70.0 | 19.5  | 159.0 |                    |

Table 24: Study 1182\_0048: Change from Baseline Total Bilirubin (mg/dL)

| TRTGRP                                      | Week | N   | Min | Max | mean | Std | Med  | p25  | p75 | P <sub>value</sub> |
|---|------|-----|-----|-----|------|-----|------|------|-----|--------------------|
| <b>Baseline Total Bilirubin</b>             |      |     |     |     |      |     |      |      |     |                    |
|   | 0    | 860 |     |     | 0.5  | 0.4 | 0.4  | 0.3  | 0.6 | 0.3865             |
| CPI/r                                       | 0    | 427 |     |     | 0.6  | 0.5 | 0.5  | 0.4  | 0.6 |                    |
| TPV/r                                       | 0    | 433 |     |     | 0.5  | 0.3 | 0.4  | 0.3  | 0.6 |                    |
| <b>Change from Baseline Total Bilirubin</b> |      |     |     |     |      |     |      |      |     |                    |
|   | 2    | 796 |     |     | -0.1 | 0.4 | -0.1 | -0.2 | 0.0 | 0.0001             |
| CPI/r                                       | 2    | 390 |     |     | -0.1 | 0.4 | -0.1 | -0.2 | 0.1 |                    |
| TPV/r                                       | 2    | 406 |     |     | -0.1 | 0.4 | -0.1 | -0.2 | 0.0 |                    |
|   | 4    | 802 |     |     | -0.1 | 0.8 | -0.1 | -0.2 | 0.0 | 0.0001             |
| CPI/r                                       | 4    | 397 |     |     | -0.1 | 1.1 | -0.1 | -0.2 | 0.1 |                    |
| TPV/r                                       | 4    | 405 |     |     | -0.2 | 0.3 | -0.1 | -0.3 | 0.0 |                    |
|   | 8    | 816 |     |     | -0.1 | 0.5 | -0.1 | -0.2 | 0.1 | 0.0001             |
| CPI/r                                       | 8    | 402 |     |     | -0.1 | 0.5 | 0.0  | -0.2 | 0.1 |                    |
| TPV/r                                       | 8    | 414 |     |     | -0.1 | 0.4 | -0.1 | -0.3 | 0.0 |                    |
|   | 16   | 736 |     |     | -0.1 | 0.4 | -0.1 | -0.2 | 0.1 | 0.0011             |
| CPI/r                                       | 16   | 340 |     |     | -0.1 | 0.5 | 0.0  | -0.2 | 0.1 |                    |
| TPV/r                                       | 16   | 396 |     |     | -0.1 | 0.3 | -0.1 | -0.2 | 0.0 |                    |
|   | 24   | 364 |     |     | -0.1 | 0.4 | 0.0  | -0.2 | 0.1 | 0.0010             |
| CPI/r                                       | 24   | 139 |     |     | 0.0  | 0.5 | 0.0  | -0.2 | 0.1 |                    |
| TPV/r                                       | 24   | 225 |     |     | -0.1 | 0.3 | -0.1 | -0.2 | 0.1 |                    |

Table 25: Study 1182\_0048: Change from Baseline Total Cholesterol (mg/dL)

| TRTGRP                                  | Week | N   | Min | Max | mean  | Std  | Med   | p25   | p75   | P <sub>value</sub> |
|---|------|-----|-----|-----|-------|------|-------|-------|-------|--------------------|
| <b>Baseline Cholesterol</b>             |      |     |     |     |       |      |       |       |       |                    |
|   | 0    | 860 |     |     | 186.4 | 46.7 | 182.5 | 153.4 | 215.0 | 0.1115             |
| CPI/r                                   | 0    | 427 |     |     | 189.3 | 48.7 | 185.7 | 154.1 | 216.4 |                    |
| TPV/r                                   | 0    | 433 |     |     | 183.5 | 44.4 | 177.3 | 152.7 | 213.8 |                    |
| <b>Change from Baseline Cholesterol</b> |      |     |     |     |       |      |       |       |       |                    |
|   | 2    | 799 |     |     | 9.9   | 36.1 | 5.5   | -11.0 | 30.4  | 0.0001             |
| CPI/r                                   | 2    | 391 |     |     | -2.0  | 30.9 | -2.5  | -16.6 | 13.9  |                    |
| TPV/r                                   | 2    | 408 |     |     | 21.3  | 37.1 | 16.3  | -1.4  | 43.5  |                    |
|   | 4    | 807 |     |     | 11.7  | 43.7 | 6.4   | -13.5 | 33.3  | 0.0001             |
| CPI/r                                   | 4    | 399 |     |     | -2.2  | 34.7 | -1.5  | -21.8 | 17.0  |                    |
| TPV/r                                   | 4    | 408 |     |     | 25.3  | 47.2 | 19.8  | -5.6  | 45.8  |                    |
|   | 8    | 818 |     |     | 14.4  | 46.2 | 8.1   | -12.8 | 35.0  | 0.0001             |
| CPI/r                                   | 8    | 403 |     |     | -1.6  | 41.9 | -2.1  | -22.0 | 17.8  |                    |
| TPV/r                                   | 8    | 415 |     |     | 29.9  | 44.9 | 19.9  | 0.0   | 51.0  |                    |
|   | 16   | 737 |     |     | 18.5  | 46.5 | 13.0  | -8.7  | 41.0  | 0.0001             |
| CPI/r                                   | 16   | 340 |     |     | 3.3   | 43.4 | 1.0   | -20.7 | 25.7  |                    |
| TPV/r                                   | 16   | 397 |     |     | 31.5  | 45.1 | 22.3  | 0.0   | 56.5  |                    |
|   | 24   | 368 |     |     | 23.6  | 49.9 | 17.3  | -8.2  | 48.7  | 0.0001             |
| CPI/r                                   | 24   | 140 |     |     | 2.9   | 44.6 | -0.6  | -22.0 | 27.5  |                    |
| TPV/r                                   | 24   | 228 |     |     | 36.4  | 48.8 | 29.0  | 6.0   | 61.1  |                    |

Table 26: Study 1182\_0048: Change from Baseline Triglycerides (mg/dL)

| TRTGRP                                    | Week | N   | Min | Max | mean  | Std   | Med   | p25    | p75   | P <sub>value</sub> |
|---|------|-----|-----|-----|-------|-------|-------|--------|-------|--------------------|
| <b>Baseline Triglycerides</b>             |      |     |     |     |       |       |       |        |       |                    |
|   | 0    | 860 |     |     | 295.1 | 190.9 | 235.8 | 160.9  | 368.5 | 0.9708             |
| CPI/r                                     | 0    | 427 |     |     | 301.2 | 203.0 | 232.5 | 159.9  | 369.4 |                    |
| TPV/r                                     | 0    | 433 |     |     | 289.1 | 178.1 | 240.5 | 166.0  | 355.2 |                    |
| <b>Change from Baseline Triglycerides</b> |      |     |     |     |       |       |       |        |       |                    |
|   | 2    | 799 |     |     | 27.7  | 222.0 | 13.7  | -60.7  | 97.4  | 0.0001             |
| CPI/r                                     | 2    | 391 |     |     | -19.2 | 200.9 | -8.0  | -95.0  | 38.5  |                    |
| TPV/r                                     | 2    | 408 |     |     | 72.7  | 232.0 | 48.9  | -21.6  | 137.6 |                    |
|   | 4    | 807 |     |     | 27.9  | 247.5 | 15.1  | -66.5  | 95.2  | 0.0001             |
| CPI/r                                     | 4    | 399 |     |     | -30.9 | 199.7 | -18.6 | -111.7 | 52.3  |                    |
| TPV/r                                     | 4    | 408 |     |     | 85.5  | 275.0 | 49.8  | -28.0  | 140.9 |                    |
|   | 8    | 818 |     |     | 39.2  | 226.3 | 19.3  | -62.5  | 121.3 | 0.0001             |
| CPI/r                                     | 8    | 403 |     |     | -24.3 | 217.0 | -16.4 | -102.2 | 57.6  |                    |
| TPV/r                                     | 8    | 415 |     |     | 100.9 | 218.3 | 59.3  | -9.3   | 180.5 |                    |
|   | 16   | 737 |     |     | 40.0  | 251.3 | 18.6  | -58.9  | 117.0 | 0.0001             |
| CPI/r                                     | 16   | 340 |     |     | -14.6 | 261.5 | -16.2 | -90.0  | 64.7  |                    |
| TPV/r                                     | 16   | 397 |     |     | 86.7  | 232.5 | 51.8  | -24.0  | 158.0 |                    |
|   | 24   | 368 |     |     | 34.9  | 228.2 | 5.2   | -76.4  | 118.9 | 0.0001             |
| CPI/r                                     | 24   | 140 |     |     | -16.2 | 243.9 | -22.6 | -123.6 | 54.9  |                    |
| TPV/r                                     | 24   | 228 |     |     | 66.3  | 212.5 | 30.8  | -50.7  | 151.0 |                    |

Table 27: Study 1182\_0048: Change from Baseline Creatinine (mg/dL)

| TRTGRP                                 | Week | N   | Min | Max | mean  | Std  | Med   | p25   | p75  | P <sub>value</sub> |
|--|------|-----|-----|-----|-------|------|-------|-------|------|--------------------|
| <b>Baseline Creatinine</b>             |      |     |     |     |       |      |       |       |      |                    |
|  | 0    | 860 |     |     | 0.84  | 0.20 | 0.82  | 0.70  | 0.93 | 0.5947             |
| CPI/r                                  | 0    | 427 |     |     | 0.84  | 0.20 | 0.81  | 0.71  | 0.94 |                    |
| TPV/r                                  | 0    | 433 |     |     | 0.83  | 0.20 | 0.83  | 0.70  | 0.93 |                    |
| <b>Change from Baseline Creatinine</b> |      |     |     |     |       |      |       |       |      |                    |
|  | 2    | 800 |     |     | 0.00  | 0.14 | 0.00  | -0.07 | 0.06 | 0.0001             |
| CPI/r                                  | 2    | 391 |     |     | 0.02  | 0.16 | 0.01  | -0.05 | 0.08 |                    |
| TPV/r                                  | 2    | 409 |     |     | -0.02 | 0.11 | -0.03 | -0.09 | 0.04 |                    |
|  | 4    | 805 |     |     | -0.01 | 0.12 | 0.00  | -0.08 | 0.07 | 0.0001             |
| CPI/r                                  | 4    | 398 |     |     | 0.02  | 0.12 | 0.01  | -0.05 | 0.09 |                    |
| TPV/r                                  | 4    | 407 |     |     | -0.03 | 0.12 | -0.02 | -0.10 | 0.05 |                    |
|  | 8    | 817 |     |     | 0.00  | 0.13 | 0.00  | -0.07 | 0.07 | 0.0001             |
| CPI/r                                  | 8    | 403 |     |     | 0.03  | 0.13 | 0.02  | -0.05 | 0.10 |                    |
| TPV/r                                  | 8    | 414 |     |     | -0.02 | 0.14 | -0.02 | -0.10 | 0.05 |                    |
|  | 16   | 739 |     |     | 0.01  | 0.16 | 0.00  | -0.07 | 0.09 | 0.0001             |
| CPI/r                                  | 16   | 342 |     |     | 0.04  | 0.17 | 0.03  | -0.05 | 0.10 |                    |
| TPV/r                                  | 16   | 397 |     |     | -0.01 | 0.14 | -0.01 | -0.10 | 0.06 |                    |
|  | 24   | 368 |     |     | 0.02  | 0.15 | 0.01  | -0.06 | 0.10 | 0.0029             |
| CPI/r                                  | 24   | 140 |     |     | 0.05  | 0.15 | 0.04  | -0.04 | 0.12 |                    |
| TPV/r                                  | 24   | 228 |     |     | 0.00  | 0.14 | -0.01 | -0.08 | 0.08 |                    |

Table 28: Study 1182\_0004: Change from Baseline AST (SGOT,U/L)

| TRTGRP                              | Week | N  | Min | Max | mean  | Std  | Med  | p25   | p75  | p-value |
|-------------------------------------|------|----|-----|-----|-------|------|------|-------|------|---------|
| <b>Baseline SGOT</b>                |      |    |     |     |       |      |      |       |      |         |
| Total                               | 0    | 79 |     |     | 38.5  | 31.7 | 27.0 | 22.0  | 38.0 | 0.6754  |
| SQV/r                               | 0    | 29 |     |     | 32.9  | 23.4 | 26.5 | 21.0  | 35.7 |         |
| TPV/r High                          | 0    | 25 |     |     | 43.7  | 38.8 | 27.5 | 21.5  | 45.5 |         |
| TPV/r Low                           | 0    | 25 |     |     | 40.0  | 32.5 | 27.0 | 23.0  | 41.0 |         |
| <b>Change from Baseline in SGOT</b> |      |    |     |     |       |      |      |       |      |         |
| Total                               | 2    | 71 |     |     | -5.8  | 18.3 | -1.5 | -8.0  | 3.0  | 0.1188  |
| SQV/r                               | 2    | 26 |     |     | -2.1  | 18.3 | 0.3  | -6.0  | 6.5  |         |
| TPV/r High                          | 2    | 23 |     |     | -9.2  | 19.2 | -1.5 | -10.5 | 0.5  |         |
| TPV/r Low                           | 2    | 22 |     |     | -6.7  | 17.3 | -2.5 | -8.0  | -0.5 |         |
| Total                               | 4    | 73 |     |     | -4.5  | 31.0 | -1.0 | -9.0  | 2.5  | 0.5602  |
| SQV/r                               | 4    | 27 |     |     | -5.5  | 19.5 | 0.0  | -9.0  | 2.5  |         |
| TPV/r High                          | 4    | 23 |     |     | -4.7  | 34.1 | -0.5 | -4.5  | 4.5  |         |
| TPV/r Low                           | 4    | 23 |     |     | -3.0  | 39.2 | -2.0 | -9.0  | 1.5  |         |
| Total                               | 8    | 67 |     |     | 2.8   | 38.6 | 0.0  | -6.0  | 7.0  | 0.0086  |
| SQV/r                               | 8    | 26 |     |     | 15.9  | 32.9 | 5.0  | -0.5  | 12.5 |         |
| TPV/r High                          | 8    | 20 |     |     | -14.8 | 33.4 | -3.0 | -18.0 | 2.5  |         |
| TPV/r Low                           | 8    | 21 |     |     | 3.5   | 44.3 | -2.0 | -6.5  | 1.5  |         |
| Total                               | 16   | 67 |     |     | 2.6   | 34.8 | 0.5  | -9.0  | 11.5 | 0.0025  |
| SQV/r                               | 16   | 25 |     |     | 17.5  | 30.5 | 8.0  | 1.0   | 16.0 |         |
| TPV/r High                          | 16   | 21 |     |     | -9.0  | 39.0 | -3.0 | -22.5 | 3.0  |         |
| TPV/r Low                           | 16   | 21 |     |     | -3.7  | 30.1 | -4.0 | -9.5  | 14.5 |         |
| Total                               | 24   | 53 |     |     | 6.3   | 31.1 | 0.3  | -5.0  | 8.0  | 0.6916  |
| SQV/r                               | 24   | 17 |     |     | 6.6   | 17.2 | 2.0  | -2.0  | 5.0  |         |
| TPV/r High                          | 24   | 19 |     |     | 0.3   | 36.6 | -0.5 | -9.0  | 9.0  |         |
| TPV/r Low                           | 24   | 17 |     |     | 12.8  | 35.5 | 0.3  | -6.0  | 14.5 |         |

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Table 29: Study 1182\_0004: Change from Baseline ALT (SGPT,U/L)

| TRTGRP                              | Week | N  | Min | Max | Mean  | Std  | Med  | p25   | p75  | p-value |
|-------------------------------------|------|----|-----|-----|-------|------|------|-------|------|---------|
| <b>Baseline SGPT</b>                |      |    |     |     |       |      |      |       |      |         |
| Total                               | 0    | 79 |     |     | 40.7  | 42.7 | 29.0 | 17.5  | 43.5 | 0.7076  |
| SQV/r                               | 0    | 29 |     |     | 32.0  | 18.2 | 27.0 | 15.0  | 39.0 |         |
| TPV/r High                          | 0    | 25 |     |     | 52.5  | 62.7 | 31.5 | 17.5  | 45.5 |         |
| TPV/r Low                           | 0    | 25 |     |     | 38.8  | 37.1 | 28.5 | 22.5  | 42.5 |         |
| <b>Change from Baseline in SGPT</b> |      |    |     |     |       |      |      |       |      |         |
| Total                               | 2    | 71 |     |     | 1.0   | 25.0 | 1.5  | -5.5  | 10.0 | 0.6467  |
| SQV/r                               | 2    | 26 |     |     | 4.0   | 20.4 | 1.5  | -5.0  | 10.5 |         |
| TPV/r High                          | 2    | 23 |     |     | -2.3  | 29.0 | 5.0  | -9.0  | 14.0 |         |
| TPV/r Low                           | 2    | 22 |     |     | 0.8   | 26.3 | 0.3  | -5.5  | 4.5  |         |
| Total                               | 4    | 73 |     |     | -2.3  | 39.0 | -0.5 | -8.0  | 5.5  | 0.4665  |
| SQV/r                               | 4    | 27 |     |     | -0.2  | 15.3 | 1.0  | -8.0  | 5.0  |         |
| TPV/r High                          | 4    | 23 |     |     | -10.1 | 43.8 | 3.5  | -8.0  | 8.5  |         |
| TPV/r Low                           | 4    | 23 |     |     | 3.1   | 51.9 | -2.5 | -14.0 | 2.5  |         |
| Total                               | 8    | 67 |     |     | 6.2   | 72.4 | -0.5 | -12.0 | 11.0 | 0.1428  |
| SQV/r                               | 8    | 26 |     |     | 22.6  | 74.4 | 1.0  | -5.0  | 11.0 |         |
| TPV/r High                          | 8    | 20 |     |     | -21.9 | 50.8 | -5.8 | -28.5 | 6.0  |         |
| TPV/r Low                           | 8    | 21 |     |     | 12.7  | 82.0 | 1.0  | -8.5  | 14.5 |         |
| Total                               | 16   | 67 |     |     | 6.3   | 48.3 | 2.5  | -9.5  | 19.5 | 0.0468  |
| SQV/r                               | 16   | 25 |     |     | 17.2  | 31.2 | 6.0  | 0.2   | 21.5 |         |
| TPV/r High                          | 16   | 21 |     |     | -4.3  | 61.6 | -3.5 | -22.5 | 6.5  |         |
| TPV/r Low                           | 16   | 21 |     |     | 3.8   | 49.5 | 1.0  | -6.0  | 19.5 |         |
| Total                               | 24   | 53 |     |     | 15.7  | 55.1 | 6.0  | -5.0  | 21.0 | 0.9326  |
| SQV/r                               | 24   | 17 |     |     | 13.1  | 26.1 | 7.0  | -4.5  | 15.2 |         |
| TPV/r High                          | 24   | 19 |     |     | 3.9   | 43.3 | 7.0  | -12.5 | 26.5 |         |
| TPV/r Low                           | 24   | 17 |     |     | 31.6  | 81.4 | 4.0  | -3.5  | 12.0 |         |

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Table 30: Study 1182\_0004: Change from Baseline Gamma GT (U/L)

| TRTGRP                                  | Week | N  | Min | Max | mean | Std   | Med  | p25  | p75   | p-value |
|---|------|----|-----|-----|------|-------|------|------|-------|---------|
| <b>Baseline Gamma GT</b>                |      |    |     |     |      |       |      |      |       |         |
| Total                                   | 0    | 79 |     |     | 83.7 | 135.6 | 40.0 | 25.0 | 70.5  | 0.9665  |
| SQV/r                                   | 0    | 29 |     |     | 81.7 | 119.6 | 39.5 | 21.0 | 78.5  |         |
| TPV/r High                              | 0    | 25 |     |     | 98.9 | 188.5 | 38.0 | 26.5 | 65.5  |         |
| TPV/r Low                               | 0    | 25 |     |     | 70.9 | 84.5  | 42.0 | 30.0 | 63.5  |         |
| <b>Change from Baseline in Gamma GT</b> |      |    |     |     |      |       |      |      |       |         |
| Total                                   | 2    | 71 |     |     | 10.4 | 27.7  | 9.0  | 1.0  | 23.5  | 0.0070  |
| SQV/r                                   | 2    | 26 |     |     | 4.1  | 29.5  | 1.8  | -2.0 | 13.0  |         |
| TPV/r High                              | 2    | 23 |     |     | 19.9 | 15.8  | 18.5 | 7.5  | 27.5  |         |
| TPV/r Low                               | 2    | 22 |     |     | 7.8  | 33.4  | 6.0  | 1.0  | 16.5  |         |
| Total                                   | 4    | 73 |     |     | 20.7 | 90.4  | 14.5 | 3.5  | 42.5  | 0.0054  |
| SQV/r                                   | 4    | 27 |     |     | 7.2  | 32.5  | 4.0  | 0.0  | 24.5  |         |
| TPV/r High                              | 4    | 23 |     |     | 18.6 | 150.4 | 22.5 | 13.0 | 59.5  |         |
| TPV/r Low                               | 4    | 23 |     |     | 38.7 | 48.2  | 21.5 | 8.0  | 68.5  |         |
| Total                                   | 8    | 67 |     |     | 37.3 | 68.2  | 23.5 | 6.0  | 63.5  | 0.6107  |
| SQV/r                                   | 8    | 26 |     |     | 27.8 | 58.7  | 17.8 | 6.0  | 45.0  |         |
| TPV/r High                              | 8    | 20 |     |     | 40.7 | 80.4  | 25.0 | 9.0  | 67.8  |         |
| TPV/r Low                               | 8    | 21 |     |     | 45.7 | 68.6  | 37.5 | 8.0  | 86.5  |         |
| Total                                   | 16   | 67 |     |     | 46.5 | 103.8 | 30.0 | 7.5  | 65.5  | 0.3937  |
| SQV/r                                   | 16   | 25 |     |     | 26.6 | 62.9  | 14.0 | 7.0  | 53.0  |         |
| TPV/r High                              | 16   | 21 |     |     | 58.5 | 142.4 | 35.0 | 11.0 | 107.5 |         |
| TPV/r Low                               | 16   | 21 |     |     | 58.2 | 98.7  | 35.5 | 7.5  | 109.5 |         |
| Total                                   | 24   | 53 |     |     | 41.8 | 115.7 | 27.5 | 7.3  | 69.5  | 0.2048  |
| SQV/r                                   | 24   | 17 |     |     | 31.1 | 57.8  | 10.0 | 2.5  | 46.5  |         |
| TPV/r High                              | 24   | 19 |     |     | 19.1 | 158.2 | 39.5 | 12.5 | 71.5  |         |
| TPV/r Low                               | 24   | 17 |     |     | 78.0 | 99.3  | 26.0 | 16.0 | 95.0  |         |

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Table 31: Study 1182\_0004: Change from Baseline Total Bilirubin (mg/dL)

| TRTGRP   | Week | N  | Min | Max | mean | Std | Med  | p25  | p75  | p-value |
|--|------|----|-----|-----|------|-----|------|------|------|---------|
| <b>Baseline Total Bilirubin</b>                |      |    |     |     |      |     |      |      |      |         |
| Total  | 0    | 79 |     |     | 0.7  | 0.3 | 0.6  | 0.5  | 0.9  | 0.1689  |
| SQV/r  | 0    | 29 |     |     | 0.6  | 0.3 | 0.6  | 0.5  | 0.7  |         |
| TPV/r High                                     | 0    | 25 |     |     | 0.8  | 0.4 | 0.7  | 0.6  | 0.9  |         |
| TPV/r Low                                      | 0    | 25 |     |     | 0.7  | 0.4 | 0.6  | 0.5  | 0.8  |         |
| <b>Change from Baseline in Total Bilirubin</b> |      |    |     |     |      |     |      |      |      |         |
| Total  | 2    | 71 |     |     | -0.1 | 0.3 | -0.1 | -0.3 | 0.1  | 0.0095  |
| SQV/r  | 2    | 26 |     |     | 0.0  | 0.3 | 0.0  | -0.1 | 0.2  |         |
| TPV/r High                                     | 2    | 23 |     |     | -0.2 | 0.2 | -0.2 | -0.4 | -0.1 |         |
| TPV/r Low                                      | 2    | 22 |     |     | -0.2 | 0.4 | -0.1 | -0.3 | 0.1  |         |
| Total  | 4    | 73 |     |     | 0.0  | 1.2 | -0.1 | -0.2 | 0.1  | 0.1766  |
| SQV/r  | 4    | 27 |     |     | 0.0  | 0.3 | 0.0  | -0.2 | 0.2  |         |
| TPV/r High                                     | 4    | 23 |     |     | 0.3  | 2.1 | -0.1 | -0.3 | 0.0  |         |
| TPV/r Low                                      | 4    | 23 |     |     | -0.2 | 0.4 | -0.1 | -0.4 | 0.1  |         |
| Total  | 8    | 67 |     |     | -0.1 | 0.4 | -0.1 | -0.3 | 0.1  | 0.0683  |
| SQV/r  | 8    | 26 |     |     | 0.0  | 0.3 | 0.1  | -0.2 | 0.1  |         |
| TPV/r High                                     | 8    | 20 |     |     | -0.2 | 0.3 | -0.1 | -0.3 | 0.0  |         |
| TPV/r Low                                      | 8    | 21 |     |     | -0.2 | 0.4 | -0.2 | -0.3 | 0.0  |         |
| Total  | 16   | 67 |     |     | -0.1 | 0.4 | 0.0  | -0.3 | 0.1  | 0.0729  |
| SQV/r  | 16   | 25 |     |     | 0.0  | 0.3 | 0.1  | -0.1 | 0.2  |         |
| TPV/r High                                     | 16   | 21 |     |     | -0.2 | 0.4 | -0.1 | -0.3 | 0.0  |         |
| TPV/r Low                                      | 16   | 21 |     |     | -0.2 | 0.4 | -0.1 | -0.3 | 0.1  |         |
| Total  | 24   | 53 |     |     | 0.0  | 0.7 | -0.1 | -0.3 | 0.2  | 0.7692  |
| SQV/r  | 24   | 17 |     |     | 0.0  | 0.4 | 0.0  | -0.3 | 0.3  |         |
| TPV/r High                                     | 24   | 19 |     |     | 0.1  | 1.0 | -0.1 | -0.4 | 0.1  |         |
| TPV/r Low                                      | 24   | 17 |     |     | -0.1 | 0.4 | 0.1  | -0.4 | 0.2  |         |

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Table 32: Study 1182\_0004: Change from Baseline Creatinine (mg/dL)

| TRTGRP <sup>1</sup>                       | Week | N  | Min | Max | mean  | Std  | Med   | p25   | p75  | p-value |
|---|------|----|-----|-----|-------|------|-------|-------|------|---------|
| <b>Baseline Creatinine</b>                |      |    |     |     |       |      |       |       |      |         |
| Total                                     | 0    | 79 |     |     | 0.91  | 0.24 | 0.90  | 0.75  | 1.00 | 0.0903  |
| SQV/r                                     | 0    | 29 |     |     | 0.90  | 0.19 | 0.95  | 0.79  | 1.00 |         |
| TPV/r High                                | 0    | 25 |     |     | 0.99  | 0.32 | 0.90  | 0.90  | 1.10 |         |
| TPV/r Low                                 | 0    | 25 |     |     | 0.83  | 0.16 | 0.75  | 0.70  | 1.00 |         |
| <b>Change from Baseline in Creatinine</b> |      |    |     |     |       |      |       |       |      |         |
| Total                                     | 2    | 71 |     |     | 0.01  | 0.15 | 0.00  | -0.10 | 0.10 | 0.0532  |
| SQV/r                                     | 2    | 26 |     |     | 0.07  | 0.15 | 0.04  | 0.00  | 0.19 |         |
| TPV/r High                                | 2    | 23 |     |     | -0.03 | 0.16 | 0.00  | -0.10 | 0.10 |         |
| TPV/r Low                                 | 2    | 22 |     |     | -0.02 | 0.10 | 0.00  | -0.10 | 0.05 |         |
| Total                                     | 4    | 73 |     |     | 0.02  | 0.16 | 0.00  | -0.05 | 0.10 | 0.0024  |
| SQV/r                                     | 4    | 27 |     |     | 0.11  | 0.15 | 0.10  | 0.00  | 0.20 |         |
| TPV/r High                                | 4    | 23 |     |     | -0.05 | 0.15 | 0.00  | -0.14 | 0.05 |         |
| TPV/r Low                                 | 4    | 23 |     |     | -0.02 | 0.14 | 0.00  | -0.08 | 0.05 |         |
| Total                                     | 8    | 67 |     |     | 0.04  | 0.18 | 0.00  | -0.05 | 0.12 | 0.0403  |
| SQV/r                                     | 8    | 26 |     |     | 0.09  | 0.13 | 0.06  | 0.00  | 0.18 |         |
| TPV/r High                                | 8    | 20 |     |     | -0.02 | 0.12 | 0.00  | -0.12 | 0.08 |         |
| TPV/r Low                                 | 8    | 21 |     |     | 0.03  | 0.27 | 0.00  | -0.10 | 0.10 |         |
| Total                                     | 16   | 67 |     |     | 0.05  | 0.15 | 0.05  | -0.08 | 0.15 | 0.1833  |
| SQV/r                                     | 16   | 25 |     |     | 0.09  | 0.15 | 0.10  | 0.00  | 0.15 |         |
| TPV/r High                                | 16   | 21 |     |     | -0.01 | 0.14 | -0.05 | -0.10 | 0.05 |         |
| TPV/r Low                                 | 16   | 21 |     |     | 0.05  | 0.17 | 0.00  | -0.06 | 0.18 |         |
| Total                                     | 24   | 53 |     |     | 0.04  | 0.17 | 0.05  | -0.10 | 0.14 | 0.3276  |
| SQV/r                                     | 24   | 17 |     |     | 0.08  | 0.19 | 0.10  | -0.05 | 0.15 |         |
| TPV/r High                                | 24   | 19 |     |     | 0.00  | 0.12 | 0.00  | -0.10 | 0.10 |         |
| TPV/r Low                                 | 24   | 17 |     |     | 0.05  | 0.18 | 0.05  | -0.10 | 0.15 |         |

1. SQV/r – SQV 400 mg and RTV 400 mg regimen; TPV/r high- TPV 1250 mg and RTV 100 mg regimen; TPV/r low- TPV 500 mg and RTV 100 mg regimen.

Table 33: 1182\_0051: Change from Baseline Platelets (1,000 cells/mm<sup>3</sup>) & Hemoglobin (g/dl)

| TRTGRP                                   | Week | N   | Min | Max | mean  | Std  | Med   | p25   | p75   | p-value |
|--|------|-----|-----|-----|-------|------|-------|-------|-------|---------|
| <b>Baseline Platelets</b>                |      |     |     |     |       |      |       |       |       |         |
|  | 0    | 310 |     |     | 200.6 | 68.1 | 198.5 | 150.0 | 240.0 | 0.5571  |
| APV/TPV/r                                | 0    | 81  |     |     | 197.5 | 75.5 | 184.5 | 145.0 | 224.5 |         |
| LPV/TPV/r                                | 0    | 83  |     |     | 204.0 | 64.9 | 198.5 | 156.0 | 241.5 |         |
| SQV/TPV/r                                | 0    | 81  |     |     | 204.9 | 67.2 | 205.5 | 144.5 | 246.5 |         |
| TPV/r                                    | 0    | 65  |     |     | 194.4 | 64.1 | 195.0 | 150.0 | 238.5 |         |
| <b>Change from Baseline in Platelets</b> |      |     |     |     |       |      |       |       |       |         |
|  | 2    | 270 |     |     | 8.2   | 41.7 | 5.0   | -13.5 | 30.5  | 0.4566  |
| APV/TPV/r                                | 2    | 66  |     |     | 4.9   | 47.5 | 0.5   | -19.5 | 23.5  |         |
| LPV/TPV/r                                | 2    | 77  |     |     | 8.7   | 37.8 | 8.0   | -5.0  | 32.0  |         |
| SQV/TPV/r                                | 2    | 70  |     |     | 5.9   | 41.9 | 1.3   | -16.5 | 30.5  |         |
| TPV/r                                    | 2    | 57  |     |     | 14.3  | 39.5 | 10.0  | -7.5  | 40.5  |         |
|  | 4    | 280 |     |     | 16.1  | 49.7 | 11.5  | -12.8 | 44.3  | 0.0010  |
| APV/TPV/r                                | 4    | 72  |     |     | 6.1   | 43.7 | 8.5   | -17.8 | 33.0  |         |
| LPV/TPV/r                                | 4    | 74  |     |     | 31.6  | 52.7 | 24.8  | 3.0   | 53.5  |         |
| SQV/TPV/r                                | 4    | 76  |     |     | 20.1  | 55.2 | 14.5  | -7.5  | 50.5  |         |
| TPV/r                                    | 4    | 58  |     |     | 3.6   | 39.0 | -3.8  | -21.0 | 28.0  |         |
| <b>Baseline HGB</b>                      |      |     |     |     |       |      |       |       |       |         |
|  | 0    | 310 |     |     | 13.9  | 1.8  | 14.1  | 12.9  | 15.1  | 0.0372  |
| APV/TPV/r                                | 0    | 81  |     |     | 13.8  | 1.6  | 13.9  | 12.8  | 15.1  |         |
| LPV/TPV/r                                | 0    | 83  |     |     | 13.9  | 1.8  | 14.1  | 12.9  | 15.0  |         |
| SQV/TPV/r                                | 0    | 81  |     |     | 13.6  | 1.7  | 13.6  | 12.6  | 14.9  |         |
| TPV/r                                    | 0    | 65  |     |     | 14.3  | 1.9  | 14.6  | 13.4  | 15.4  |         |
| <b>Change from Baseline in HGB</b>       |      |     |     |     |       |      |       |       |       |         |
|  | 2    | 275 |     |     | -0.1  | 0.8  | -0.2  | -0.7  | 0.4   | <0.0001 |
| APV/TPV/r                                | 2    | 68  |     |     | -0.1  | 0.6  | -0.1  | -0.5  | 0.4   |         |
| LPV/TPV/r                                | 2    | 78  |     |     | -0.1  | 0.8  | -0.2  | -0.7  | 0.5   |         |
| SQV/TPV/r                                | 2    | 71  |     |     | 0.2   | 0.8  | 0.0   | -0.4  | 0.6   |         |
| TPV/r                                    | 2    | 58  |     |     | -0.6  | 0.6  | -0.6  | -1.0  | -0.1  |         |
|  | 4    | 283 |     |     | -0.4  | 0.9  | -0.3  | -1.0  | 0.1   | 0.7466  |
| APV/TPV/r                                | 4    | 73  |     |     | -0.3  | 0.7  | -0.2  | -0.8  | 0.2   |         |
| LPV/TPV/r                                | 4    | 74  |     |     | -0.4  | 0.9  | -0.4  | -1.0  | 0.1   |         |
| SQV/TPV/r                                | 4    | 76  |     |     | -0.4  | 1.2  | -0.3  | -1.0  | -0.1  |         |
| TPV/r                                    | 4    | 60  |     |     | -0.5  | 0.9  | -0.4  | -1.0  | 0.1   |         |

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Table 34: 1182\_0051: Change from Baseline AST (SGOT,U/L) and ALT (SGPT,U/L)

| TRTGRP                              | Week | N   | Min | Max | mean | Std   | Med  | p25  | p75  | p-value |
|-------------------------------------|------|-----|-----|-----|------|-------|------|------|------|---------|
| <b>Baseline SGOT</b>                |      |     |     |     |      |       |      |      |      |         |
|                                     | 0    | 314 |     |     | 37.8 | 16.8  | 34.0 | 26.0 | 44.5 | 0.2961  |
| APV/TPV/r                           | 0    | 83  |     |     | 39.2 | 16.1  | 36.0 | 26.5 | 48.0 |         |
| LPV/TPV/r                           | 0    | 83  |     |     | 36.9 | 14.0  | 35.5 | 24.5 | 45.0 |         |
| SQV/TPV/r                           | 0    | 81  |     |     | 38.5 | 18.7  | 32.5 | 27.0 | 44.5 |         |
| TPV/r                               | 0    | 67  |     |     | 36.5 | 18.5  | 31.0 | 24.0 | 40.0 |         |
| <b>Change from Baseline in SGOT</b> |      |     |     |     |      |       |      |      |      |         |
|                                     | 2    | 267 |     |     | 1.7  | 16.0  | 0.0  | -5.0 | 6.0  | 0.0305  |
| APV/TPV/r                           | 2    | 65  |     |     | 1.2  | 14.6  | -0.5 | -6.3 | 5.5  |         |
| LPV/TPV/r                           | 2    | 73  |     |     | -0.2 | 14.9  | -2.0 | -5.5 | 2.5  |         |
| SQV/TPV/r                           | 2    | 69  |     |     | 4.0  | 16.3  | 2.5  | -2.5 | 9.5  |         |
| TPV/r                               | 2    | 60  |     |     | 1.8  | 18.1  | 0.0  | -5.3 | 7.5  |         |
|                                     | 4    | 284 |     |     | 3.3  | 26.7  | 0.8  | -5.8 | 7.8  | 0.4644  |
| APV/TPV/r                           | 4    | 72  |     |     | 10.0 | 43.4  | 2.3  | -6.3 | 11.0 |         |
| LPV/TPV/r                           | 4    | 75  |     |     | 1.6  | 14.5  | -0.5 | -5.5 | 6.0  |         |
| SQV/TPV/r                           | 4    | 78  |     |     | 0.4  | 16.1  | 1.0  | -5.0 | 5.5  |         |
| TPV/r                               | 4    | 59  |     |     | 1.1  | 22.3  | 0.5  | -5.5 | 7.0  |         |
| <b>Baseline SGPT</b>                |      |     |     |     |      |       |      |      |      |         |
|                                     | 0    | 314 |     |     | 37.4 | 20.1  | 32.3 | 22.5 | 44.5 | 0.7982  |
| APV/TPV/r                           | 0    | 83  |     |     | 37.5 | 19.0  | 33.0 | 23.0 | 45.5 |         |
| LPV/TPV/r                           | 0    | 83  |     |     | 37.4 | 17.7  | 34.5 | 22.0 | 44.0 |         |
| SQV/TPV/r                           | 0    | 81  |     |     | 37.9 | 22.3  | 31.5 | 22.5 | 46.0 |         |
| TPV/r                               | 0    | 67  |     |     | 36.5 | 21.7  | 29.5 | 22.0 | 43.5 |         |
| <b>Change from Baseline in SGPT</b> |      |     |     |     |      |       |      |      |      |         |
|                                     | 2    | 272 |     |     | 4.8  | 21.1  | 1.5  | -5.0 | 10.8 | <0.0001 |
| APV/TPV/r                           | 2    | 66  |     |     | 2.8  | 15.1  | 0.5  | -5.0 | 10.5 |         |
| LPV/TPV/r                           | 2    | 76  |     |     | -2.1 | 15.4  | -1.8 | -9.5 | 3.3  |         |
| SQV/TPV/r                           | 2    | 70  |     |     | 6.7  | 17.9  | 4.0  | -0.5 | 16.0 |         |
| TPV/r                               | 2    | 60  |     |     | 13.5 | 31.2  | 5.5  | -2.5 | 21.5 |         |
|                                     | 4    | 296 |     |     | 15.6 | 60.2  | 4.0  | -4.0 | 20.5 | 0.0643  |
| APV/TPV/r                           | 4    | 75  |     |     | 33.8 | 106.2 | 9.5  | -3.0 | 36.5 |         |
| LPV/TPV/r                           | 4    | 78  |     |     | 8.2  | 26.1  | 2.5  | -7.0 | 14.0 |         |
| SQV/TPV/r                           | 4    | 78  |     |     | 6.0  | 20.7  | 2.8  | -4.0 | 10.5 |         |
| TPV/r                               | 4    | 65  |     |     | 15.0 | 42.1  | 4.0  | -3.0 | 15.5 |         |

Table 35: 1182\_0051: Change from Baseline Gamma GT (U/L) and Total Bilirubin (mg/dL)

| TRTGRP   | Week | N   | Min | Max | mean  | Std   | Med  | p25  | p75   | p-value |
|--|------|-----|-----|-----|-------|-------|------|------|-------|---------|
| <b>Baseline Gamma GT</b>                       |      |     |     |     |       |       |      |      |       |         |
|  | 0    | 314 |     |     | 84.8  | 135.3 | 48.0 | 30.5 | 87.0  | 0.6077  |
| APV/TPV/r                                      | 0    | 83  |     |     | 89.2  | 106.4 | 47.5 | 31.5 | 105.0 |         |
| LPV/TPV/r                                      | 0    | 83  |     |     | 66.9  | 73.4  | 46.5 | 30.0 | 67.0  |         |
| SQV/TPV/r                                      | 0    | 81  |     |     | 86.6  | 119.9 | 52.0 | 27.0 | 96.0  |         |
| TPV/r  | 0    | 67  |     |     | 99.4  | 219.2 | 54.5 | 27.0 | 93.0  |         |
| <b>Change from Baseline in Gamma GT</b>        |      |     |     |     |       |       |      |      |       |         |
|  | 2    | 276 |     |     | 0.8   | 70.8  | 1.0  | -6.0 | 11.0  | <0.0001 |
| APV/TPV/r                                      | 2    | 69  |     |     | -11.8 | 47.2  | -1.5 | -7.0 | 7.0   |         |
| LPV/TPV/r                                      | 2    | 76  |     |     | -4.9  | 27.4  | -2.0 | -8.0 | 3.5   | 0.0002  |
| SQV/TPV/r                                      | 2    | 70  |     |     | 7.7   | 45.9  | 0.0  | -6.5 | 13.0  |         |
| TPV/r  | 2    | 61  |     |     | 14.4  | 128.8 | 12.0 | 1.5  | 39.5  |         |
|  | 4    | 296 |     |     | 27.5  | 128.6 | 11.8 | 1.0  | 43.4  |         |
| APV/TPV/r                                      | 4    | 75  |     |     | 21.2  | 82.8  | 10.0 | -0.5 | 43.3  |         |
| LPV/TPV/r                                      | 4    | 78  |     |     | 13.6  | 56.5  | 8.0  | -0.5 | 23.5  |         |
| SQV/TPV/r                                      | 4    | 78  |     |     | 30.8  | 112.7 | 9.0  | 0.5  | 42.5  |         |
| TPV/r  | 4    | 65  |     |     | 47.3  | 220.1 | 31.5 | 13.0 | 71.0  |         |
| <b>Baseline Total Bilirubin</b>                |      |     |     |     |       |       |      |      |       |         |
|  | 0    | 314 |     |     | 0.58  | 0.38  | 0.47 | 0.35 | 0.67  | 0.6080  |
| APV/TPV/r                                      | 0    | 83  |     |     | 0.57  | 0.33  | 0.50 | 0.35 | 0.70  |         |
| LPV/TPV/r                                      | 0    | 83  |     |     | 0.64  | 0.48  | 0.50 | 0.38 | 0.70  |         |
| SQV/TPV/r                                      | 0    | 81  |     |     | 0.55  | 0.34  | 0.47 | 0.32 | 0.64  |         |
| TPV/r  | 0    | 67  |     |     | 0.57  | 0.36  | 0.44 | 0.35 | 0.67  |         |
| <b>Change from Baseline in Total Bilirubin</b> |      |     |     |     |       |       |      |      |       |         |
|  | 2    | 280 |     |     | -0.1  | 0.3   | -0.1 | -0.2 | 0.1   | 0.0012  |
| APV/TPV/r                                      | 2    | 69  |     |     | -0.1  | 0.3   | -0.1 | -0.2 | 0.0   |         |
| LPV/TPV/r                                      | 2    | 77  |     |     | -0.1  | 0.4   | -0.1 | -0.1 | 0.1   | 0.5707  |
| SQV/TPV/r                                      | 2    | 73  |     |     | 0.0   | 0.3   | 0.0  | -0.1 | 0.1   |         |
| TPV/r  | 2    | 61  |     |     | -0.2  | 0.3   | -0.1 | -0.3 | 0.0   |         |
|  | 4    | 298 |     |     | -0.2  | 0.4   | -0.1 | -0.2 | 0.0   |         |
| APV/TPV/r                                      | 4    | 76  |     |     | -0.1  | 0.5   | -0.1 | -0.2 | 0.0   |         |
| LPV/TPV/r                                      | 4    | 79  |     |     | -0.2  | 0.4   | -0.1 | -0.2 | 0.1   |         |
| SQV/TPV/r                                      | 4    | 78  |     |     | -0.2  | 0.3   | -0.1 | -0.2 | 0.0   |         |
| TPV/r  | 4    | 65  |     |     | -0.2  | 0.3   | -0.1 | -0.3 | 0.0   |         |

Table 36:1182\_0051: Change from Baseline Total Cholesterol and Triglycerides (mg/dL)

| TRTGRP                                       | Week | N   | Min | Max | mean  | Std   | Med   | p25   | p75   | p-value |
|--|------|-----|-----|-----|-------|-------|-------|-------|-------|---------|
| <b>Baseline Cholesterol</b>                  |      |     |     |     |       |       |       |       |       |         |
|  | 0    | 314 |     |     | 179.1 | 46.4  | 176.2 | 146.0 | 205.0 | 0.4336  |
| APV/TPV/r                                    | 0    | 83  |     |     | 176.4 | 46.4  | 163.0 | 142.3 | 195.5 |         |
| LPV/TPV/r                                    | 0    | 83  |     |     | 177.5 | 51.2  | 170.5 | 136.1 | 218.5 |         |
| SQV/TPV/r                                    | 0    | 81  |     |     | 180.6 | 44.2  | 179.0 | 161.0 | 208.8 |         |
| TPV/r  | 0    | 67  |     |     | 182.7 | 43.3  | 183.5 | 152.0 | 204.4 |         |
| <b>Change from Baseline in Cholesterol</b>   |      |     |     |     |       |       |       |       |       |         |
|  | 2    | 278 |     |     | 2.0   | 29.4  | 0.5   | -15.5 | 21.1  | 0.0007  |
| APV/TPV/r                                    | 2    | 69  |     |     | -0.8  | 28.2  | -0.5  | -21.0 | 18.9  |         |
| LPV/TPV/r                                    | 2    | 77  |     |     | -1.9  | 30.5  | -3.9  | -15.5 | 15.7  | 0.2513  |
| SQV/TPV/r                                    | 2    | 71  |     |     | -3.5  | 25.5  | -5.5  | -19.0 | 11.8  |         |
| TPV/r  | 2    | 61  |     |     | 16.3  | 29.5  | 16.4  | -6.5  | 28.6  |         |
|  | 4    | 298 |     |     | 20.0  | 37.9  | 17.0  | -6.0  | 41.6  |         |
| APV/TPV/r                                    | 4    | 76  |     |     | 24.3  | 35.5  | 25.6  | 1.0   | 50.2  |         |
| LPV/TPV/r                                    | 4    | 79  |     |     | 17.9  | 37.7  | 17.4  | -8.7  | 44.3  | 0.2513  |
| SQV/TPV/r                                    | 4    | 78  |     |     | 14.3  | 37.7  | 12.5  | -6.0  | 34.8  |         |
| TPV/r  | 4    | 65  |     |     | 24.2  | 40.8  | 15.0  | -2.3  | 41.0  |         |
| <b>Baseline Triglycerides</b>                |      |     |     |     |       |       |       |       |       |         |
|  | 0    | 314 |     |     | 0.58  | 0.38  | 0.47  | 0.35  | 0.67  | 0.6080  |
| APV/TPV/r                                    | 0    | 83  |     |     | 0.57  | 0.33  | 0.50  | 0.35  | 0.70  |         |
| LPV/TPV/r                                    | 0    | 83  |     |     | 0.64  | 0.48  | 0.50  | 0.38  | 0.70  |         |
| SQV/TPV/r                                    | 0    | 81  |     |     | 0.55  | 0.34  | 0.47  | 0.32  | 0.64  |         |
| TPV/r  | 0    | 67  |     |     | 0.57  | 0.36  | 0.44  | 0.35  | 0.67  |         |
| <b>Change from Baseline in Triglycerides</b> |      |     |     |     |       |       |       |       |       |         |
|  | 2    | 277 |     |     | 2.2   | 187.2 | -13.0 | -66.9 | 66.4  | <0.0001 |
| APV/TPV/r                                    | 2    | 69  |     |     | -40.7 | 144.3 | -35.0 | -82.8 | 19.9  |         |
| LPV/TPV/r                                    | 2    | 77  |     |     | 17.7  | 184.5 | 2.7   | -65.1 | 77.1  | 0.0599  |
| SQV/TPV/r                                    | 2    | 70  |     |     | -30.4 | 174.2 | -25.2 | -83.3 | 30.6  |         |
| TPV/r  | 2    | 61  |     |     | 68.7  | 226.9 | 46.5  | -24.8 | 125.8 |         |
|  | 4    | 298 |     |     | 96.7  | 247.9 | 51.8  | -21.7 | 160.8 |         |
| APV/TPV/r                                    | 4    | 76  |     |     | 84.0  | 210.4 | 61.3  | -24.4 | 143.2 |         |
| LPV/TPV/r                                    | 4    | 79  |     |     | 140.2 | 264.6 | 66.4  | -1.0  | 221.0 | 0.0599  |
| SQV/TPV/r                                    | 4    | 78  |     |     | 43.5  | 216.0 | 19.0  | -33.5 | 100.1 |         |
| TPV/r  | 4    | 65  |     |     | 122.4 | 291.9 | 56.7  | 4.0   | 163.0 |         |

Table 37: 1182\_0051: Change from Baseline Creatinine (mg/dL)

| TRTGRP                                    | Week | N   | Min | Max | mean  | Std  | Med   | p25   | p75   | p-value |
|---|------|-----|-----|-----|-------|------|-------|-------|-------|---------|
| <b>Baseline Creatinine</b>                |      |     |     |     |       |      |       |       |       |         |
|   | 0    | 314 |     |     | 0.94  | 0.27 | 0.87  | 0.75  | 1.05  | 0.8818  |
| APV/TPV/r                                 | 0    | 83  |     |     | 0.94  | 0.27 | 0.90  | 0.75  | 1.05  |         |
| LPV/TPV/r                                 | 0    | 83  |     |     | 0.92  | 0.24 | 0.87  | 0.75  | 1.05  |         |
| SQV/TPV/r                                 | 0    | 81  |     |     | 0.94  | 0.31 | 0.88  | 0.78  | 1.03  |         |
| <b>Change from Baseline in Creatinine</b> |      |     |     |     |       |      |       |       |       |         |
|   | 2    | 280 |     |     | 0.03  | 0.16 | 0.01  | -0.06 | 0.10  | <0.0001 |
| APV/TPV/r                                 | 2    | 69  |     |     | -0.02 | 0.09 | -0.01 | -0.07 | 0.05  |         |
| LPV/TPV/r                                 | 2    | 77  |     |     | 0.03  | 0.12 | 0.02  | -0.05 | 0.10  |         |
| SQV/TPV/r                                 | 2    | 73  |     |     | 0.14  | 0.21 | 0.12  | 0.03  | 0.23  |         |
| TPV/r                                     | 2    | 61  |     |     | -0.05 | 0.14 | -0.05 | -0.10 | -0.01 | 0.2432  |
|   | 4    | 298 |     |     | 0.00  | 0.13 | 0.00  | -0.07 | 0.06  |         |
| APV/TPV/r                                 | 4    | 76  |     |     | -0.02 | 0.14 | -0.03 | -0.09 | 0.07  |         |
| LPV/TPV/r                                 | 4    | 79  |     |     | 0.01  | 0.12 | 0.01  | -0.05 | 0.07  |         |
| SQV/TPV/r                                 | 4    | 78  |     |     | 0.01  | 0.13 | 0.00  | -0.08 | 0.07  | 0.0140  |
| TPV/r                                     | 4    | 65  |     |     | -0.02 | 0.13 | -0.02 | -0.10 | 0.04  |         |
|   | 8    | 301 |     |     | 0.00  | 0.18 | 0.00  | -0.10 | 0.06  |         |
| APV/TPV/r                                 | 8    | 77  |     |     | -0.02 | 0.13 | 0.00  | -0.09 | 0.05  |         |
| LPV/TPV/r                                 | 8    | 80  |     |     | 0.02  | 0.26 | 0.00  | -0.08 | 0.08  | 0.0178  |
| SQV/TPV/r                                 | 8    | 78  |     |     | 0.01  | 0.16 | 0.03  | -0.08 | 0.10  |         |
| TPV/r                                     | 8    | 66  |     |     | -0.03 | 0.15 | -0.05 | -0.10 | 0.01  |         |
|   | 16   | 292 |     |     | -0.01 | 0.16 | 0.00  | -0.10 | 0.07  |         |
| APV/TPV/r                                 | 16   | 72  |     |     | -0.02 | 0.15 | -0.02 | -0.10 | 0.10  | 0.0046  |
| LPV/TPV/r                                 | 16   | 79  |     |     | 0.02  | 0.17 | 0.00  | -0.06 | 0.10  |         |
| SQV/TPV/r                                 | 16   | 75  |     |     | 0.00  | 0.20 | 0.02  | -0.09 | 0.09  |         |
| TPV/r                                     | 16   | 66  |     |     | -0.05 | 0.12 | -0.05 | -0.13 | 0.03  |         |
|   | 24   | 272 |     |     | -0.02 | 0.16 | 0.00  | -0.10 | 0.06  | 0.0046  |
| APV/TPV/r                                 | 24   | 65  |     |     | -0.04 | 0.16 | -0.03 | -0.12 | 0.06  |         |
| LPV/TPV/r                                 | 24   | 77  |     |     | 0.01  | 0.16 | 0.03  | -0.07 | 0.10  |         |
| SQV/TPV/r                                 | 24   | 70  |     |     | 0.00  | 0.18 | 0.00  | -0.08 | 0.06  |         |
| TPV/r                                     | 24   | 60  |     |     | -0.05 | 0.11 | -0.05 | -0.13 | 0.01  |         |

Table 38: Study 1182\_0052: Change from Baseline AST (SGOT,U/L)

| TRTGRP                              | Week | N   | Min | Max | mean  | Std   | Med  | p25   | p75  | P-value |
|-------------------------------------|------|-----|-----|-----|-------|-------|------|-------|------|---------|
| <b>Baseline SGOT</b>                |      |     |     |     |       |       |      |       |      |         |
| TPV/r                               | 0    | 216 |     |     | 43.1  | 68.2  | 31.3 | 24.5  | 46.0 | 0.5665  |
| 500/100                             | 0    | 73  |     |     | 51.1  | 113.5 | 30.0 | 23.0  | 42.5 |         |
| 500/200                             | 0    | 72  |     |     | 38.0  | 18.3  | 33.5 | 25.3  | 43.5 |         |
| 750/200                             | 0    | 71  |     |     | 40.1  | 24.2  | 30.7 | 24.5  | 52.0 |         |
| <b>Change from Baseline in SGOT</b> |      |     |     |     |       |       |      |       |      |         |
| TPV/r                               | 2    | 215 |     |     | 1.0   | 69.2  | 1.3  | -2.8  | 8.8  | 0.0041  |
| 500/100                             | 2    | 73  |     |     | -13.2 | 111.3 | -0.3 | -5.3  | 3.0  |         |
| 500/200                             | 2    | 72  |     |     | 6.0   | 21.4  | 1.9  | -1.9  | 8.8  |         |
| 750/200                             | 2    | 70  |     |     | 10.6  | 33.3  | 4.8  | -2.8  | 16.3 |         |
| TPV/r                               | 4    | 206 |     |     | -1.4  | 70.1  | -0.5 | -6.0  | 7.0  | 0.0021  |
| 500/100                             | 4    | 69  |     |     | -17.0 | 113.6 | -2.5 | -7.5  | 1.5  |         |
| 500/200                             | 4    | 70  |     |     | 5.0   | 25.4  | 2.0  | -4.5  | 9.5  |         |
| 750/200                             | 4    | 67  |     |     | 7.9   | 30.3  | 2.5  | -4.0  | 18.5 |         |
| TPV/r                               | 8    | 204 |     |     | -1.7  | 74.0  | -1.8 | -8.5  | 7.8  | 0.0881  |
| 500/100                             | 8    | 69  |     |     | -16.2 | 115.9 | -2.5 | -9.5  | 2.0  |         |
| 500/200                             | 8    | 68  |     |     | 4.1   | 35.6  | -1.0 | -7.8  | 8.8  |         |
| 750/200                             | 8    | 67  |     |     | 7.3   | 36.9  | 0.5  | -8.0  | 13.0 |         |
| TPV/r                               | 16   | 195 |     |     | -1.5  | 77.7  | -1.0 | -9.0  | 7.5  | 0.4783  |
| 500/100                             | 16   | 68  |     |     | -15.6 | 117.0 | -2.7 | -9.0  | 7.8  |         |
| 500/200                             | 16   | 65  |     |     | 2.7   | 34.7  | -1.0 | -9.0  | 6.5  |         |
| 750/200                             | 16   | 62  |     |     | 9.6   | 50.3  | 2.0  | -7.0  | 14.0 |         |
| TPV/r                               | 24   | 182 |     |     | -2.5  | 75.1  | -0.5 | -8.0  | 12.5 | 0.1261  |
| 500/100                             | 24   | 64  |     |     | -19.0 | 118.5 | -3.0 | -10.5 | 6.5  |         |
| 500/200                             | 24   | 61  |     |     | 4.9   | 29.4  | -0.5 | -7.0  | 14.0 |         |
| 750/200                             | 24   | 57  |     |     | 8.2   | 31.7  | 3.5  | -6.0  | 13.0 |         |

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Table 39: Study 1182\_0052: Change from Baseline ALT(SGPT,U/L)

| TRTGRP                             | Week | N   | Min | Max | mean  | Std   | Med  | p25   | p75  | p-value |
|------------------------------------|------|-----|-----|-----|-------|-------|------|-------|------|---------|
| <b>Baseline ALT</b>                |      |     |     |     |       |       |      |       |      |         |
| TPV/r                              | 0    | 216 |     |     | 47.2  | 94.6  | 32.0 | 21.5  | 49.3 | 0.6702  |
| 500/100                            | 0    | 73  |     |     | 58.3  | 157.4 | 29.5 | 21.0  | 47.0 |         |
| 500/200                            | 0    | 72  |     |     | 40.0  | 25.6  | 32.8 | 22.5  | 49.8 |         |
| 750/200                            | 0    | 71  |     |     | 43.1  | 33.9  | 34.5 | 21.5  | 49.7 |         |
| <b>Change from Baseline in AST</b> |      |     |     |     |       |       |      |       |      |         |
| TPV/r                              | 2    | 215 |     |     | 9.0   | 99.9  | 5.8  | -1.5  | 19.9 | <0.0001 |
| 500/100                            | 2    | 73  |     |     | -14.8 | 153.1 | 1.0  | -3.8  | 8.0  |         |
| 500/200                            | 2    | 72  |     |     | 17.4  | 43.8  | 7.4  | -0.6  | 19.3 |         |
| 750/200                            | 2    | 70  |     |     | 25.0  | 59.9  | 16.8 | 2.0   | 27.8 |         |
| TPV/r                              | 4    | 206 |     |     | 12.2  | 106.4 | 6.3  | -3.5  | 25.0 | <0.0001 |
| 500/100                            | 4    | 69  |     |     | -17.7 | 158.6 | 1.0  | -6.0  | 9.5  |         |
| 500/200                            | 4    | 70  |     |     | 23.6  | 53.8  | 9.3  | -1.0  | 29.3 |         |
| 750/200                            | 4    | 67  |     |     | 31.0  | 68.9  | 14.5 | 1.0   | 36.5 |         |
| TPV/r                              | 8    | 204 |     |     | 8.0   | 107.7 | 4.3  | -5.5  | 19.3 | 0.0006  |
| 500/100                            | 8    | 69  |     |     | -20.6 | 160.8 | -1.0 | -10.0 | 6.0  |         |
| 500/200                            | 8    | 68  |     |     | 20.4  | 60.0  | 4.8  | -4.0  | 20.0 |         |
| 750/200                            | 8    | 67  |     |     | 24.8  | 63.9  | 12.0 | -5.5  | 33.0 |         |
| TPV/r                              | 16   | 195 |     |     | 13.0  | 129.0 | 4.0  | -7.5  | 23.0 | 0.0577  |
| 500/100                            | 16   | 68  |     |     | -15.1 | 161.1 | 0.8  | -9.0  | 16.0 |         |
| 500/200                            | 16   | 65  |     |     | 22.7  | 115.2 | 7.5  | -6.0  | 21.5 |         |
| 750/200                            | 16   | 62  |     |     | 33.5  | 95.2  | 11.3 | -6.8  | 36.5 |         |
| TPV/r                              | 24   | 182 |     |     | 10.8  | 113.5 | 3.8  | -8.5  | 28.0 | 0.0633  |
| 500/100                            | 24   | 64  |     |     | -18.8 | 161.7 | 0.3  | -12.0 | 14.3 |         |
| 500/200                            | 24   | 61  |     |     | 25.6  | 73.1  | 5.5  | -6.5  | 36.5 |         |
| 750/200                            | 24   | 57  |     |     | 28.0  | 70.2  | 9.5  | -8.5  | 36.0 |         |

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Table 40: Study 1182\_0052: Change from Baseline Gamma GT (U/L)

| TRTGRP                                  | Week | N   | Min | Max | mean  | Std   | Med  | p25  | p75   | p-value |
|---|------|-----|-----|-----|-------|-------|------|------|-------|---------|
| <b>Baseline Gamma GT</b>                |      |     |     |     |       |       |      |      |       |         |
| TPV/r                                   | 0    | 216 |     |     | 88.4  | 105.3 | 51.3 | 31.5 | 106.3 | 0.1733  |
| 500/100                                 | 0    | 73  |     |     | 86.3  | 117.8 | 45.0 | 28.0 | 83.0  |         |
| 500/200                                 | 0    | 72  |     |     | 84.0  | 95.4  | 50.5 | 32.5 | 86.5  |         |
| 750/200                                 | 0    | 71  |     |     | 95.1  | 102.5 | 73.3 | 34.5 | 115.5 |         |
| <b>Change from Baseline in Gamma GT</b> |      |     |     |     |       |       |      |      |       |         |
| TPV/r                                   | 2    | 215 |     |     | 20.6  | 71.7  | 6.3  | 0.0  | 20.8  | 0.0114  |
| 500/100                                 | 2    | 73  |     |     | 6.3   | 40.0  | 3.3  | -1.8 | 11.3  |         |
| 500/200                                 | 2    | 72  |     |     | 21.2  | 60.1  | 6.3  | 0.8  | 21.7  |         |
| 750/200                                 | 2    | 70  |     |     | 34.8  | 100.7 | 10.8 | 0.7  | 30.3  |         |
| TPV/r                                   | 4    | 206 |     |     | 82.7  | 151.3 | 36.8 | 14.5 | 90.5  | <0.0001 |
| 500/100                                 | 4    | 69  |     |     | 44.3  | 94.1  | 21.5 | 8.0  | 47.3  |         |
| 500/200                                 | 4    | 70  |     |     | 106.4 | 194.7 | 38.3 | 15.0 | 117.5 |         |
| 750/200                                 | 4    | 67  |     |     | 97.4  | 141.4 | 72.5 | 28.5 | 119.0 |         |
| TPV/r                                   | 8    | 204 |     |     | 101.7 | 174.0 | 48.5 | 17.8 | 138.5 | 0.0026  |
| 500/100                                 | 8    | 69  |     |     | 51.6  | 102.8 | 33.5 | 14.0 | 69.0  |         |
| 500/200                                 | 8    | 68  |     |     | 126.4 | 232.8 | 49.8 | 16.3 | 145.8 |         |
| 750/200                                 | 8    | 67  |     |     | 128.3 | 152.5 | 76.5 | 27.0 | 196.0 |         |
| TPV/r                                   | 16   | 195 |     |     | 113.1 | 183.3 | 57.0 | 22.5 | 162.0 | 0.0545  |
| 500/100                                 | 16   | 68  |     |     | 69.1  | 107.0 | 42.8 | 15.4 | 108.8 |         |
| 500/200                                 | 16   | 65  |     |     | 125.7 | 207.6 | 55.0 | 22.0 | 178.5 |         |
| 750/200                                 | 16   | 62  |     |     | 148.3 | 213.2 | 79.8 | 34.0 | 232.0 |         |
| TPV/r                                   | 24   | 182 |     |     | 114.1 | 196.4 | 54.3 | 19.0 | 148.5 | 0.0747  |
| 500/100                                 | 24   | 64  |     |     | 66.9  | 124.7 | 44.5 | 15.3 | 102.8 |         |
| 500/200                                 | 24   | 61  |     |     | 133.3 | 222.8 | 65.5 | 25.5 | 184.0 |         |
| 750/200                                 | 24   | 57  |     |     | 146.5 | 223.5 | 61.5 | 21.5 | 250.0 |         |

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Table 41: Study 1182\_0052: Change from Baseline Triglycerides (mg/dL)

| TRTGRP                                       | Week | N   | Min | Max | mean  | Std   | Med   | p25   | p75   | p-value |
|--|------|-----|-----|-----|-------|-------|-------|-------|-------|---------|
| <b>Baseline Triglycerides</b>                |      |     |     |     |       |       |       |       |       |         |
| TPV/r  | 0    | 216 |     |     | 317.6 | 202.9 | 251.0 | 178.3 | 415.0 | 0.9918  |
| 500/100                                      | 0    | 73  |     |     | 324.9 | 215.1 | 254.5 | 176.1 | 432.5 |         |
| 500/200                                      | 0    | 72  |     |     | 309.3 | 193.6 | 256.3 | 180.0 | 358.8 |         |
| 750/200                                      | 0    | 71  |     |     | 318.6 | 201.6 | 239.5 | 181.0 | 452.0 |         |
| <b>Change from Baseline in Triglycerides</b> |      |     |     |     |       |       |       |       |       |         |
| TPV/r  | 4    | 202 |     |     | 93.3  | 289.3 | 46.8  | -32.0 | 169.0 | 0.2287  |
| 500/100                                      | 4    | 68  |     |     | 51.5  | 234.0 | 21.3  | -53.5 | 128.3 |         |
| 500/200                                      | 4    | 68  |     |     | 119.2 | 297.3 | 52.5  | -11.7 | 200.3 |         |
| 750/200                                      | 4    | 66  |     |     | 109.7 | 329.5 | 69.0  | -11.5 | 164.0 |         |
| TPV/r  | 8    | 204 |     |     | 98.1  | 313.8 | 52.3  | -34.3 | 166.8 | 0.0142  |
| 500/100                                      | 8    | 69  |     |     | 73.0  | 366.9 | 45.0  | -40.5 | 123.0 |         |
| 500/200                                      | 8    | 68  |     |     | 167.0 | 320.5 | 114.6 | -14.3 | 237.6 |         |
| 750/200                                      | 8    | 67  |     |     | 53.9  | 228.8 | 34.5  | -44.5 | 137.1 |         |
| TPV/r  | 16   | 195 |     |     | 83.0  | 287.4 | 26.5  | -51.5 | 144.0 | 0.1791  |
| 500/100                                      | 16   | 68  |     |     | 49.1  | 256.0 | 2.2   | -49.3 | 90.3  |         |
| 500/200                                      | 16   | 65  |     |     | 139.1 | 356.7 | 63.0  | -31.0 | 229.5 |         |
| 750/200                                      | 16   | 62  |     |     | 61.2  | 228.4 | 33.7  | -52.5 | 115.1 |         |
| TPV/r  | 24   | 182 |     |     | 56.0  | 293.4 | 6.2   | -84.5 | 136.5 | 0.2181  |
| 500/100                                      | 24   | 64  |     |     | -0.1  | 178.3 | -10.0 | -90.3 | 89.5  |         |
| 500/200                                      | 24   | 61  |     |     | 111.6 | 381.3 | 27.0  | -50.5 | 174.5 |         |
| 750/200                                      | 24   | 57  |     |     | 59.4  | 282.4 | 7.0   | -82.5 | 96.5  |         |

Study: 1182\_0004

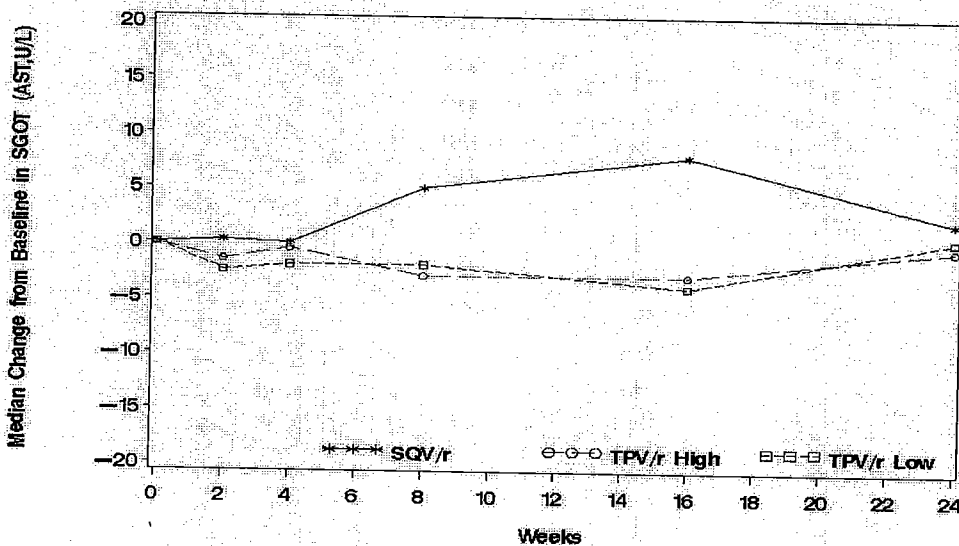


Figure 15: 1182\_0004: Median Change from Baseline AST (SGOT, U/L)

Study 1182\_0004

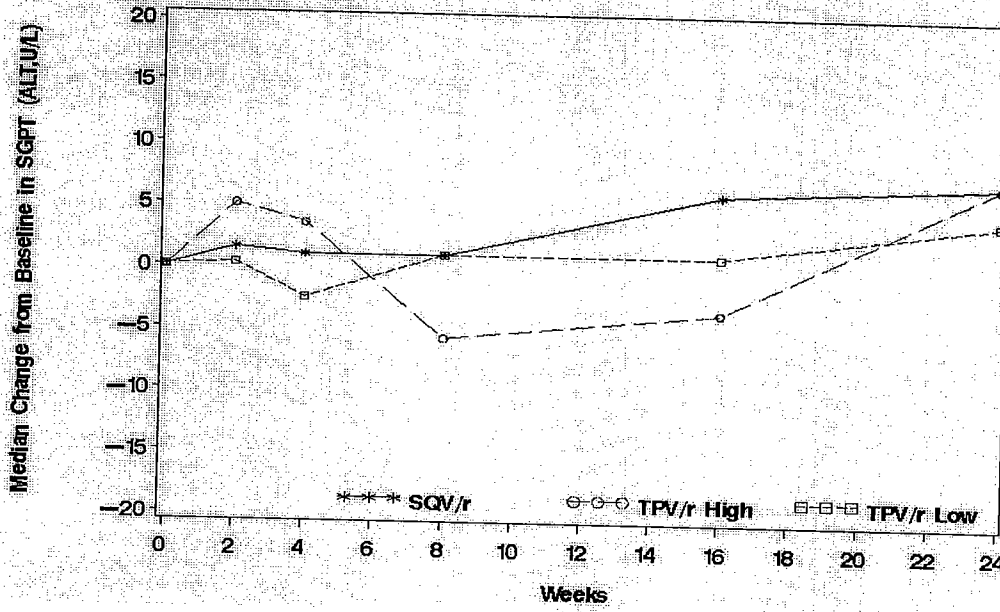


Figure 16: 1182\_0004: Median Change from Baseline ALT (SGPT, U/L)

Study 1182\_0004

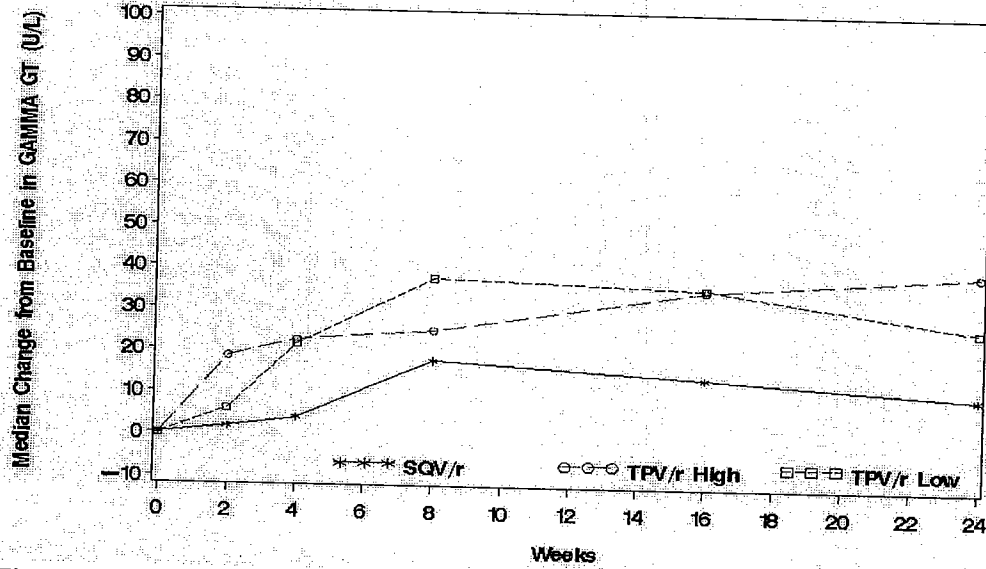


Figure 17: 1182\_0004: Median Change from Baseline Gamma GT (U/L)

Study 1182\_0004

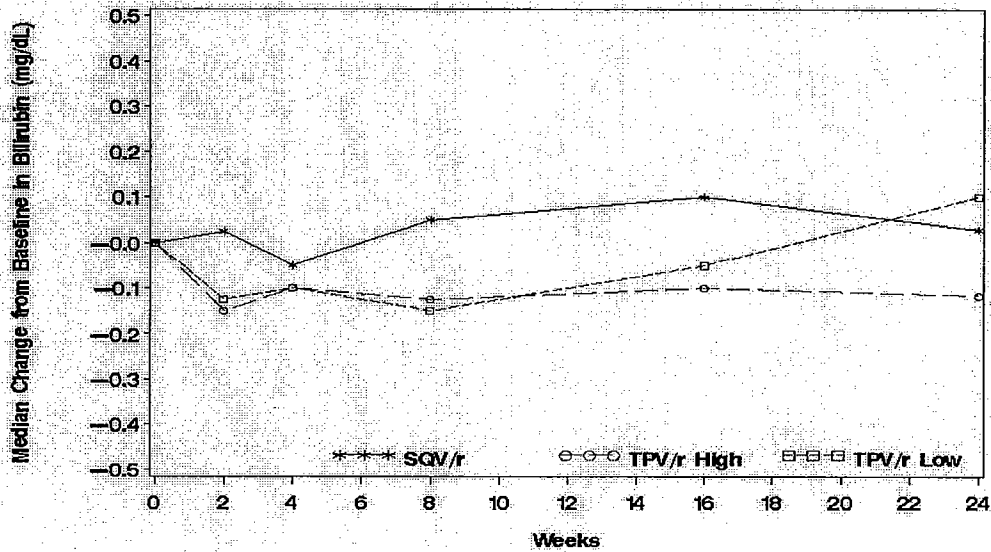


Figure 18: 1182\_0004: Median Change from Baseline Total Bilirubin (mg/dL)

Study 1182\_0004

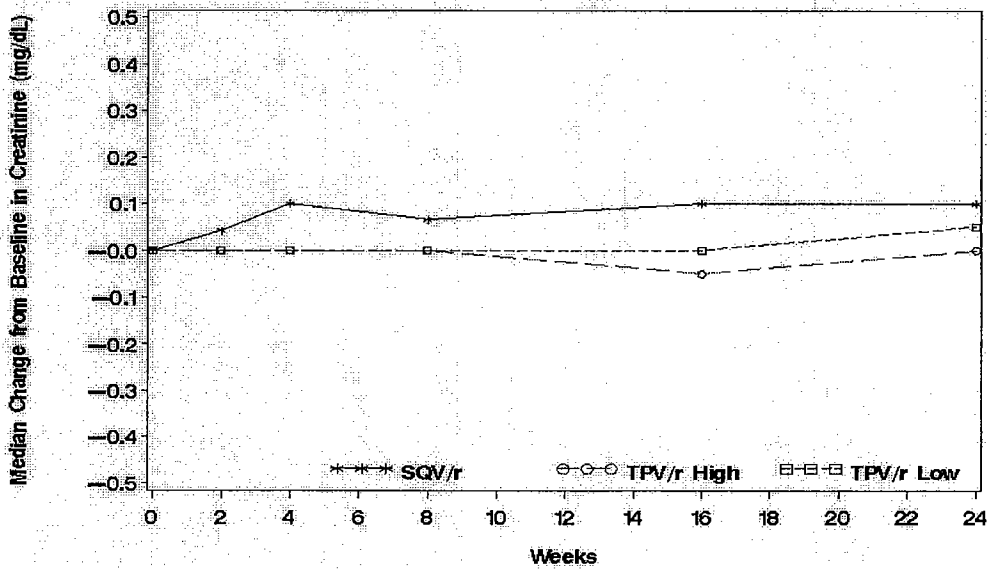


Figure 19: 1182\_0004: Median Change from Baseline Creatinine (mg/dL)

1182\_0051: Median Change from Baseline HGB (g/dL)

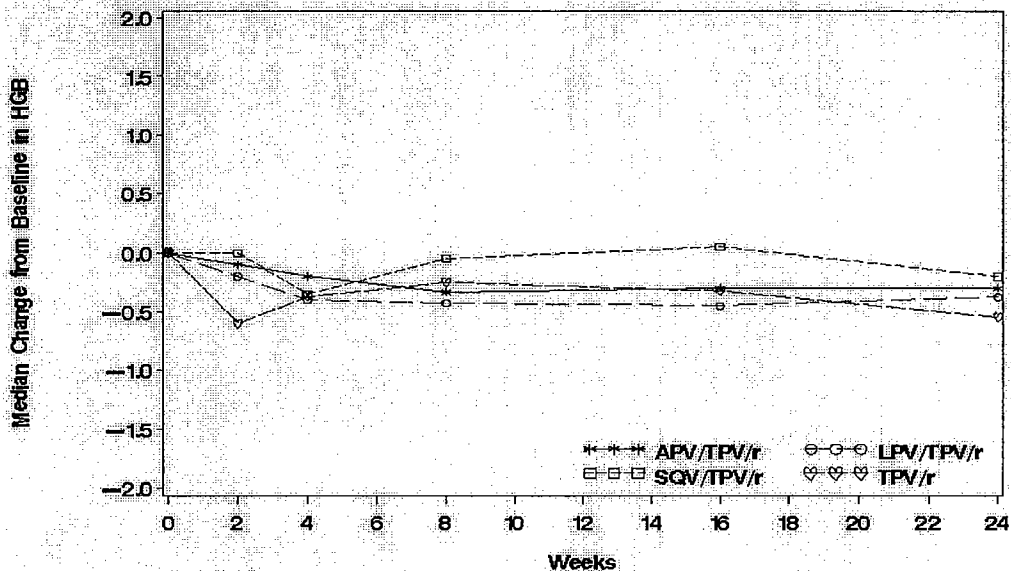


Figure 20: 1182\_0051: Median Change from Baseline Hemoglobin (g/dL)

Study 1182\_0051

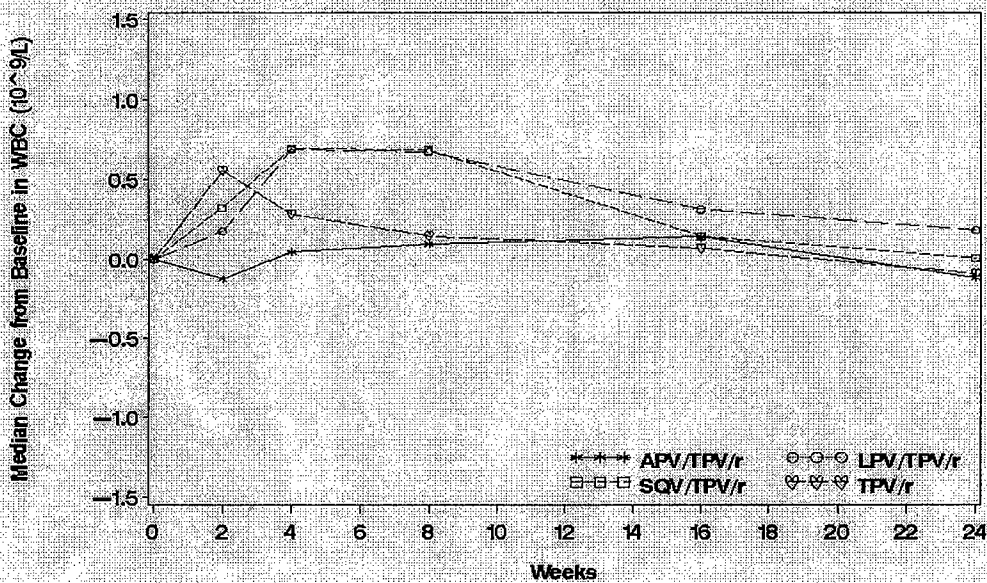


Figure 21: 1182\_0051: Median Change from Baseline WBC

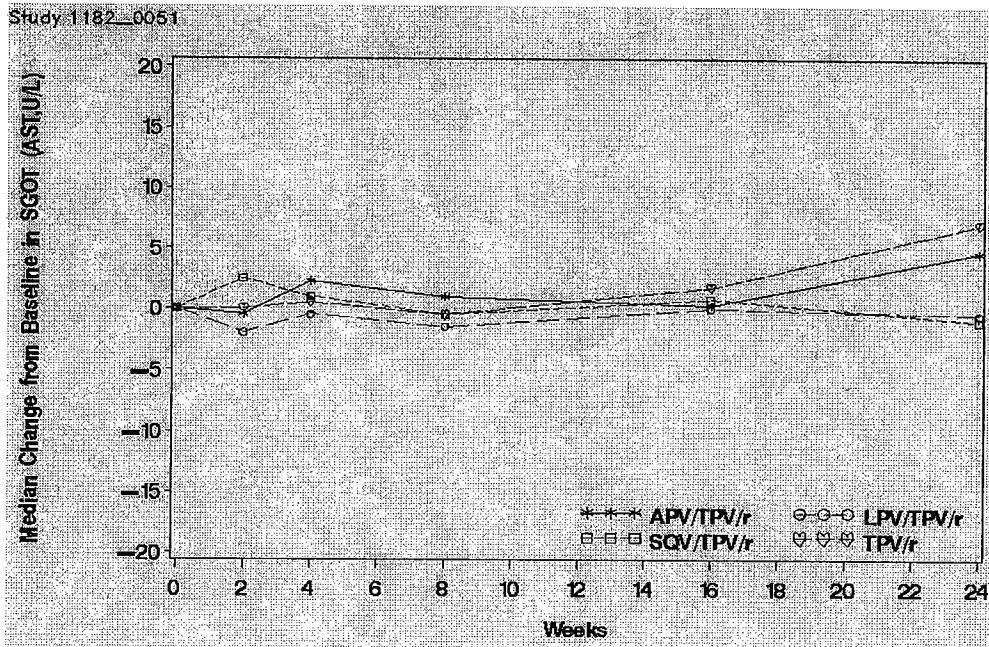


Figure 22: 1182\_0051: Median Change from Baseline AST (SGOT,U/L)

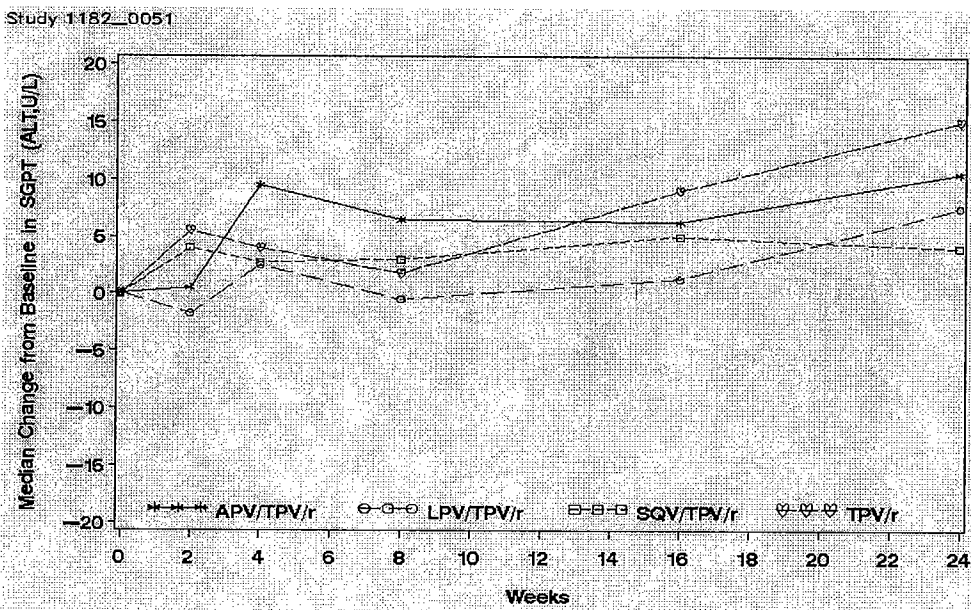


Figure 23: 1182\_0051: Median Change from Baseline ALT (SGPT,U/L)

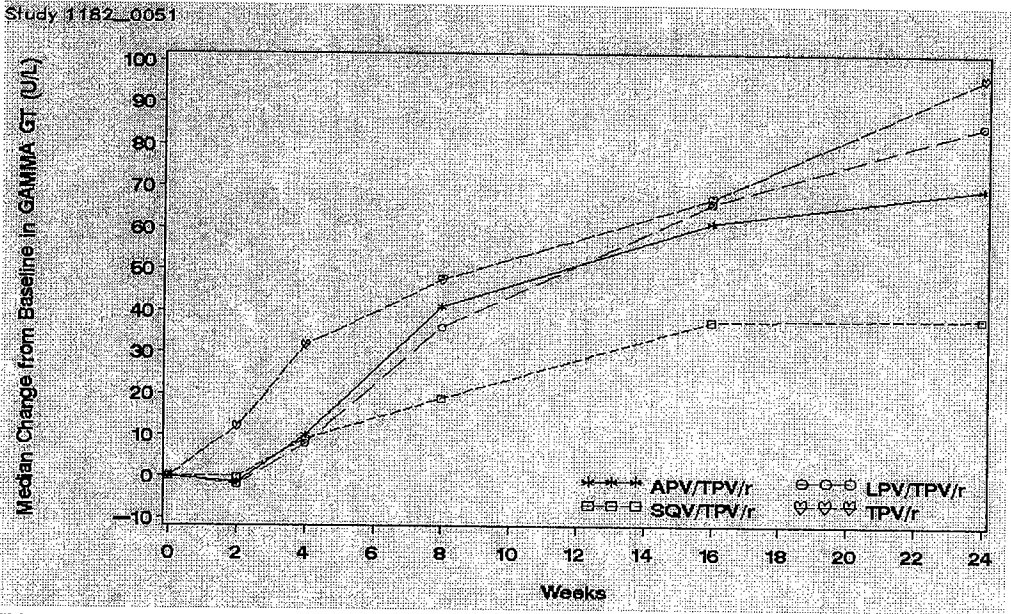


Figure 24: 1182\_0051: Median Change from Baseline Gamma GT

1182\_0051: Median Change from Baseline in Total Bilirubin (mg/dL)

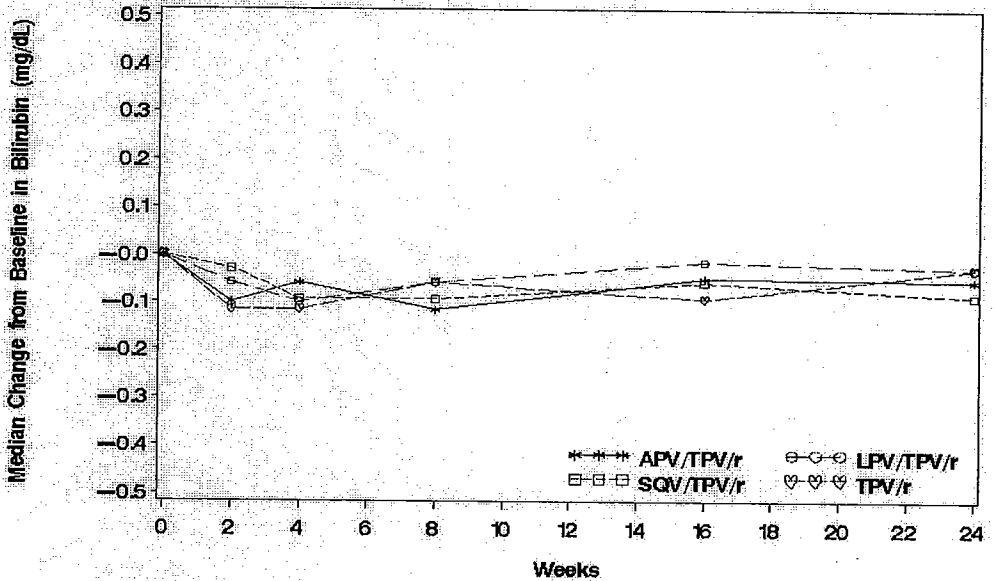


Figure 25: 1182\_0051: Median Change from Baseline Total Bilirubin (mg/dL)



1182\_0051: Median Change From Baseline In Cholesterol mg/dL

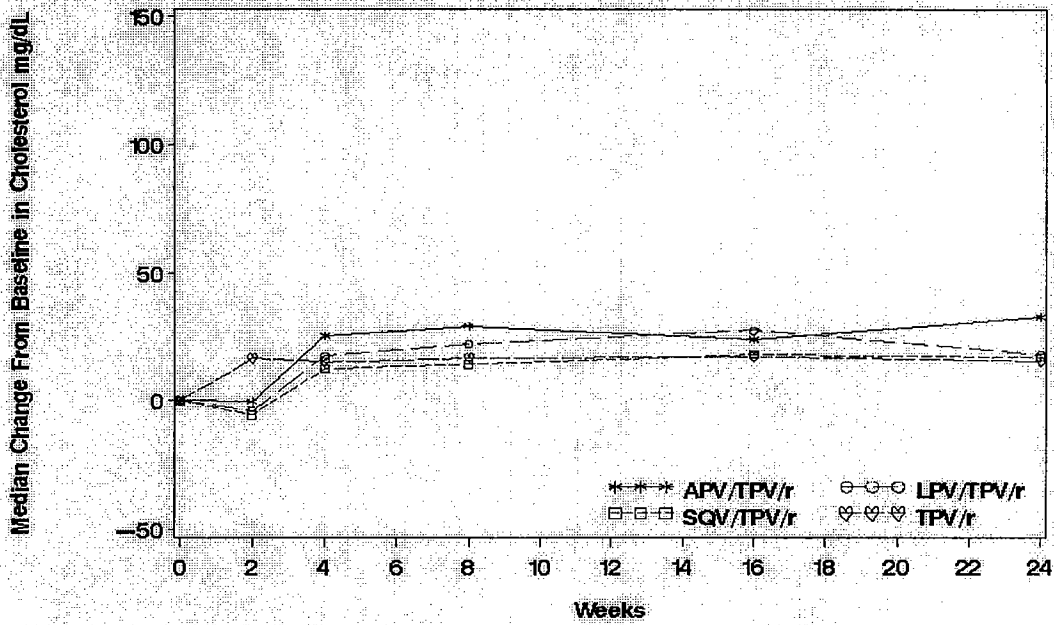


Figure 26: 1182\_0051: Median Change from Baseline Total Cholesterol (mg/dL)

1182\_0051: Median Triglycerides mg/dL

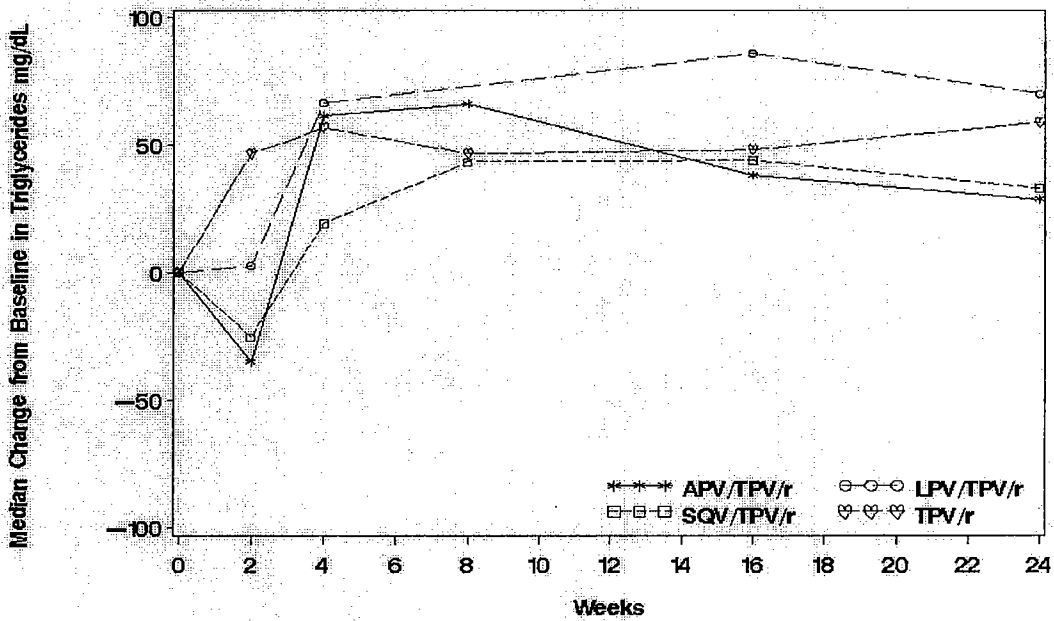


Figure 27: 1182\_0051: Median Change from Baseline Triglycerides (mg/dL)

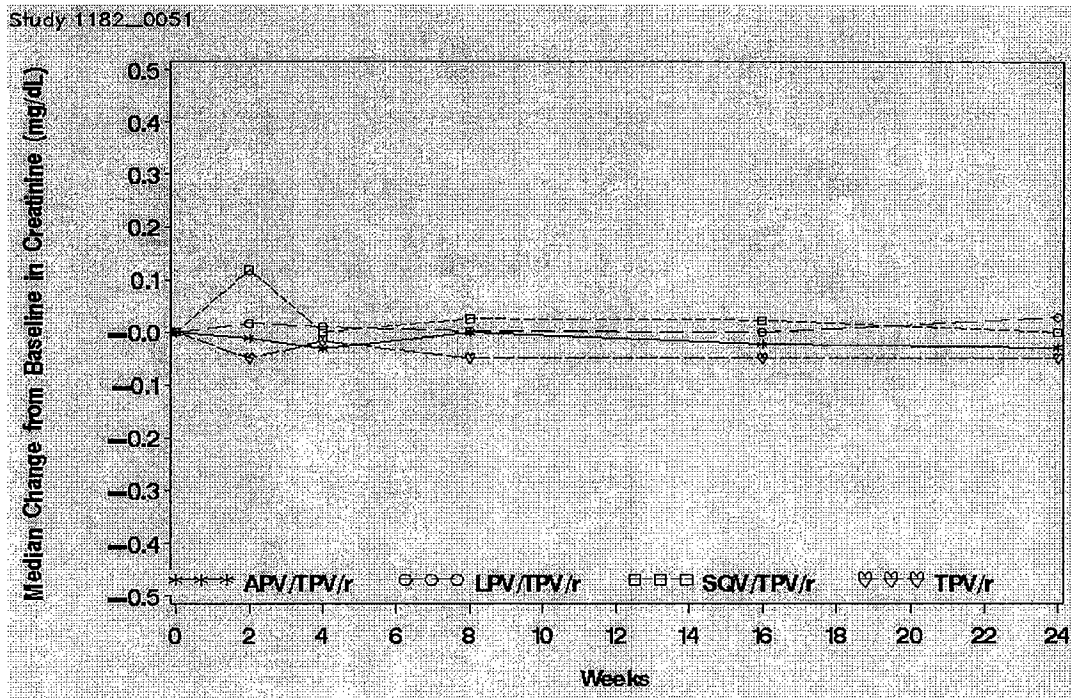


Figure 28: 1182\_0051: Median Change from Baseline Creatinine (mg/dL)

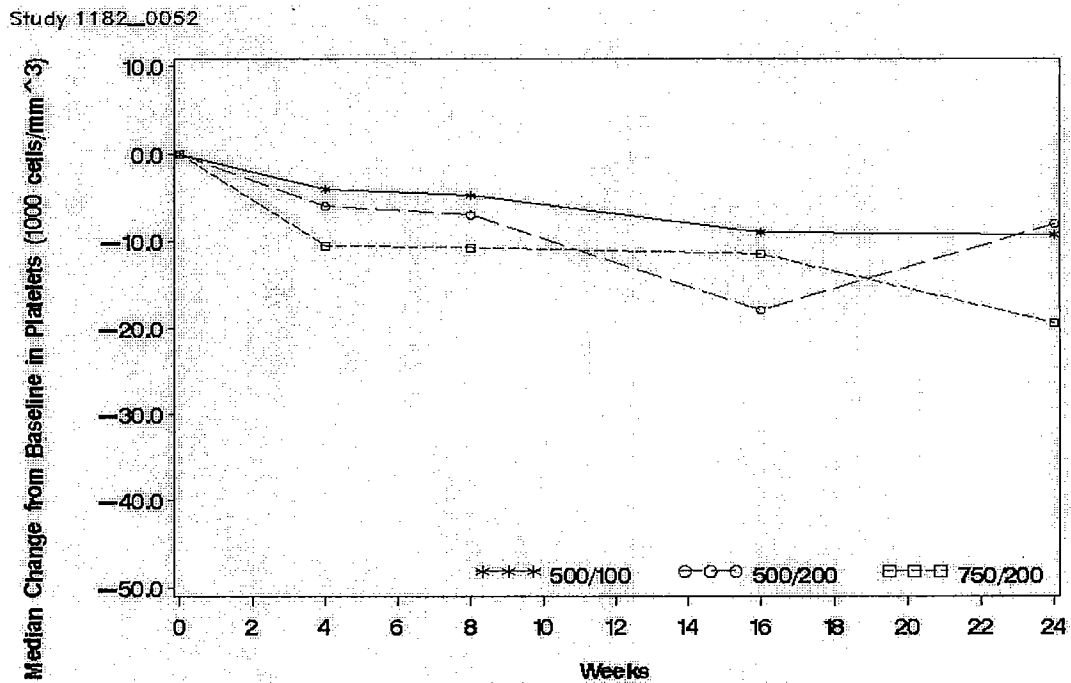


Figure 29: 1182\_0052: Median Change from Baseline Platelet \*1,000 cells/mm<sup>3</sup>

Study 1182\_0052

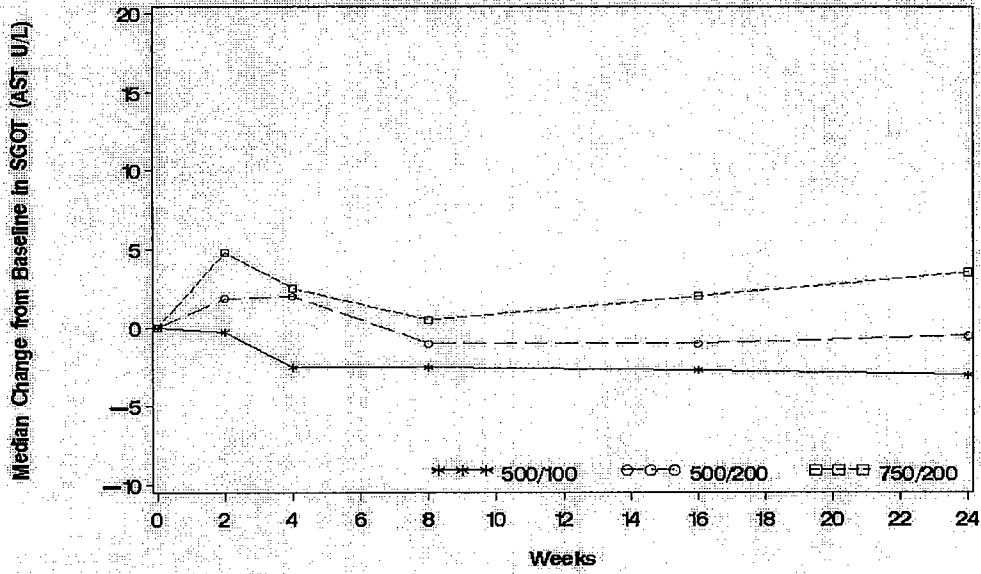


Figure 30: 1182\_0052: Median Change from Baseline AST (SGOT, U/L)

Study 1182\_0052

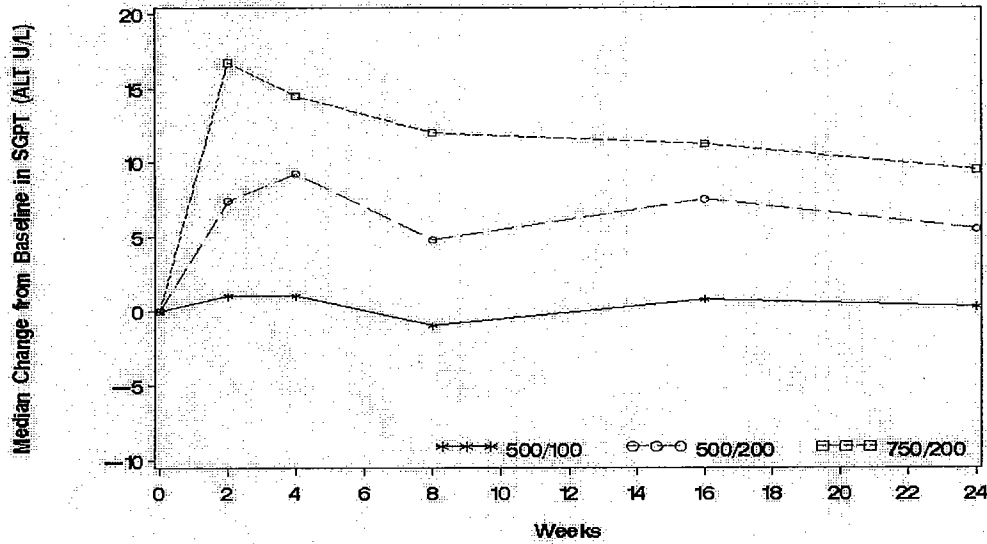


Figure 31: 1182\_0052: Median Change from Baseline ALT (SGPT, U/L)

Study 1182\_0052

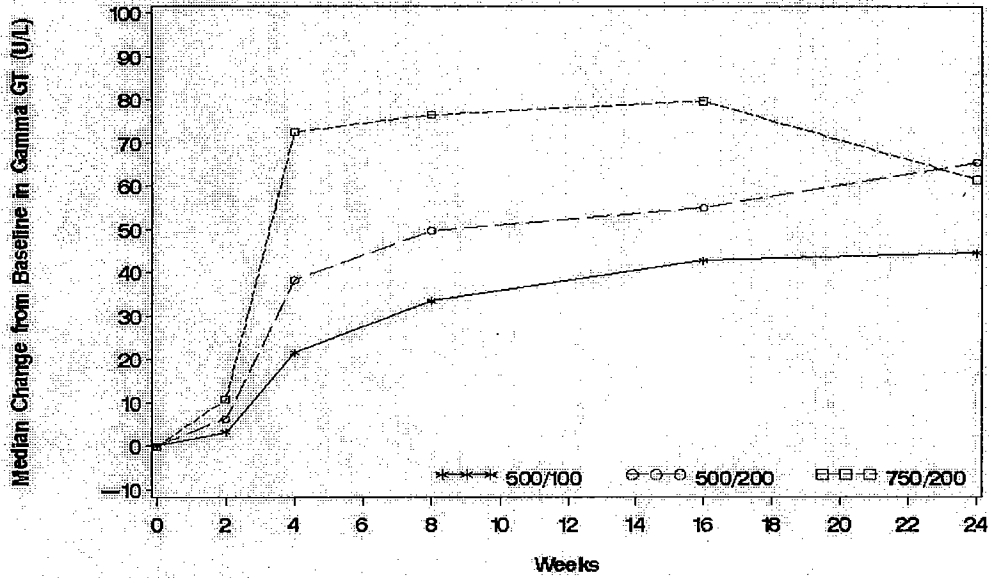


Figure 32: 1182\_0052: Median Change from Baseline Gamma GT (U/L)

Study 1182\_0052

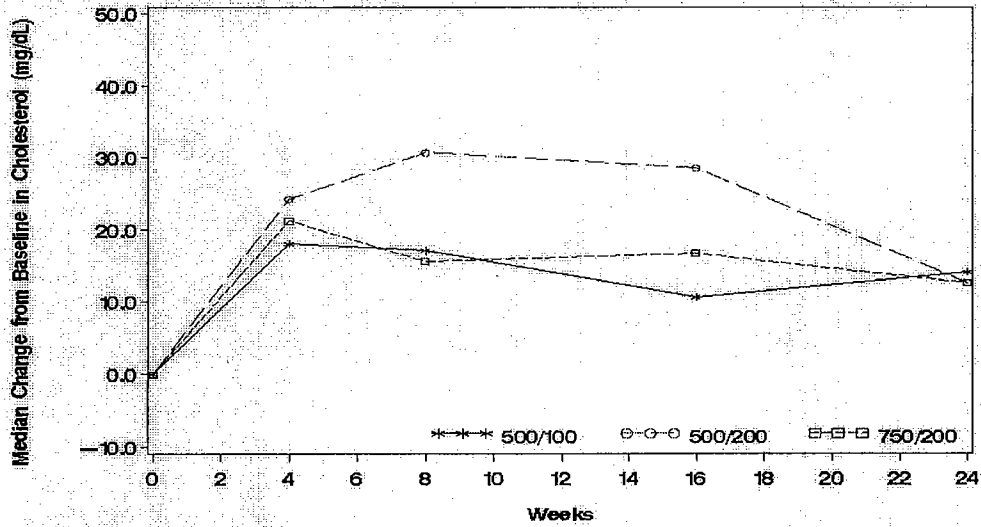


Figure 33: 1182\_0052: Median Change from Baseline Total Cholesterol (mg/dL)

Study 1182\_0052

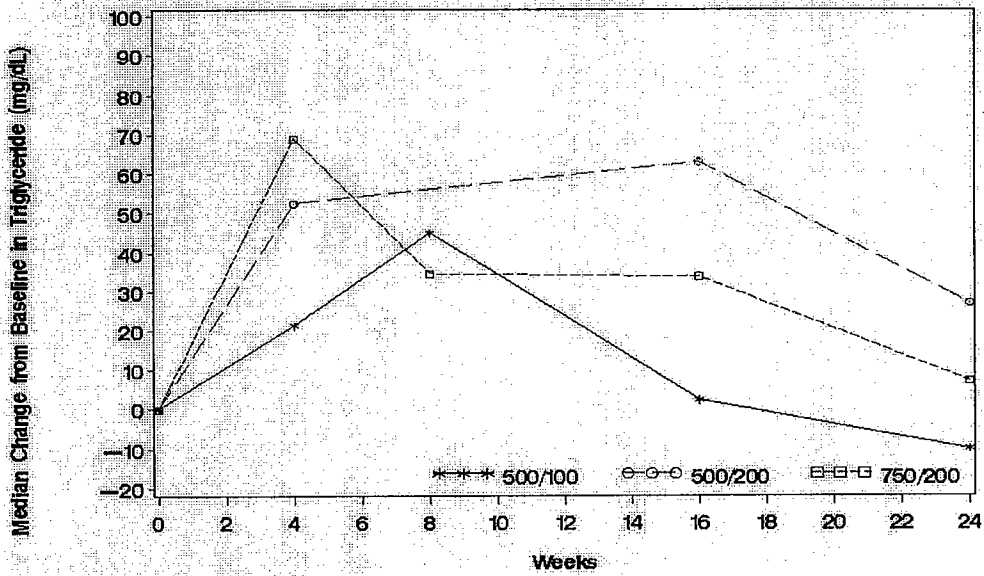


Figure 34: 1182\_0052: Median Change from Baseline Triglycerides (mg/dL)

Study 1182\_0052

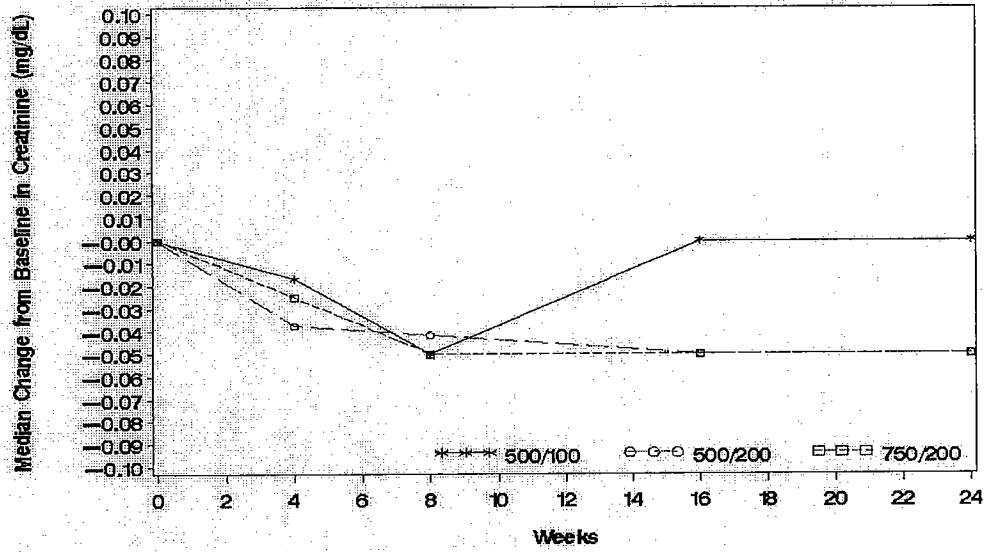


Figure 35: 1182\_0052: Median Change from Baseline Creatinine (mg/dL)

**Table 42: Study 1182\_0012: Shift in DAIDS Toxicity Grade in Hematology Parameters**

|                     | CPI/r |       | TPV/r |       |
|---------------------|-------|-------|-------|-------|
|                     | #     | %     | #     | %     |
| <b>HGB</b>          |       |       |       |       |
| Normal to Gr1       | 13    | 4.21  | 15    | 4.82  |
| Normal to Gr2       | 8     | 2.59  | 8     | 2.57  |
| Normal to Gr3       | 3     | 0.97  | 0     | 0.00  |
| Normal to Gr4       | 0     | 0.00  | 0     | 0.00  |
| Gr1 to Gr2          | 1     | 0.32  | 8     | 2.57  |
| Gr1 to Gr3          | 0     | 0.00  | 2     | 0.64  |
| Gr1 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr2 to Gr3          | 0     | 0.00  | 0     | 0.00  |
| Gr2 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr3 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| No Change or better | 279   | 90.29 | 273   | 87.78 |
| missing             | 5     | 1.62  | 5     | 1.61  |
| <b>Platelets</b>    |       |       |       |       |
| Normal to Gr1       | 4     | 1.29  | 8     | 2.57  |
| Normal to Gr2       | 1     | 0.32  | 1     | 0.32  |
| Normal to Gr3       | 0     | 0.00  | 1     | 0.32  |
| Normal to Gr4       | 0     | 0.00  | 1     | 0.32  |
| Gr1 to Gr2          | 3     | 0.97  | 0     | 0.00  |
| Gr1 to Gr3          | 0     | 0.00  | 0     | 0.00  |
| Gr1 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr2 to Gr3          | 1     | 0.32  | 1     | 0.32  |
| Gr2 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr3 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| No Change or better | 293   | 94.82 | 291   | 93.57 |
| Missing             | 7     | 2.27  | 8     | 2.57  |
| <b>WBC</b>          |       |       |       |       |
| Normal to Gr1       | 40    | 12.94 | 37    | 11.90 |
| Normal to Gr2       | 9     | 2.91  | 11    | 3.54  |
| Normal to Gr3       | 3     | 0.97  | 5     | 1.61  |
| Normal to Gr4       | 0     | 0.00  | 0     | 0.00  |
| Gr1 to Gr2          | 18    | 5.83  | 18    | 5.79  |
| Gr1 to Gr3          | 0     | 0.00  | 3     | 0.96  |
| Gr1 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr2 to Gr3          | 8     | 2.59  | 6     | 1.93  |
| Gr2 to Gr4          | 2     | 0.65  | 1     | 0.32  |
| Gr3 to Gr4          | 3     | 0.97  | 0     | 0.00  |
| No Change or better | 221   | 71.52 | 224   | 72.03 |
| missing             | 5     | 1.62  | 6     | 1.93  |

Table 43: Study 1182\_0012: Shift in DAIDS Toxicity Grade in Liver Function Parameters

|                     | CPI/r       |       | TPV/r |       | CPI/r        |       | TPV/r |       |
|---------------------|-------------|-------|-------|-------|--------------|-------|-------|-------|
|                     | #           | %     | #     | %     | #            | %     | #     | %     |
|                     | <b>SGOT</b> |       |       |       | <b>SGPT</b>  |       |       |       |
| Normal to Gr1       | 51          | 16.5  | 54    | 17.36 | 45           | 14.56 | 85    | 27.33 |
| Normal to Gr2       | 9           | 2.91  | 17    | 5.47  | 9            | 2.91  | 23    | 7.4   |
| Normal to Gr3       | 1           | 0.32  | 5     | 1.61  | 1            | 0.32  | 9     | 2.89  |
| Normal to Gr4       | 0           | 0     | 1     | 0.32  | 0            | 0     | 7     | 2.25  |
| Gr1 to Gr2          | 9           | 2.91  | 8     | 2.57  | 7            | 2.27  | 15    | 4.82  |
| Gr1 to Gr3          | 1           | 0.32  | 0     | 0     | 1            | 0.32  | 3     | 0.96  |
| Gr1 to Gr4          | 0           | 0     | 1     | 0.32  | 0            | 0     | 1     | 0.32  |
| Gr2 to Gr3          | 1           | 0.32  | 0     | 0     | 1            | 0.32  | 2     | 0.64  |
| Gr2 to Gr4          | 0           | 0     | 0     | 0     | 1            | 0.32  | 0     | 0     |
| Gr3 to Gr4          | 0           | 0     | 0     | 0     | 0            | 0     | 0     | 0     |
| No Change or better | 233         | 75.4  | 222   | 71.38 | 241          | 77.99 | 163   | 52.41 |
| missing             | 4           | 1.29  | 3     | 0.96  | 3            | 0.97  | 3     | 0.96  |
|                     | <b>GGT</b>  |       |       |       | <b>TBILI</b> |       |       |       |
| Normal to Gr1       | 31          | 10.03 | 57    | 18.33 | 16           | 5.18  | 9     | 2.89  |
| Normal to Gr2       | 4           | 1.29  | 57    | 18.33 | 7            | 2.27  | 3     | 0.96  |
| Normal to Gr3       | 4           | 1.29  | 16    | 5.14  | 2            | 0.65  | 1     | 0.32  |
| Normal to Gr4       | 1           | 0.32  | 8     | 2.57  | 0            | 0     | 0     | 0     |
| Gr1 to Gr2          | 22          | 7.12  | 22    | 7.07  | 2            | 0.65  | 1     | 0.32  |
| Gr1 to Gr3          | 5           | 1.62  | 15    | 4.82  | 2            | 0.65  | 1     | 0.32  |
| Gr1 to Gr4          | 1           | 0.32  | 3     | 0.96  | 0            | 0     | 0     | 0     |
| Gr2 to Gr3          | 3           | 0.97  | 7     | 2.25  | 0            | 0     | 0     | 0     |
| Gr2 to Gr4          | 2           | 0.65  | 6     | 1.93  | 0            | 0     | 0     | 0     |
| Gr3 to Gr4          | 3           | 0.97  | 6     | 1.93  | 0            | 0     | 0     | 0     |
| No Change or better | 230         | 74.43 | 111   | 35.69 | 277          | 89.64 | 293   | 94.21 |
| missing             | 3           | 0.97  | 3     | 0.96  | 3            | 0.97  | 3     | 0.96  |

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Table 44: Study 1182\_0012: Shift in DAIDS Toxicity Grade in Lipids

|                      | CPI/r |       | TPV/r |       |
|----------------------|-------|-------|-------|-------|
|                      | #     | %     | #     | %     |
| <b>Cholesterol</b>   |       |       |       |       |
| Normal to Gr1        | 72    | 23.30 | 117   | 37.62 |
| Normal to Gr2        | 6     | 1.94  | 12    | 3.86  |
| Normal to Gr3        | 0     | 0.00  | 3     | 0.96  |
| Normal to Gr4        | 0     | 0.00  | 1     | 0.32  |
| Gr1 to Gr2           | 9     | 2.91  | 23    | 7.40  |
| Gr1 to Gr3           | 0     | 0.00  | 5     | 1.61  |
| Gr1 to Gr4           | 0     | 0.00  | 4     | 1.29  |
| Gr2 to Gr3           | 0     | 0.00  | 0     | 0.00  |
| Gr2 to Gr4           | 0     | 0.00  | 0     | 0.00  |
| Gr3 to Gr4           | 0     | 0.00  | 0     | 0.00  |
| No Change or better  | 219   | 70.87 | 143   | 45.98 |
| Missing              | 3     | 0.97  | 3     | 0.96  |
| <b>Triglycerides</b> |       |       |       |       |
| Normal to Gr1        | 42    | 13.59 | 43    | 13.83 |
| Normal to Gr2        | 4     | 1.29  | 18    | 5.79  |
| Normal to Gr3        | 0     | 0.00  | 0     | 0.00  |
| Normal to Gr4        | 0     | 0.00  | 1     | 0.32  |
| Gr1 to Gr2           | 45    | 14.56 | 60    | 19.29 |
| Gr1 to Gr3           | 12    | 3.88  | 19    | 6.11  |
| Gr1 to Gr4           | 3     | 0.97  | 6     | 1.93  |
| Gr2 to Gr3           | 8     | 2.59  | 19    | 6.11  |
| Gr2 to Gr4           | 6     | 1.94  | 10    | 3.22  |
| Gr3 to Gr4           | 2     | 0.65  | 7     | 2.25  |
| No Change or better  | 184   | 59.55 | 125   | 40.19 |
| Missing              | 3     | 0.97  | 3     | 0.96  |

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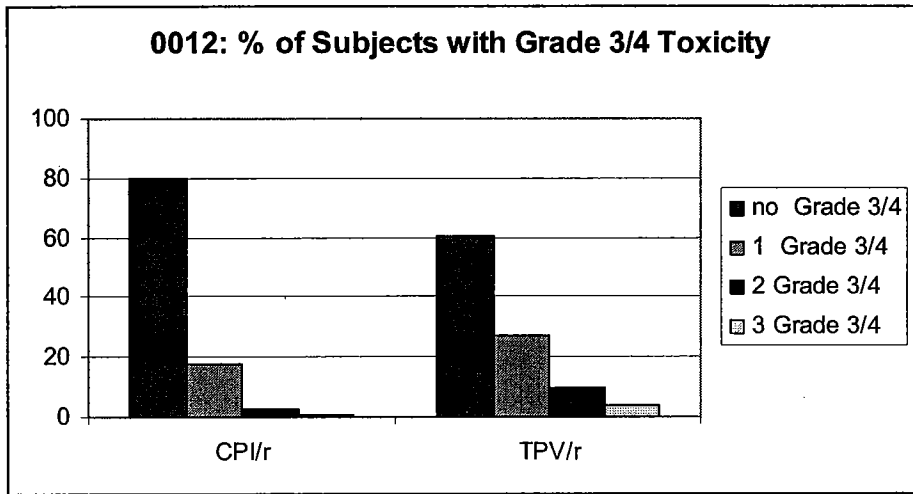


Figure 36: 1182\_0012: Percentage of Subjects with Grade 3 or 4 Toxicity

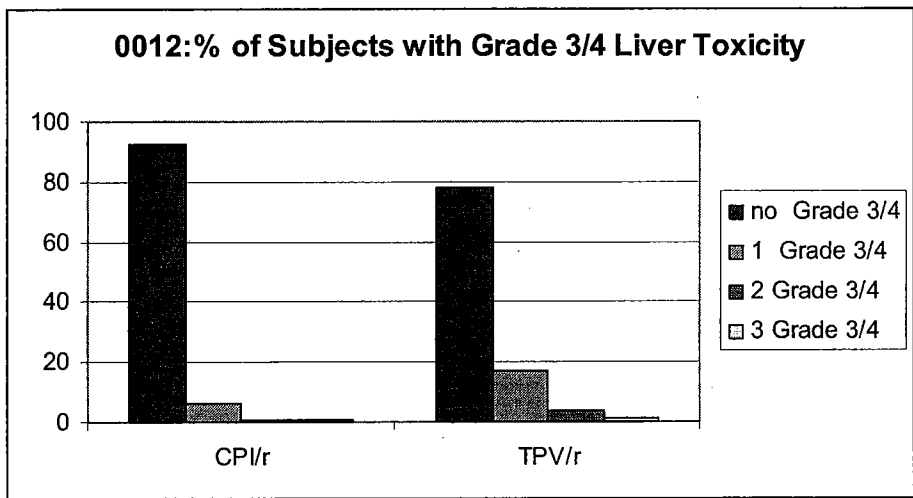


Figure 37: 1182\_0012: Percentage of Subjects with Grade 3 or 4 Liver Toxicity

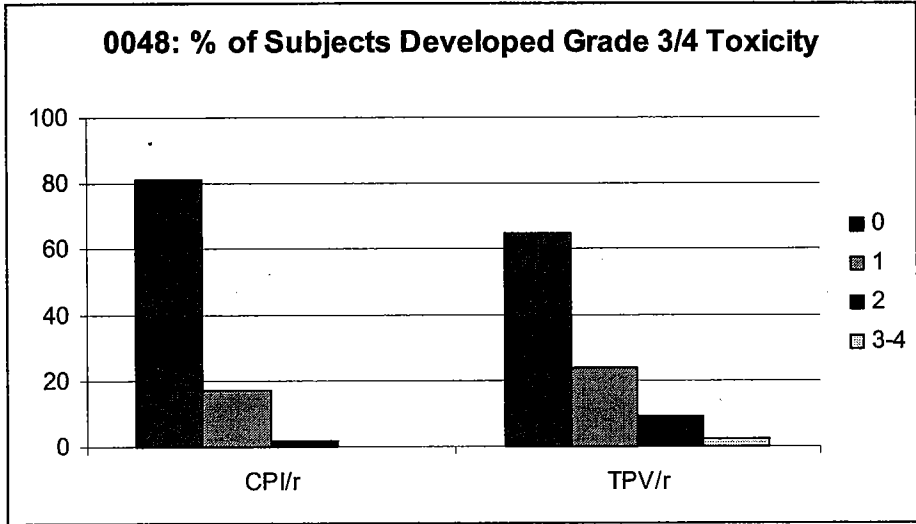


Figure 38: 1182\_0048: Percentage of Subjects with Grade 3 or 4 Toxicity

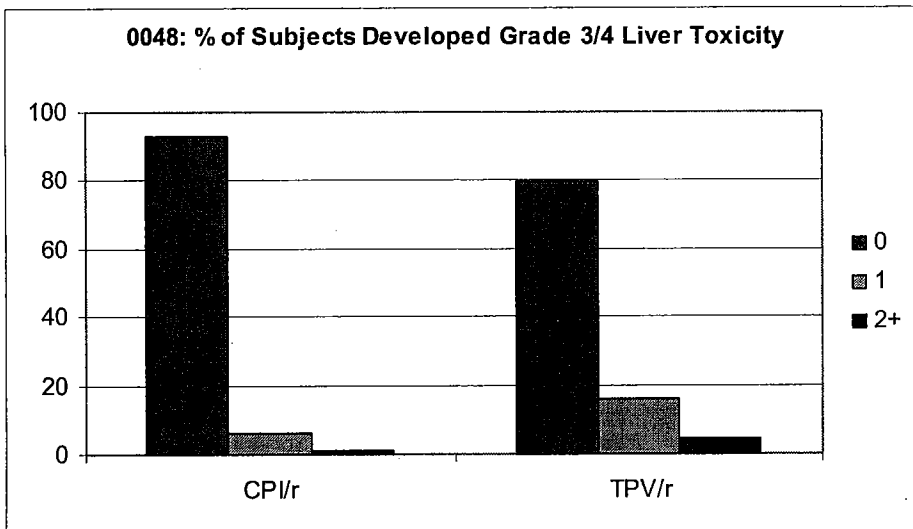


Figure 39: 1182\_0048: Percentage of Subjects with Grade 3 or 4 LFTs

Table 45: Study 1182\_0048: DAIDS Grade Shift in Selected Hematology Parameters

|                     | CPI/r |       | TPV/r |       |
|---------------------|-------|-------|-------|-------|
|                     | #     | %     | #     | %     |
| <b>HGB</b>          |       |       |       |       |
| Normal to Gr1       | 16    | 3.74  | 18    | 4.14  |
| Normal to Gr2       | 4     | 0.93  | 4     | 0.92  |
| Normal to Gr3       | 0     | 0.00  | 0     | 0.00  |
| Normal to Gr4       | 0     | 0.00  | 0     | 0.00  |
| Gr1 to Gr2          | 2     | 0.47  | 3     | 0.69  |
| Gr1 to Gr3          | 0     | 0.00  | 1     | 0.23  |
| Gr1 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr2 to Gr3          | 2     | 0.47  | 2     | 0.46  |
| Gr2 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr3 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| No Change or better | 387   | 90.42 | 394   | 90.57 |
| missing             | 17    | 3.97  | 13    | 2.99  |
| <b>Platelets</b>    |       |       |       |       |
| Normal to Gr1       | 16    | 3.74  | 9     | 2.07  |
| Normal to Gr2       | 1     | 0.23  | 1     | 0.23  |
| Normal to Gr3       | 1     | 0.23  | 0     | 0.00  |
| Normal to Gr4       | 0     | 0.00  | 0     | 0.00  |
| Gr1 to Gr2          | 3     | 0.70  | 4     | 0.92  |
| Gr1 to Gr3          | 0     | 0.00  | 0     | 0.00  |
| Gr1 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr2 to Gr3          | 1     | 0.23  | 0     | 0.00  |
| Gr2 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr3 to Gr4          | 1     | 0.23  | 0     | 0.00  |
| No Change or better | 384   | 89.72 | 403   | 92.64 |
| Missing             | 21    | 4.91  | 18    | 4.14  |
| <b>WBC</b>          |       |       |       |       |
| Normal to Gr1       | 42    | 9.81  | 42    | 9.66  |
| Normal to Gr2       | 17    | 3.97  | 12    | 2.76  |
| Normal to Gr3       | 1     | 0.23  | 2     | 0.46  |
| Normal to Gr4       | 0     | 0.00  | 0     | 0.00  |
| Gr1 to Gr2          | 13    | 3.04  | 17    | 3.91  |
| Gr1 to Gr3          | 1     | 0.23  | 2     | 0.46  |
| Gr1 to Gr4          | 0     | 0.00  | 1     | 0.23  |
| Gr2 to Gr3          | 11    | 2.57  | 3     | 0.69  |
| Gr2 to Gr4          | 0     | 0.00  | 0     | 0.00  |
| Gr3 to Gr4          | 1     | 0.23  | 0     | 0.00  |
| No Change or better | 325   | 75.93 | 342   | 78.62 |
| missing             | 17    | 3.97  | 14    | 3.22  |

Table 46: Study 1182\_0048: DAIDS Grade Shift in Liver Function Parameters

|                     | CPI/r       |       | TPV/r |       | CPI/r        |       | TPV/r |       |
|---------------------|-------------|-------|-------|-------|--------------|-------|-------|-------|
|                     | #           | %     | #     | %     | #            | %     | #     | %     |
|                     | <b>SGOT</b> |       |       |       | <b>SGPT</b>  |       |       |       |
| Normal to Gr1       | 76          | 17.76 | 68    | 15.63 | 77           | 17.99 | 120   | 27.59 |
| Normal to Gr2       | 16          | 3.74  | 15    | 3.45  | 13           | 3.04  | 25    | 5.75  |
| Normal to Gr3       | 2           | 0.47  | 8     | 1.84  | 4            | 0.93  | 9     | 2.07  |
| Normal to Gr4       | 0           | 0.00  | 3     | 0.69  | 1            | 0.23  | 10    | 2.30  |
| Gr1 to Gr2          | 32          | 7.48  | 8     | 1.84  | 12           | 2.80  | 20    | 4.60  |
| Gr1 to Gr3          | 6           | 1.40  | 1     | 0.23  | 2            | 0.47  | 1     | 0.23  |
| Gr1 to Gr4          | 0           | 0.00  | 0     | 0.00  | 1            | 0.23  | 1     | 0.23  |
| Gr2 to Gr3          | 0           | 0.00  | 1     | 0.23  | 1            | 0.23  | 1     | 0.23  |
| Gr2 to Gr4          | 0           | 0.00  | 0     | 0.00  | 0            | 0.00  | 1     | 0.23  |
| Gr3 to Gr4          | 0           | 0.00  | 0     | 0.00  | 0            | 0.00  | 0     | 0.00  |
| No Change or better | 289         | 67.52 | 326   | 74.94 | 311          | 72.66 | 242   | 55.63 |
| missing             | 7           | 1.64  | 5     | 1.15  | 6            | 1.40  | 5     | 1.15  |
|                     | <b>GGT</b>  |       |       |       | <b>TBILI</b> |       |       |       |
| Normal to Gr1       | 58          | 13.55 | 88    | 20.23 | 20           | 4.67  | 8     | 1.84  |
| Normal to Gr2       | 9           | 2.10  | 63    | 14.48 | 5            | 1.17  | 1     | 0.23  |
| Normal to Gr3       | 5           | 1.17  | 20    | 4.60  | 3            | 0.70  | 0     | 0.00  |
| Normal to Gr4       | 1           | 0.23  | 4     | 0.92  | 1            | 0.23  | 1     | 0.23  |
| Gr1 to Gr2          | 19          | 4.44  | 39    | 8.97  | 1            | 0.23  | 0     | 0.00  |
| Gr1 to Gr3          | 4           | 0.93  | 26    | 5.98  | 0            | 0.00  | 0     | 0.00  |
| Gr1 to Gr4          | 0           | 0.00  | 6     | 1.38  | 0            | 0.00  | 0     | 0.00  |
| Gr2 to Gr3          | 6           | 1.40  | 16    | 3.68  | 2            | 0.47  | 0     | 0.00  |
| Gr2 to Gr4          | 0           | 0.00  | 6     | 1.38  | 0            | 0.00  | 0     | 0.00  |
| Gr3 to Gr4          | 3           | 0.70  | 4     | 0.92  | 0            | 0.00  | 1     | 0.23  |
| No Change or better | 317         | 74.07 | 158   | 36.32 | 390          | 91.12 | 419   | 96.32 |
| missing             | 6           | 1.40  | 5     | 1.15  | 6            | 1.40  | 5     | 1.15  |

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Table 47: Study 1182\_0048: DAIDS Grade Shift in Lipids

|                      | CPI/r |       | TPV/r |       |
|----------------------|-------|-------|-------|-------|
|                      | #     | %     | #     | %     |
| <b>Cholesterol</b>   |       |       |       |       |
| Normal to Gr1        | 77    | 17.99 | 144   | 33.10 |
| Normal to Gr2        | 2     | 0.47  | 13    | 2.99  |
| Normal to Gr3        | 2     | 0.47  | 2     | 0.46  |
| Normal to Gr4        | 0     | 0.00  | 1     | 0.23  |
| Gr1 to Gr2           | 15    | 3.50  | 91    | 20.92 |
| Gr1 to Gr3           | 0     | 0.00  | 36    | 8.28  |
| Gr1 to Gr4           | 0     | 0.00  | 7     | 1.61  |
| Gr2 to Gr3           | 0     | 0.00  | 2     | 0.46  |
| Gr2 to Gr4           | 0     | 0.00  | 0     | 0.00  |
| Gr3 to Gr4           | 0     | 0.00  | 0     | 0.00  |
| No Change or better  | 326   | 76.17 | 134   | 30.80 |
| missing              | 6     | 1.40  | 5     | 1.15  |
| <b>Triglycerides</b> |       |       |       |       |
| Normal to Gr1        | 57    | 13.32 | 71    | 16.32 |
| Normal to Gr2        | 3     | 0.70  | 11    | 2.53  |
| Normal to Gr3        | 3     | 0.70  | 1     | 0.23  |
| Normal to Gr4        | 1     | 0.23  | 0     | 0.00  |
| Gr1 to Gr2           | 55    | 12.85 | 102   | 23.45 |
| Gr1 to Gr3           | 11    | 2.57  | 31    | 7.13  |
| Gr1 to Gr4           | 2     | 0.47  | 4     | 0.92  |
| Gr2 to Gr3           | 7     | 1.64  | 25    | 5.75  |
| Gr2 to Gr4           | 11    | 2.57  | 12    | 2.76  |
| Gr3 to Gr4           | 0     | 0.00  | 5     | 1.15  |
| No Change or better  | 272   | 63.55 | 168   | 38.62 |
| Missing              | 6     | 1.40  | 5     | 1.15  |

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**Table 48: Study 1182\_0004: DAIDS Grade Shift in Liver Function Parameters**

|                    | SQV/r 400/400<br>(n=28) |      | TPV/r 1250/100<br>(n=25) |      | TPV/r 500/100<br>(n=24) |      |
|--------------------|-------------------------|------|--------------------------|------|-------------------------|------|
|                    | #                       | %    | #                        | %    | #                       | %    |
| <b>SGOT</b>        |                         |      |                          |      |                         |      |
| Normal to Gr1      | 5                       | 17.9 | 1                        | 4.0  | 3                       | 12.5 |
| Normal to Gr2      | 3                       | 10.7 | 0                        | 0.0  | 3                       | 12.5 |
| Normal to Gr3      | 1                       | 3.6  | 1                        | 4.0  | 0                       | 0.0  |
| Normal to Gr4      | 0                       | 0.0  | 0                        | 0.0  | 1                       | 4.2  |
| Gr1 to Gr2         | 1                       | 3.6  | 1                        | 4.0  | 0                       | 0.0  |
| Gr1 to Gr3         | 0                       | 0.0  | 0                        | 0.0  | 1                       | 4.2  |
| Gr1 to Gr4         | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr2 to Gr3         | 0                       | 0.0  | 1                        | 4.0  | 0                       | 0.0  |
| Gr2 to Gr4         | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr3 to Gr4         | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| No Change / better | 18                      | 64.3 | 21                       | 84.0 | 16                      | 66.7 |
| <b>SGPT</b>        |                         |      |                          |      |                         |      |
| Normal to Gr1      | 6                       | 21.4 | 6                        | 24.0 | 5                       | 20.8 |
| Normal to Gr2      | 2                       | 7.1  | 0                        | 0.0  | 0                       | 0.0  |
| Normal to Gr3      | 0                       | 0.0  | 0                        | 0.0  | 1                       | 4.2  |
| Normal to Gr4      | 1                       | 3.6  | 1                        | 4.0  | 2                       | 8.3  |
| Gr1 to Gr2         | 0                       | 0.0  | 0                        | 0.0  | 1                       | 4.2  |
| Gr1 to Gr3         | 1                       | 3.6  | 0                        | 0.0  | 0                       | 0.0  |
| Gr1 to Gr4         | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr2 to Gr3,4       | 0                       | 0.0  | 1                        | 4.0  | 0                       | 0.0  |
| Gr3 to Gr4         | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| No Change / better | 18                      | 64.3 | 17                       | 68.0 | 15                      | 62.5 |
| <b>GGT</b>         |                         |      |                          |      |                         |      |
| Normal to Gr1      | 6                       | 21.4 | 7                        | 28.0 | 2                       | 8.3  |
| Normal to Gr2      | 1                       | 3.6  | 2                        | 8.0  | 5                       | 20.8 |
| Normal to Gr3      | 0                       | 0.0  | 1                        | 4.0  | 1                       | 4.2  |
| Normal to Gr4      | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr1 to Gr2         | 2                       | 7.1  | 3                        | 12.0 | 0                       | 0.0  |
| Gr1 to Gr3         | 2                       | 7.1  | 0                        | 0.0  | 1                       | 4.2  |
| Gr1 to Gr4         | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr2 to Gr3         | 0                       | 0.0  | 0                        | 0.0  | 2                       | 8.3  |
| Gr2 to Gr4         | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr3 to Gr4         | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |

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|                    |    |      |    |      |    |      |
|--------------------|----|------|----|------|----|------|
| No Change / better | 17 | 60.7 | 12 | 48.0 | 13 | 54.2 |
|--------------------|----|------|----|------|----|------|

Table 49: Study 1182\_0004: DAIDS Grade Shift in Lipids

|                          | SQV/r 400/400<br>(n=28) |      | TPV/r 1250/100<br>(n=25) |      | TPV/r 500/100<br>(n=24) |      |
|--------------------------|-------------------------|------|--------------------------|------|-------------------------|------|
|                          | #                       | %    | #                        | %    | #                       | %    |
| <b>Total Cholesterol</b> |                         |      |                          |      |                         |      |
| Normal to Gr1            | 9                       | 32.1 | 6                        | 24.0 | 4                       | 16.7 |
| Normal to Gr2            | 1                       | 3.6  | 0                        | 0.0  | 0                       | 0.0  |
| Normal to Gr3            | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Normal to Gr4            | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr1 to Gr2               | 3                       | 10.7 | 1                        | 4.0  | 3                       | 12.5 |
| Gr1 to Gr3               | 0                       | 0.0  | 0                        | 0.0  | 2                       | 8.3  |
| Gr1 to Gr4               | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr2 to Gr3               | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr2 to Gr4               | 1                       | 3.6  | 0                        | 0.0  | 0                       | 0.0  |
| Gr3 to Gr4               | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| No Change / better       | 14                      | 50.0 | 18                       | 72.0 | 15                      | 62.5 |
| <b>Triglycerides</b>     |                         |      |                          |      |                         |      |
| Normal to Gr1            | 13                      | 46.4 | 8                        | 32.0 | 7                       | 29.2 |
| Normal to Gr2            | 1                       | 3.6  | 1                        | 4.0  | 0                       | 0.0  |
| Normal to Gr3            | 1                       | 3.6  | 0                        | 0.0  | 0                       | 0.0  |
| Normal to Gr4            | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| Gr1 to Gr2               | 6                       | 21.4 | 6                        | 24.0 | 4                       | 16.7 |
| Gr1 to Gr3               | 0                       | 0.0  | 2                        | 8.0  | 1                       | 4.2  |
| Gr1 to Gr4               | 0                       | 0.0  | 1                        | 4.0  | 1                       | 4.2  |
| Gr2 to Gr3               | 0                       | 0.0  | 0                        | 0.0  | 2                       | 8.3  |
| Gr2 to Gr4               | 1                       | 3.6  | 0                        | 0.0  | 0                       | 0.0  |
| Gr3 to Gr4               | 0                       | 0.0  | 0                        | 0.0  | 0                       | 0.0  |
| No Change / better       | 6                       | 21.4 | 7                        | 28.0 | 9                       | 37.5 |

Table 50: Study 1182\_0051: DAIDS Grade Shift in Hematology Parameters

|                       | APV/TPV/r<br>(n=82) |       | LPV/TPV/r<br>(n=83) |       | SQV/TPV/r<br>(n=83) |       | TPV/r (n=67) |       |
|-----------------------|---------------------|-------|---------------------|-------|---------------------|-------|--------------|-------|
|                       | #                   | %     | #                   | %     | #                   | %     | #            | %     |
| <b>Platelet Count</b> |                     |       |                     |       |                     |       |              |       |
| Normal to Gr1         | 1                   | 1.25  | 3                   | 3.7   | 3                   | 3.75  | 3            | 4.62  |
| Normal to Gr2         | 1                   | 1.25  | 1                   | 1.23  | 1                   | 1.25  | 0            | 0     |
| Normal to Gr3         | 0                   | 0     | 0                   | 0     | 0                   | 0     | 2            | 3.08  |
| Normal to Gr4         | 0                   | 0     | 0                   | 0     | 0                   | 0     | 0            | 0     |
| Gr1 to Gr2            | 0                   | 0     | 0                   | 0     | 1                   | 1.25  | 1            | 1.54  |
| Gr1 to Gr3            | 1                   | 1.25  | 0                   | 0     | 0                   | 0     | 0            | 0     |
| Gr1 to Gr4            | 0                   | 0     | 0                   | 0     | 0                   | 0     | 0            | 0     |
| Gr2 to Gr3            | 1                   | 1.25  | 1                   | 1.23  | 0                   | 0     | 0            | 0     |
| Gr(2+j) to Gr4, j=0,1 | 0                   | 0     | 0                   | 0     | 0                   | 0     | 0            | 0     |
| No Change or better   | 76                  | 92.5  | 77                  | 92.59 | 76                  | 90    | 59           | 86.15 |
| Missing               | 2                   | 2.5   | 1                   | 1.23  | 2                   | 3.75  | 2            | 4.62  |
| <b>Hemoglobin</b>     |                     |       |                     |       |                     |       |              |       |
| Normal to Gr1         | 3                   | 3.61  | 3                   | 3.61  | 4                   | 4.88  | 2            | 2.99  |
| Normal to Gr2         | 0                   | 1.2   | 1                   | 1.2   | 0                   | 0     | 1            | 1.49  |
| Normal to Gr3         | 0                   | 0     | 0                   | 0     | 1                   | 1.22  | 0            | 0     |
| Normal to Gr4         | 0                   | 0     | 0                   | 0     | 0                   | 0     | 0            | 0     |
| Gr1 to Gr2            | 1                   | 1.2   | 2                   | 2.41  | 1                   | 1.22  | 4            | 5.97  |
| Gr1 to Gr3            | 0                   | 0     | 0                   | 0     | 0                   | 0     | 1            | 1.49  |
| Gr1 to Gr4            | 0                   | 0     | 0                   | 0     | 0                   | 0     | 0            | 0     |
| Gr2 to Gr3            | 1                   | 1.2   | 0                   | 0     | 0                   | 0     | 0            | 0     |
| Gr(2+j) to Gr4, j=0,1 | 0                   | 0     | 0                   | 0     | 0                   | 0     | 0            | 0     |
| No Change or better   | 75                  | 87.95 | 76                  | 89.16 | 75                  | 87.8  | 57           | 80.6  |
| Missing               | 2                   | 4.82  | 1                   | 3.61  | 2                   | 4.88  | 2            | 7.46  |
| <b>WBC</b>            |                     |       |                     |       |                     |       |              |       |
| Normal to Gr1         | 13                  | 15.85 | 19                  | 22.89 | 14                  | 16.87 | 9            | 13.43 |
| Normal to Gr2         | 0                   | 0.00  | 2                   | 2.41  | 4                   | 4.82  | 1            | 1.49  |
| Normal to Gr3         | 0                   | 0.00  | 0                   | 0.00  | 1                   | 1.20  | 0            | 0.00  |
| Normal to Gr4         | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| Gr1 to Gr2            | 1                   | 1.22  | 5                   | 6.02  | 3                   | 3.61  | 2            | 2.99  |
| Gr1 to Gr3            | 2                   | 2.44  | 0                   | 0.00  | 1                   | 1.20  | 0            | 0.00  |
| Gr1 to Gr4            | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| Gr2 to Gr3            | 6                   | 7.32  | 1                   | 1.20  | 1                   | 1.20  | 3            | 4.48  |
| Gr(2+j) to Gr4, j=0,1 | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| No Change or better   | 58                  | 70.73 | 55                  | 66.27 | 57                  | 68.67 | 50           | 74.63 |
| Missing               | 2                   | 2.44  | 1                   | 1.20  | 2                   | 2.41  | 2            | 2.99  |



Table 51: Study 1182\_0051: DAIDS Grade Shift in Liver Enzymes

|                     | APV/TPV/r (n=80) |       | LPV/TPV/r (n=81) |       | SQV/TPV/r (n=80) |       | TPV/r (n=65) |       |
|---------------------|------------------|-------|------------------|-------|------------------|-------|--------------|-------|
|                     | #                | %     | #                | %     | #                | %     | #            | %     |
| <b>Gamma GT</b>     |                  |       |                  |       |                  |       |              |       |
| Normal to Gr1       | 21               | 25.61 | 19               | 22.89 | 20               | 24.10 | 12           | 17.91 |
| Normal to Gr2       | 18               | 21.95 | 23               | 27.71 | 9                | 10.84 | 14           | 20.90 |
| Normal to Gr3       | 6                | 7.32  | 2                | 2.41  | 5                | 6.02  | 5            | 7.46  |
| Normal to Gr4       | 3                | 3.66  | 1                | 1.20  | 0                | 0.00  | 0            | 0.00  |
| Gr1 to Gr2          | 4                | 4.88  | 8                | 9.64  | 5                | 6.02  | 4            | 5.97  |
| Gr1 to Gr3          | 3                | 3.66  | 1                | 1.20  | 3                | 3.61  | 7            | 10.45 |
| Gr1 to Gr4          | 2                | 2.44  | 1                | 1.20  | 1                | 1.20  | 4            | 5.97  |
| Gr2 to Gr3          | 4                | 4.88  | 3                | 3.61  | 2                | 2.41  | 1            | 1.49  |
| Gr2 to Gr4          | 1                | 1.22  | 0                | 0.00  | 1                | 1.20  | 0            | 0.00  |
| Gr3 to Gr4          | 1                | 1.22  | 1                | 1.20  | 2                | 2.41  | 0            | 0.00  |
| No Change or better | 18               | 21.95 | 23               | 27.71 | 33               | 39.76 | 20           | 29.85 |
| Missing             | 1                | 1.22  | 1                | 1.20  | 2                | 2.41  | 0            | 0.00  |
| <b>AST</b>          |                  |       |                  |       |                  |       |              |       |
| Normal to Gr1       | 21               | 25.61 | 18               | 21.69 | 17               | 20.48 | 17           | 25.37 |
| Normal to Gr2       | 4                | 4.88  | 6                | 7.23  | 3                | 3.61  | 7            | 10.45 |
| Normal to Gr3       | 5                | 6.10  | 0                | 0.00  | 0                | 0.00  | 1            | 1.49  |
| Normal to Gr4       | 2                | 2.44  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr1 to Gr2          | 3                | 3.66  | 3                | 3.61  | 2                | 2.41  | 3            | 4.48  |
| Gr1 to Gr3          | 0                | 0.00  | 0                | 0.00  | 1                | 1.20  | 0            | 0.00  |
| Gr1 to Gr4          | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr2 to Gr3          | 0                | 0.00  | 0                | 0.00  | 1                | 1.20  | 0            | 0.00  |
| Gr2 to Gr4          | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr3 to Gr4          | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| No Change or better | 46               | 56.10 | 55               | 66.27 | 57               | 68.67 | 39           | 58.21 |
| Missing             | 1                | 1.22  | 1                | 1.20  | 2                | 2.41  | 0            | 0.00  |

Table 52: Study 1182\_0051: DAIDS Grade Shift in Liver Enzymes (Continued)

|                        | APV/TPV/r (n=80) |       | LPV/TPV/r (n=81) |       | SQV/TPV/r (n=80) |       | TPV/r (n=65) |       |
|------------------------|------------------|-------|------------------|-------|------------------|-------|--------------|-------|
|                        | #                | %     | #                | %     | #                | %     | #            | %     |
| <b>ALT</b>             |                  |       |                  |       |                  |       |              |       |
| Normal to Gr1          | 21               | 25.61 | 17               | 20.48 | 22               | 26.51 | 20           | 29.85 |
| Normal to Gr2          | 9                | 10.98 | 8                | 9.64  | 7                | 8.43  | 5            | 7.46  |
| Normal to Gr3          | 3                | 3.66  | 2                | 2.41  | 1                | 1.20  | 2            | 2.99  |
| Normal to Gr4          | 6                | 7.32  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr1 to Gr2             | 4                | 4.88  | 7                | 8.43  | 2                | 2.41  | 1            | 1.49  |
| Gr1 to Gr3             | 2                | 2.44  | 0                | 0.00  | 0                | 0.00  | 4            | 5.97  |
| Gr1 to Gr4             | 0                | 0.00  | 0                | 0.00  | 1                | 1.20  | 0            | 0.00  |
| Gr2 to Gr3             | 0                | 0.00  | 0                | 0.00  | 1                | 1.20  | 1            | 1.49  |
| Gr2 to Gr4             | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr3 to Gr4             | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| No Change or better    | 36               | 43.90 | 48               | 57.83 | 47               | 56.63 | 34           | 50.75 |
| Missing                | 1                | 1.22  | 1                | 1.20  | 2                | 2.41  | 0            | 0.00  |
| <b>Total Bilirubin</b> |                  |       |                  |       |                  |       |              |       |
| Normal to Gr1          | 6                | 7.32  | 9                | 10.84 | 2                | 2.41  | 1            | 1.49  |
| Normal to Gr2          | 1                | 1.22  | 2                | 2.41  | 0                | 0.00  | 1            | 1.49  |
| Normal to Gr3          | 0                | 0.00  | 1                | 1.20  | 0                | 0.00  | 0            | 0.00  |
| Normal to Gr4          | 1                | 1.22  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr1 to Gr2             | 0                | 0.00  | 2                | 2.41  | 0                | 0.00  | 0            | 0.00  |
| Gr1 to Gr3             | 0                | 0.00  | 1                | 1.20  | 0                | 0.00  | 0            | 0.00  |
| Gr1 to Gr4             | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr2 to Gr3             | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr2 to Gr4             | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| Gr3 to Gr4             | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0            | 0.00  |
| No Change or better    | 73               | 89.02 | 67               | 80.72 | 79               | 95.18 | 65           | 97.01 |
| Missing                | 1                | 1.22  | 1                | 1.20  | 2                | 2.41  | 0            | 0.00  |

Table 53: Study 1182\_0051: DAIDS Grade Shift in Lipids and Renal Enzymes

|                                   | APV/TPV/r<br>(n=82) |       | LPV/TPV/r<br>(n=83) |       | SQV/TPV/r<br>(n=83) |       | TPV/r (n=67) |       |
|-----------------------------------|---------------------|-------|---------------------|-------|---------------------|-------|--------------|-------|
|                                   | #                   | %     | #                   | %     | #                   | %     | #            | %     |
| <b>Triglycerides (no missing)</b> |                     |       |                     |       |                     |       |              |       |
| Normal to Gr1                     | 19                  | 23.75 | 14                  | 17.28 | 18                  | 22.50 | 10           | 15.38 |
| Normal to Gr2                     | 5                   | 6.25  | 9                   | 11.11 | 4                   | 5.00  | 7            | 10.77 |
| Normal to Gr3                     | 0                   | 0.00  | 3                   | 3.70  | 0                   | 0.00  | 0            | 0.00  |
| Gr1 to Gr2                        | 11                  | 13.75 | 13                  | 16.05 | 7                   | 8.75  | 10           | 15.38 |
| Gr1 to Gr3                        | 7                   | 8.75  | 8                   | 9.88  | 4                   | 5.00  | 5            | 7.69  |
| Gr1 to Gr4                        | 0                   | 0.00  | 2                   | 2.47  | 2                   | 2.50  | 2            | 3.08  |
| Gr2 to Gr3                        | 5                   | 6.25  | 2                   | 2.47  | 0                   | 0.00  | 2            | 3.08  |
| Gr2 to Gr4                        | 1                   | 1.25  | 5                   | 6.17  | 3                   | 3.75  | 1            | 1.54  |
| Gr3 to Gr4                        | 1                   | 1.25  | 1                   | 1.23  | 2                   | 2.50  | 0            | 0.00  |
| No Change or better               | 31                  | 38.75 | 24                  | 29.63 | 40                  | 50.00 | 28           | 43.08 |
| <b>Cholesterol</b>                |                     |       |                     |       |                     |       |              |       |
|                                   | No missing          |       |                     |       |                     |       |              |       |
| Normal to Gr1                     | 30                  | 41.10 | 28                  | 34.57 | 23                  | 28.75 | 20           | 30.77 |
| Normal to Gr2                     | 2                   | 2.74  | 0                   | 0.00  | 2                   | 2.50  | 3            | 4.62  |
| Normal to Gr3                     | 0                   | 0.00  | 0                   | 0.00  | 1                   | 1.25  | 1            | 1.54  |
| Normal to Gr4                     | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| Gr1 to Gr2                        | 8                   | 10.96 | 8                   | 9.88  | 2                   | 2.50  | 2            | 3.08  |
| Gr1 to Gr3                        | 1                   | 1.37  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| Gr1 to Gr4                        | 0                   | 0.00  | 1                   | 1.23  | 0                   | 0.00  | 0            | 0.00  |
| Gr2 to Gr3                        | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 1            | 1.54  |
| Gr(2+j) to<br>Gr4,j=0,1           | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| No Change or better               | 39                  | 53.42 | 44                  | 54.32 | 52                  | 65.00 | 38           | 58.46 |
| <b>Renal: Creatinine</b>          |                     |       |                     |       |                     |       |              |       |
| Normal to Gr1                     | 3                   | 3.75  | 5                   | 6.17  | 5                   | 6.25  | 1            | 1.54  |
| Normal to Gr2                     | 0                   | 0.00  | 2                   | 2.47  | 0                   | 0.00  | 0            | 0.00  |
| Normal to Gr3/4                   | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| Gr1 to Gr2                        | 0                   | 0.00  | 1                   | 1.23  | 1                   | 1.25  | 1            | 1.54  |
| Gr1 to Gr3/4                      | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| Gr2 to Gr3/4                      | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| Gr3 to Gr4                        | 0                   | 0.00  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |
| No Change or better               | 76                  | 95.00 | 73                  | 90.12 | 74                  | 92.50 | 63           | 96.92 |
| Missing                           | 1                   | 1.25  | 0                   | 0.00  | 0                   | 0.00  | 0            | 0.00  |

Table 54: Study 1182\_0052: DAIDS Grade Shift in Selected Hematology Parameters

|                          | 500/100 (n=73) |       | 500/200 (n=72) |       | 750/200 (n=71) |       |
|--------------------------|----------------|-------|----------------|-------|----------------|-------|
|                          | #              | %     | #              | %     | #              | %     |
| <b>Platelet Count</b>    |                |       |                |       |                |       |
| Normal to Gr1            | 1              | 1.37  | 1              | 1.39  | 3              | 4.23  |
| Normal to Gr2            | 2              | 2.74  | 1              | 1.39  | 1              | 1.41  |
| Normal to Gr3            | 0              | 0.00  | 1              | 1.39  | 1              | 1.41  |
| Normal to Gr4            | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr1 to Gr2               | 0              | 0.00  | 0              | 0.00  | 1              | 1.41  |
| Gr1 to Gr3               | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr1 to Gr4               | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr2 to Gr3               | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr(2+j) to Gr4,<br>j=0,1 | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| No Change or<br>better   | 67             | 91.78 | 69             | 95.83 | 64             | 90.14 |
| Missing                  | 3              | 4.11  | 0              | 0.00  | 1              | 1.41  |
| <b>Hemoglobin</b>        |                |       |                |       |                |       |
| Normal to Gr1            | 1              | 1.37  | 8              | 11.11 | 1              | 1.41  |
| Normal to Gr2            | 0              | 0.00  | 0              | 0.00  | 2              | 2.82  |
| Normal to Gr3            | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Normal to Gr4            | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr1 to Gr2               | 1              | 1.37  | 0              | 0.00  | 1              | 1.41  |
| Gr1 to Gr3               | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr1 to Gr4               | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr2 to Gr3               | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr(2+j) to Gr4,<br>j=0,1 | 1              | 1.37  | 0              | 0.00  | 0              | 0.00  |
| No Change or<br>better   | 67             | 91.78 | 64             | 88.89 | 67             | 94.37 |
| Missing                  | 3              | 4.11  | 0              | 0.00  | 0              | 0.00  |
| <b>WBC</b>               |                |       |                |       |                |       |
| Normal to Gr1            | 11             | 15.07 | 13             | 18.06 | 11             | 15.49 |
| Normal to Gr2            | 3              | 4.11  | 4              | 5.56  | 2              | 2.82  |
| Normal to Gr3            | 0              | 0.00  | 0              | 0.00  | 1              | 1.41  |
| Normal to Gr4            | 0              | 0.00  | 0              | 0.00  | 6              | 8.45  |
| Gr1 to Gr2               | 2              | 2.74  | 4              | 5.56  | 1              | 1.41  |
| Gr1 to Gr3               | 1              | 1.37  | 1              | 1.39  | 0              | 0.00  |
| Gr1 to Gr4               | 0              | 0.00  | 0              | 0.00  | 0              | 0.00  |
| Gr2 to Gr3               | 1              | 1.37  | 1              | 1.39  | 4              | 5.63  |
| Gr(2+j) to Gr4,<br>j=0,1 | 2              | 2.74  | 1              | 1.39  | 0              | 0.00  |
| No Change or<br>better   | 50             | 68.49 | 48             | 66.67 | 45             | 63.38 |
| Missing                  | 3              | 4.11  | 0              | 0.00  | 1              | 1.41  |

Table 55: Study 1182\_0052: DAIDS Grade Shift in Liver Function Parameters

|                        | 500/100 (n=73) |      | 500/200 (n=72) |      | 750/200 (n=71) |      |
|------------------------|----------------|------|----------------|------|----------------|------|
|                        | #              | %    | #              | %    | #              | %    |
| <b>AST</b>             |                |      |                |      |                |      |
| Normal to Gr1          | 14             | 19.2 | 19             | 26.4 | 21             | 29.6 |
| Normal to Gr2          | 4              | 5.5  | 3              | 4.2  | 7              | 9.9  |
| Normal to Gr3          | 0              | 0.0  | 1              | 1.4  | 1              | 1.4  |
| Normal to Gr4          | 0              | 0.0  | 1              | 1.4  | 2              | 2.8  |
| Gr1 to Gr2             | 2              | 2.7  | 4              | 5.6  | 5              | 7.0  |
| Gr1 to Gr3             | 1              | 1.4  | 2              | 2.8  | 1              | 1.4  |
| Gr1 to Gr4             | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Gr2 to Gr3             | 1              | 1.4  | 0              | 0.0  | 1              | 1.4  |
| Gr2,3 to Gr4           | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| No Change/better       | 51             | 69.9 | 42             | 58.3 | 33             | 46.5 |
| <b>ALT</b>             |                |      |                |      |                |      |
| Normal to Gr1          | 13             | 17.8 | 24             | 33.3 | 22             | 31.0 |
| Normal to Gr2          | 4              | 5.5  | 8              | 11.1 | 10             | 14.1 |
| Normal to Gr3          | 1              | 1.4  | 2              | 2.8  | 5              | 7.0  |
| Normal to Gr4          | 0              | 0.0  | 1              | 1.4  | 3              | 4.2  |
| Gr1 to Gr2             | 4              | 5.5  | 4              | 5.6  | 5              | 7.0  |
| Gr1 to Gr3             | 0              | 0.0  | 2              | 2.8  | 4              | 5.6  |
| Gr1 to Gr4             | 0              | 0.0  | 1              | 1.4  | 1              | 1.4  |
| Gr2 to Gr3             | 1              | 1.4  | 1              | 1.4  | 3              | 4.2  |
| Gr2 to Gr4             | 0              | 0.0  | 1              | 1.4  | 1              | 1.4  |
| Gr3 to Gr4             | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| No Change/ better      | 50             | 68.5 | 28             | 38.9 | 17             | 23.9 |
| <b>Gamma GT</b>        |                |      |                |      |                |      |
| Normal to Gr1          | 19             | 26.0 | 17             | 23.6 | 13             | 18.3 |
| Normal to Gr2          | 11             | 15.1 | 6              | 8.3  | 10             | 14.1 |
| Normal to Gr3          | 2              | 2.7  | 8              | 11.1 | 6              | 8.5  |
| Normal to Gr4          | 0              | 0.0  | 1              | 1.4  | 3              | 4.2  |
| Gr1 to Gr2             | 2              | 2.7  | 4              | 5.6  | 11             | 15.5 |
| Gr1 to Gr3             | 4              | 5.5  | 4              | 5.6  | 7              | 9.9  |
| Gr1 to Gr4             | 1              | 1.4  | 1              | 1.4  | 3              | 4.2  |
| Gr2 to Gr3             | 1              | 1.4  | 3              | 4.2  | 2              | 2.8  |
| Gr2 to Gr4             | 2              | 2.7  | 4              | 5.6  | 1              | 1.4  |
| Gr3 to Gr4             | 0              | 0.0  | 0              | 0.0  | 1              | 1.4  |
| No Change/ better      | 31             | 42.5 | 24             | 33.3 | 14             | 19.7 |
| <b>Total Bilirubin</b> |                |      |                |      |                |      |
| Normal to Gr1          | 3              | 4.1  | 4              | 5.6  | 9              | 12.7 |
| Normal to Gr2          | 1              | 1.4  | 2              | 2.8  | 1              | 1.4  |
| Normal to Gr3          | 0              | 0.0  | 1              | 1.4  | 1              | 1.4  |
| Normal to Gr4          | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Gr1 to Gr2             | 1              | 1.4  | 1              | 1.4  | 0              | 0.0  |
| Gr1 to Gr3             | 0              | 0.0  | 0              | 0.0  | 1              | 1.4  |
| Gr1 to Gr4             | 0              | 0.0  | 0              | 0.0  | 1              | 1.4  |
| Gr2,3 to Gr3,4         | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |

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No Change/better 68 93.2 64 88.9 58 81.7

Table 56: Study 1182\_0052: DAIDS Grade Shift in Lipids & Creatinine

|                          | 500/100 (n=73) |      | 500/200 (n=72) |      | 750/200 (n=71) |      |
|--------------------------|----------------|------|----------------|------|----------------|------|
|                          | #              | %    | #              | %    | #              | %    |
| <b>Total Cholesterol</b> |                |      |                |      |                |      |
| Normal to Gr1            | 21             | 28.8 | 24             | 33.3 | 27             | 38.0 |
| Normal to Gr2            | 1              | 1.4  | 3              | 4.2  | 3              | 4.2  |
| Normal to Gr3            | 0              | 0.0  | 1              | 1.4  | 0              | 0.0  |
| Normal to Gr4            | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Gr1 to Gr2               | 3              | 4.1  | 8              | 11.1 | 5              | 7.0  |
| Gr1 to Gr3               | 0              | 0.0  | 1              | 1.4  | 3              | 4.2  |
| Gr1 to Gr4               | 0              | 0.0  | 0              | 0.0  | 1              | 1.4  |
| Gr2 to Gr3               | 1              | 1.4  | 0              | 0.0  | 0              | 0.0  |
| Gr2,3 to Gr4             | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| No Change/better         | 44             | 60.3 | 35             | 48.6 | 31             | 43.7 |
| Missing                  | 3              | 4.1  | 0              | 0.0  | 1              | 1.4  |
| <b>Triglycerides</b>     |                |      |                |      |                |      |
| Normal to Gr1            | 8              | 11.0 | 10             | 13.9 | 10             | 14.1 |
| Normal to Gr2            | 4              | 5.5  | 1              | 1.4  | 2              | 2.8  |
| Normal to Gr3            | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Normal to Gr4            | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Gr1 to Gr2               | 12             | 16.4 | 20             | 27.8 | 12             | 16.9 |
| Gr1 to Gr3               | 2              | 2.7  | 6              | 8.3  | 3              | 4.2  |
| Gr1 to Gr4               | 0              | 0.0  | 7              | 9.7  | 2              | 2.8  |
| Gr2 to Gr3               | 5              | 6.8  | 3              | 4.2  | 6              | 8.5  |
| Gr2 to Gr4               | 3              | 4.1  | 1              | 1.4  | 4              | 5.6  |
| Gr3 to Gr4               | 2              | 2.7  | 1              | 1.4  | 2              | 2.8  |
| No Change /better        | 34             | 46.6 | 23             | 31.9 | 29             | 40.8 |
| Missing                  | 3              | 4.1  | 0              | 0.0  | 1              | 1.4  |
| <b>Creatinine</b>        |                |      |                |      |                |      |
| Normal to Gr1            | 4              | 5.5  | 1              | 1.4  | 6              | 8.5  |
| Normal to Gr2            | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Normal to Gr3            | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Normal to Gr4            | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Gr1 to Gr2               | 0              | 0.0  | 2              | 2.8  | 0              | 0.0  |
| Gr1 to Gr3,4             | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| Gr2,3 to Gr3,4           | 0              | 0.0  | 0              | 0.0  | 0              | 0.0  |
| No Change or better      | 66             | 90.4 | 69             | 95.8 | 64             | 90.1 |
| Missing                  | 3              | 4.1  | 0              | 0.0  | 1              | 1.4  |

Table 57: 1182\_0052: Frequencies of DAIDS Grade 3 or 4 Elevations by Lab Parameter<sup>1</sup>

|       | TPV/r 500/100 mg |       | TPV/r 500/200 mg |       | TPV/r 750/200 mg |       | Total |       |
|-------|------------------|-------|------------------|-------|------------------|-------|-------|-------|
|       | #                | %     | #                | %     | #                | %     | #     | %     |
| WBC   | 2                | 2.74  | 2                | 2.78  | 6                | 8.45  | 10    | 4.63  |
| HGB   | 1                | 1.37  | 0                | 0.00  | 0                | 0.00  | 1     | 0.46  |
| PLTCT | 0                | 0.00  | 1                | 1.39  | 1                | 1.41  | 2     | 0.93  |
| ALT   | 2                | 2.74  | 8                | 11.11 | 17               | 23.94 | 27    | 12.50 |
| AST   | 2                | 2.74  | 4                | 5.56  | 5                | 7.04  | 11    | 5.09  |
| GGT   | 10               | 13.70 | 21               | 29.17 | 22               | 30.99 | 53    | 24.54 |
| TBILI | 0                | 0.00  | 1                | 1.39  | 3                | 4.23  | 4     | 1.85  |
| CHOL  | 1                | 1.37  | 2                | 2.78  | 4                | 5.63  | 7     | 3.24  |
| TRIGL | 10               | 13.70 | 17               | 23.61 | 15               | 21.13 | 42    | 19.44 |
| CRE   | 0                | 0.00  | 0                | 0.00  | 0                | 0.00  | 0     | 0.00  |
| Total | 28               |       | 56               |       | 73               |       | 157   |       |

Table 58: RESIST Trials: DAIDS Grade 3 or 4 Liver Enzymes and Lipids Toxicities

| Study     |        | CPI/r               |       | TPV/r |       | P-value <sup>1</sup> |        |
|-----------|--------|---------------------|-------|-------|-------|----------------------|--------|
|           |        | #                   | %     | #     | %     |                      |        |
| 1182_0012 | Liver  | n=309               |       | n=311 |       |                      |        |
|           |        | ALT                 | 4     | 1.29  | 21    | 6.75                 | 0.0028 |
|           |        | AST                 | 7     | 2.27  | 15    | 4.82                 | 0.1358 |
|           |        | GGT                 | 30    | 9.71  | 70    | 22.51                | 0.0002 |
|           |        | TBILI               | 3     | 0.97  | 1     | 0.32                 | 0.2522 |
|           |        | LFT(3) <sup>2</sup> | 9     | 2.91  | 24    | 7.72                 | 0.0277 |
|           |        | LFT <sup>3</sup>    | 34    | 11.00 | 78    | 25.08                | 0.0001 |
|           | Lipids | CHOL                | 0     | 0.00  | 13    | 4.18                 | 0.0007 |
|           | TRIGL  | 43                  | 13.92 | 71    | 22.83 | 0.0186               |        |
| 1182_0048 | Liver  | n=428               |       | n=435 |       |                      |        |
|           |        | ALT                 | 9     | 2.10  | 23    | 5.29                 | 0.0255 |
|           |        | AST                 | 6     | 1.40  | 15    | 3.45                 | 0.0914 |
|           |        | GGT                 | 28    | 6.54  | 90    | 20.69                | 0.0001 |
|           |        | TBILI               | 7     | 1.64  | 2     | 0.46                 | 0.0882 |
|           |        | LFT (3)             | 12    | 2.80  | 23    | 5.29                 | 0.1077 |
|           |        | LFT                 | 34    | 7.94  | 101   | 23.22                | 0.0001 |
|           | Lipids | CHOL                | 2     | 0.47  | 12    | 2.76                 | 0.0189 |
|           | TRIGL  | 49                  | 11.45 | 90    | 20.69 | 0.0011               |        |

1. P-values by the log-rank test.

2. LFT(3)- liver function toxicities summarized by ALT, AST and total bilirubin.

3. LFT- liver function toxicities summarized by ALT, AST, Gamma GT and total bilirubin.

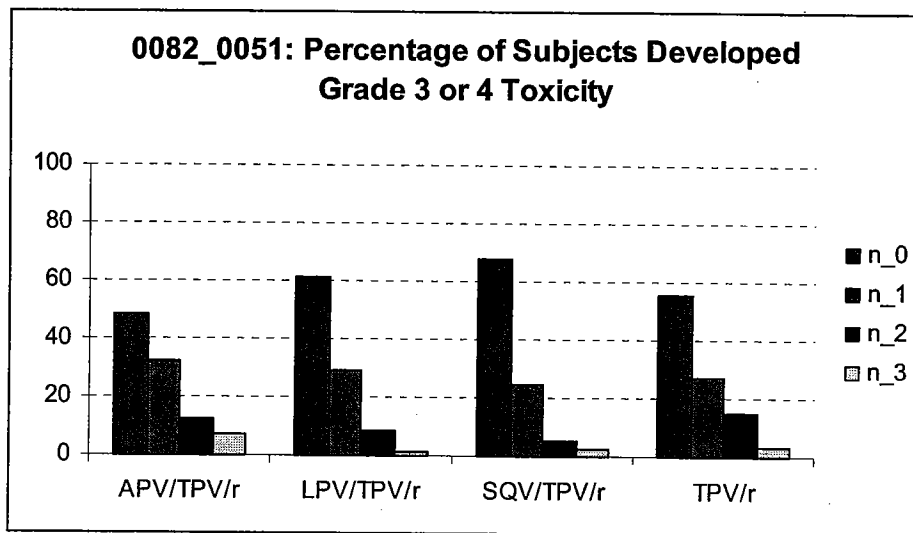


Figure 40: 1182\_0051: Percentage of Subjects with Grade 3 or 4 Toxicity

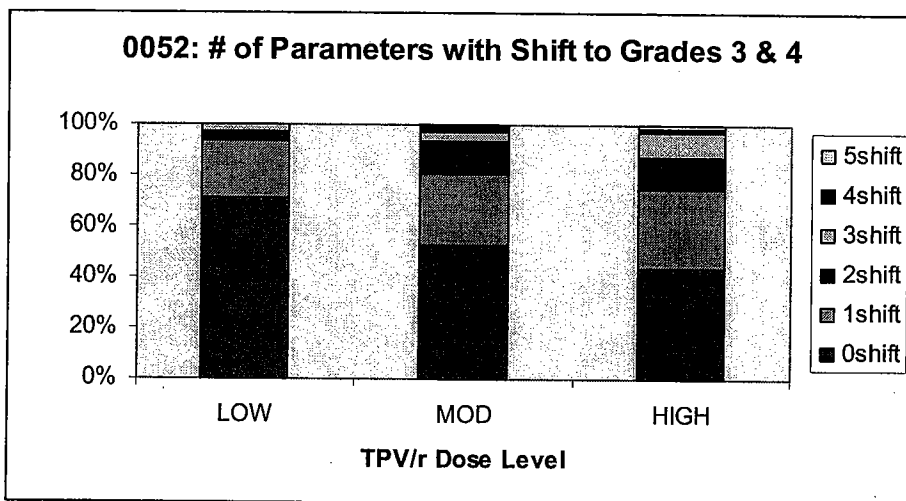


Figure 41: 1182\_0052: Percentage of Subjects with Grade 3 or 4 Toxicity



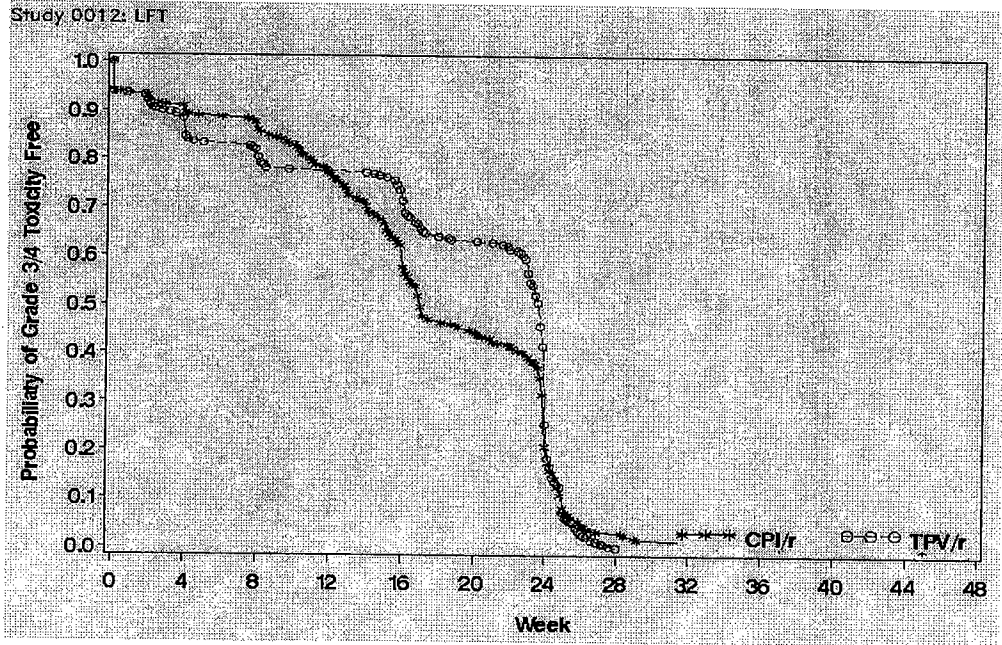


Figure 42: 1182\_0012: Time to First Grade 3 or 4 Elevations in LFTs (four enzymes)

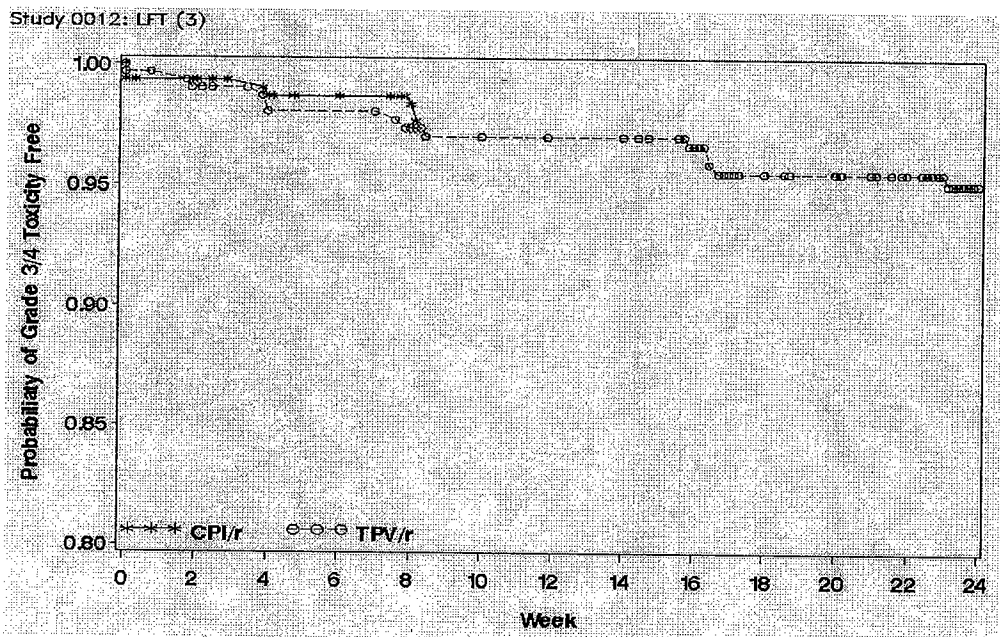


Figure 43: 1182\_0012: Time to First Grade 3 or 4 LFTs (ALT, AST and Total Bilirubin)

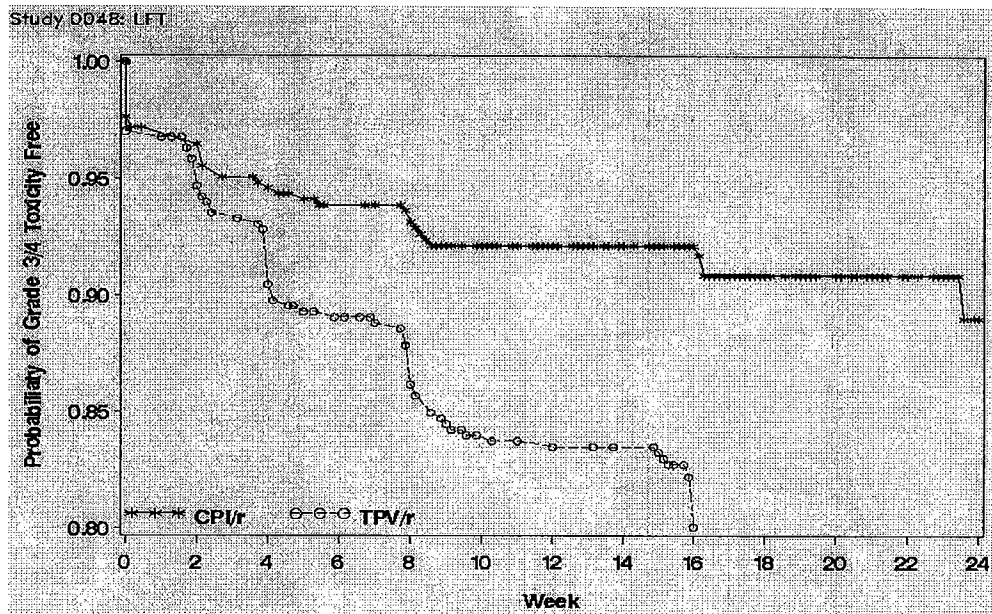


Figure 44: 1182\_0048: Time to First Grade 3 or 4 LFTs (four enzymes)

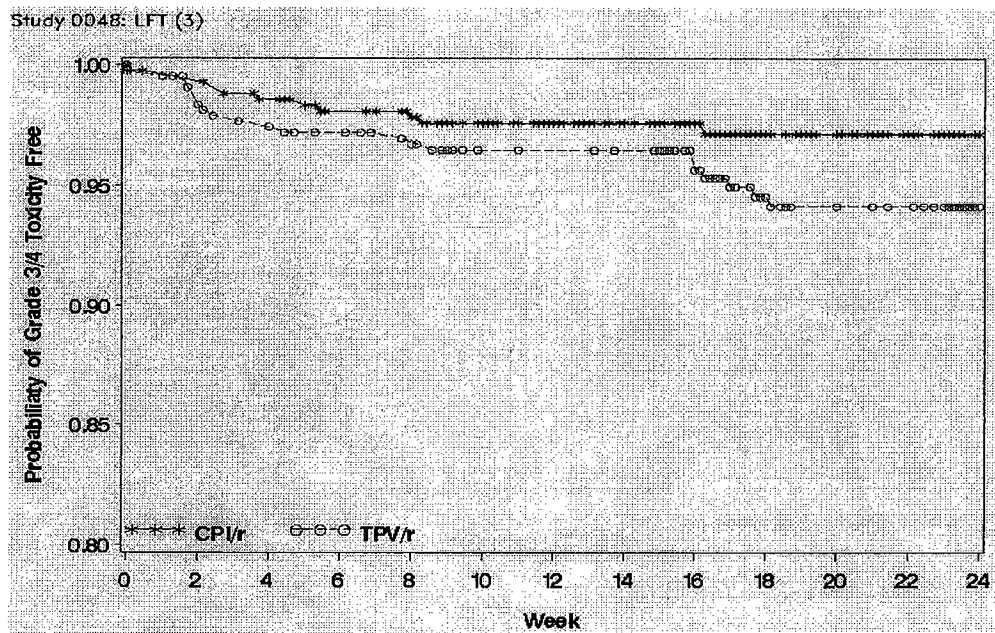


Figure 45: 1182\_0048: Time to Grade 3 or 4 LFTs (ALT, AST Total Bilirubin)

RESIST 1: Lipids

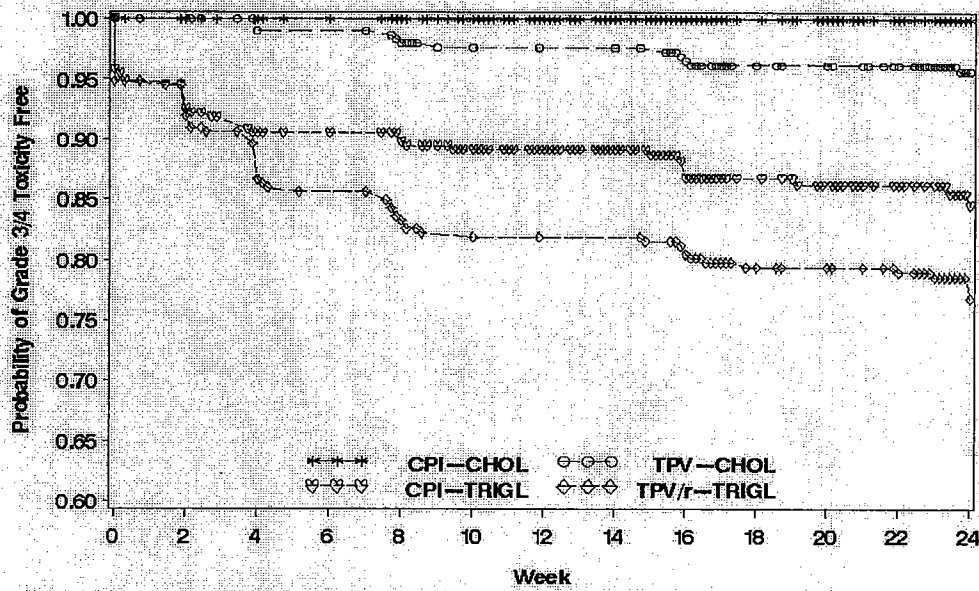


Figure 46: 1182\_0012: Time to Grade 3 or 4 Elevations in Lipids

RESIST 2: Lipids

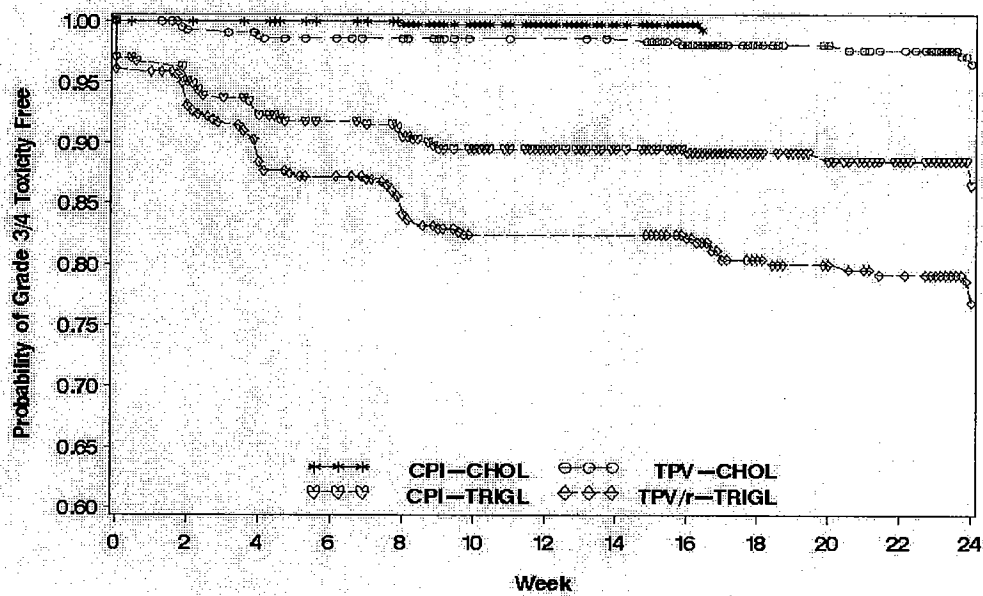


Figure 47: 1182\_0048: Time to First Grade 3 or 4 Elevations in Lipids

NDA 21-814, N000; APTIVUS™ (tipranavir)  
 Statistical Review and Evaluation

Table 59: RESIST Trials: Change from Baseline LDL (mg/dL)

| TRTGRP                                     | Week | N   | Min | Max | mean  | Std   | Med  | p25   | p75   | Pvalue |
|--|------|-----|-----|-----|-------|-------|------|-------|-------|--------|
| <b>1182 0012: Baseline LDL</b>             |      |     |     |     |       |       |      |       |       |        |
|  | 0    | 521 |     |     | 95.0  | 155.2 | 86.5 | 65.5  | 109.5 | 0.6535 |
| CPI/r                                      | 0    | 266 |     |     | 102.4 | 214.4 | 87.0 | 65.5  | 108.7 |        |
| TPV/r                                      | 0    | 255 |     |     | 87.3  | 35.2  | 85.5 | 65.0  | 112.0 |        |
| <b>1182 0012: Change from Baseline LDL</b> |      |     |     |     |       |       |      |       |       |        |
|  | 2    | 394 |     |     | -0.8  | 169.6 | 7.5  | -8.5  | 22.0  | 0.0001 |
| CPI/r                                      | 2    | 219 |     |     | -13.0 | 225.9 | 1.0  | -14.5 | 19.0  |        |
| TPV/r                                      | 2    | 175 |     |     | 14.6  | 25.4  | 14.0 | -1.0  | 28.5  |        |
|  | 4    | 391 |     |     | 0.2   | 169.1 | 7.5  | -8.0  | 25.0  | 0.0001 |
| CPI/r                                      | 4    | 216 |     |     | -11.7 | 225.7 | 2.5  | -12.6 | 19.5  |        |
| TPV/r                                      | 4    | 175 |     |     | 14.9  | 28.0  | 12.5 | -4.0  | 31.0  |        |
|  | 8    | 395 |     |     | -0.8  | 171.4 | 7.7  | -11.2 | 25.0  | 0.0001 |
| CPI/r                                      | 8    | 218 |     |     | -14.2 | 228.6 | 1.3  | -16.0 | 19.5  |        |
| TPV/r                                      | 8    | 177 |     |     | 15.6  | 28.2  | 16.5 | -0.5  | 32.5  |        |
|  | 16   | 356 |     |     | 1.0   | 180.0 | 8.0  | -9.8  | 31.0  | 0.0001 |
| CPI/r                                      | 16   | 192 |     |     | -13.2 | 242.9 | 4.3  | -16.0 | 19.0  |        |
| TPV/r                                      | 16   | 164 |     |     | 17.6  | 30.7  | 16.0 | -3.3  | 37.8  |        |
|  | 24   | 279 |     |     | 4.7   | 204.6 | 13.0 | -3.9  | 40.0  | 0.0001 |
| CPI/r                                      | 24   | 119 |     |     | -21.0 | 309.8 | 6.0  | -12.0 | 29.5  |        |
| TPV/r                                      | 24   | 160 |     |     | 23.9  | 33.5  | 22.5 | 1.8   | 45.5  |        |
| <b>1182 0048: Baseline LDL</b>             |      |     |     |     |       |       |      |       |       |        |
|  | 0    | 748 |     |     | 99.7  | 39.1  | 96.5 | 72.5  | 123.8 | 0.1033 |
| CPI/r                                      | 0    | 367 |     |     | 102.3 | 40.8  | 99.1 | 74.0  | 127.0 |        |
| TPV/r                                      | 0    | 381 |     |     | 97.3  | 37.3  | 94.4 | 71.2  | 120.6 |        |
| <b>1182 0048: Change from Baseline LDL</b> |      |     |     |     |       |       |      |       |       |        |
|  | 2    | 565 |     |     | 4.3   | 23.7  | 3.5  | -9.7  | 18.2  | 0.0002 |
| CPI/r                                      | 2    | 293 |     |     | 0.5   | 23.2  | 1.0  | -14.7 | 14.2  |        |
| TPV/r                                      | 2    | 272 |     |     | 8.3   | 23.6  | 6.8  | -6.9  | 22.8  |        |
|  | 4    | 565 |     |     | 4.5   | 25.9  | 4.0  | -12.4 | 18.8  | 0.0159 |
| CPI/r                                      | 4    | 296 |     |     | 1.2   | 24.9  | 3.0  | -15.9 | 17.8  |        |
| TPV/r                                      | 4    | 269 |     |     | 8.1   | 26.5  | 6.0  | -9.0  | 24.0  |        |
|  | 8    | 559 |     |     | 6.2   | 29.7  | 4.8  | -9.9  | 22.6  | 0.0002 |
| CPI/r                                      | 8    | 304 |     |     | 1.6   | 30.4  | 2.0  | -13.0 | 18.5  |        |
| TPV/r                                      | 8    | 255 |     |     | 11.6  | 28.1  | 8.1  | -5.6  | 27.1  |        |
|  | 16   | 516 |     |     | 11.0  | 29.8  | 9.4  | -8.4  | 27.1  | 0.0066 |
| CPI/r                                      | 16   | 249 |     |     | 6.7   | 27.9  | 7.3  | -9.7  | 23.2  |        |
| TPV/r                                      | 16   | 267 |     |     | 15.0  | 31.0  | 13.0 | -5.8  | 33.1  |        |
|  | 24   | 249 |     |     | 13.0  | 30.9  | 15.1 | -6.6  | 30.0  | 0.0001 |
| CPI/r                                      | 24   | 127 |     |     | 24.5  | 94.2  | 13.0 | -31.0 | 86.0  |        |
| TPV/r                                      | 24   | 200 |     |     | 54.8  | 94.2  | 37.0 | -1.0  | 105.5 |        |

Table 60: RESIST Trials: Change from Baseline HDL (mg/dL)

| TRTGRP                                     | Week | N   | Min | Max | mean | Std  | Med  | p25  | p75  | Pvalue |
|--|------|-----|-----|-----|------|------|------|------|------|--------|
| <b>1182_0012: Baseline HDL</b>             |      |     |     |     |      |      |      |      |      |        |
|  | 0    | 604 |     |     | 35.2 | 23.0 | 32.5 | 27.5 | 39.7 | 0.6964 |
| CPI/r                                      | 0    | 299 |     |     | 35.9 | 30.6 | 32.0 | 27.5 | 39.7 |        |
| TPV/r                                      | 0    | 305 |     |     | 34.5 | 11.7 | 33.0 | 27.5 | 39.6 |        |
| <b>1182_0012: Change from Baseline HDL</b> |      |     |     |     |      |      |      |      |      |        |
|  | 2    | 543 |     |     | -0.5 | 22.3 | 0.5  | -4.0 | 5.0  | 0.2152 |
| CPI/r                                      | 2    | 269 |     |     | -0.9 | 30.8 | 1.0  | -3.0 | 5.0  |        |
| TPV/r                                      | 2    | 274 |     |     | -0.1 | 7.6  | 0.5  | -4.5 | 5.0  |        |
|  | 4    | 537 |     |     | 0.0  | 22.4 | 0.8  | -3.5 | 5.0  | 0.6912 |
| CPI/r                                      | 4    | 269 |     |     | -0.9 | 30.6 | 1.0  | -3.0 | 5.0  |        |
| TPV/r                                      | 4    | 268 |     |     | 0.8  | 8.3  | 0.5  | -4.0 | 5.6  |        |
|  | 8    | 550 |     |     | -0.2 | 22.4 | 0.5  | -4.0 | 5.0  | 0.9523 |
| CPI/r                                      | 8    | 273 |     |     | -1.2 | 30.7 | 0.5  | -4.0 | 5.0  |        |
| TPV/r                                      | 8    | 277 |     |     | 0.7  | 8.3  | 0.8  | -4.0 | 4.6  |        |
|  | 16   | 496 |     |     | 0.2  | 23.4 | 0.5  | -3.7 | 5.1  | 0.5186 |
| CPI/r                                      | 16   | 236 |     |     | -1.1 | 32.7 | 0.5  | -3.5 | 4.6  |        |
| TPV/r                                      | 16   | 260 |     |     | 1.4  | 8.6  | 1.0  | -4.0 | 6.0  |        |
|  | 24   | 382 |     |     | -0.2 | 26.9 | 1.0  | -4.0 | 6.0  | 0.2093 |
| CPI/r                                      | 24   | 144 |     |     | -3.2 | 41.9 | 0.6  | -5.0 | 5.0  |        |
| TPV/r                                      | 24   | 238 |     |     | 1.6  | 9.9  | 1.0  | -4.0 | 6.7  |        |
| <b>1182_0048: Baseline HDL</b>             |      |     |     |     |      |      |      |      |      |        |
|  | 0    | 853 |     |     | 36.8 | 11.5 | 34.6 | 28.6 | 42.2 | 0.9655 |
| CPI/r                                      | 0    | 423 |     |     | 36.8 | 11.5 | 34.8 | 28.6 | 41.6 |        |
| TPV/r                                      | 0    | 430 |     |     | 36.8 | 11.5 | 34.5 | 28.4 | 42.7 |        |
| <b>1182_0048: Change from Baseline HDL</b> |      |     |     |     |      |      |      |      |      |        |
|  | 2    | 768 |     |     | -1.0 | 7.9  | -0.8 | -5.0 | 3.4  | 0.0844 |
| CPI/r                                      | 2    | 378 |     |     | -0.7 | 8.0  | -0.4 | -4.3 | 3.7  |        |
| TPV/r                                      | 2    | 390 |     |     | -1.3 | 7.8  | -1.0 | -5.5 | 3.0  |        |
|  | 4    | 787 |     |     | -0.7 | 8.2  | -0.5 | -5.5 | 3.9  | 0.8294 |
| CPI/r                                      | 4    | 391 |     |     | -0.9 | 8.3  | -0.4 | -5.8 | 3.5  |        |
| TPV/r                                      | 4    | 396 |     |     | -0.5 | 8.0  | -0.9 | -5.5 | 4.0  |        |
|  | 8    | 786 |     |     | -0.7 | 9.2  | -0.6 | -5.6 | 4.1  | 0.7153 |
| CPI/r                                      | 8    | 392 |     |     | -0.9 | 9.4  | -0.8 | -5.0 | 4.2  |        |
| TPV/r                                      | 8    | 394 |     |     | -0.6 | 9.0  | -0.6 | -6.0 | 4.0  |        |
|  | 16   | 708 |     |     | -1.2 | 8.9  | -1.4 | -7.0 | 3.9  | 0.0637 |
| CPI/r                                      | 16   | 328 |     |     | -2.1 | 8.7  | -1.9 | -7.0 | 3.0  |        |
| TPV/r                                      | 16   | 380 |     |     | -0.4 | 9.0  | -0.7 | -6.9 | 4.5  |        |
|  | 24   | 354 |     |     | 0.6  | 12.8 | 0.5  | -5.8 | 5.6  | 0.2555 |
| CPI/r                                      | 24   | 135 |     |     | -0.9 | 9.6  | 0.4  | -6.0 | 4.6  |        |
| TPV/r                                      | 24   | 219 |     |     | 1.5  | 14.3 | 1.0  | -5.5 | 6.5  |        |

Table 61: RESIST Trials: LDL and HDL Abnormality

| LDL      | HDL     | CPI/r |      | TPV/r |      |
|----------|---------|-------|------|-------|------|
|          |         | n     | %    | n     | %    |
| Missing  | 40-high | 222   | 14.0 | 447   | 26.7 |
| Missing  | 0-40    | 36    | 2.3  | 56    | 3.3  |
| 0-<160   | 40-high | 855   | 53.9 | 676   | 40.4 |
| 0-<160   | 0-40    | 392   | 24.7 | 392   | 23.4 |
| 160-high | 40-high | 40    | 2.5  | 46    | 2.7  |
| 160-high | 0-40    | 40    | 2.5  | 56    | 3.3  |

Table 62: RESIST Trials: Total Cholesterol (mg/dL) by LDL/HDL Abnormality\*

| LDL/HDL  | n    | mean  | std   | med   | min | max | p25   | p75   | p-value <sup>6</sup> |
|----------|------|-------|-------|-------|-----|-----|-------|-------|----------------------|
| TPV/r    |      |       |       |       |     |     |       |       |                      |
| Total    | 5249 | 194.2 | 52.8  | 189.1 |     |     | 157.0 | 225.1 | 0.5630               |
| Normal   | 1322 | 191.7 | 37.9  | 193.5 |     |     | 164.0 | 220.4 |                      |
| Abnormal | 3927 | 195.1 | 56.9  | 187.9 |     |     | 155.1 | 228.9 |                      |
| CPI/r    |      |       |       |       |     |     |       |       |                      |
| Total    | 5071 | 183.9 | 187.5 | 177.0 |     |     | 147.3 | 209.2 | <0.0001              |
| Normal   | 1230 | 188.1 | 33.8  | 188.9 |     |     | 165.0 | 211.1 |                      |
| Abnormal | 3841 | 182.6 | 214.6 | 172.9 |     |     | 143.0 | 208.0 |                      |

\*. LDL/HDL abnormality: LDL>160 mg/dL or HDL<40 mg/dL. &. P-value by the K-W test.

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Table 63: RESIST Trials (TPV/r Arm): Viral Responder and PI Mutations<sup>1</sup>

| Mutation   | NA         | YA         | %_A       | NP         | YP         | %_P       | P value       |
|------------|------------|------------|-----------|------------|------------|-----------|---------------|
| L10        | 22         | 27         | 55        | 250        | 214        | 46        | 0.2309        |
| <b>I13</b> | <b>169</b> | <b>171</b> | <b>50</b> | <b>103</b> | <b>70</b>  | <b>40</b> | <b>0.0349</b> |
| <b>K20</b> | <b>85</b>  | <b>106</b> | <b>55</b> | <b>187</b> | <b>135</b> | <b>42</b> | <b>0.0029</b> |
| D30        | 269        | 233        | 46        | 3          | 8          | 73        | 0.0837        |
| V32        | 227        | 212        | 48        | 45         | 29         | 39        | 0.1467        |
| L33        | 210        | 184        | 47        | 62         | 57         | 48        | 0.8184        |
| E34        | 243        | 222        | 48        | 29         | 19         | 40        | 0.2809        |
| <b>E36</b> | <b>138</b> | <b>145</b> | <b>51</b> | <b>134</b> | <b>96</b>  | <b>42</b> | <b>0.0321</b> |
| <b>M36</b> | <b>86</b>  | <b>117</b> | <b>58</b> | <b>186</b> | <b>124</b> | <b>40</b> | <b>0.0001</b> |
| K45        | 265        | 235        | 47        | 7          | 6          | 46        | 0.9519        |
| M46        | 73         | 63         | 46        | 199        | 178        | 47        | 0.8583        |
| <b>I47</b> | <b>208</b> | <b>212</b> | <b>50</b> | <b>64</b>  | <b>29</b>  | <b>31</b> | <b>0.0007</b> |
| <b>G48</b> | <b>242</b> | <b>191</b> | <b>44</b> | <b>30</b>  | <b>50</b>  | <b>63</b> | <b>0.0025</b> |
| I50        | 257        | 222        | 46        | 15         | 19         | 56        | 0.2817        |
| F53        | 229        | 195        | 46        | 43         | 46         | 52        | 0.3278        |
| <b>I54</b> | <b>47</b>  | <b>68</b>  | <b>59</b> | <b>225</b> | <b>173</b> | <b>43</b> | <b>0.0030</b> |
| Q58        | 226        | 213        | 49        | 46         | 28         | 38        | 0.0885        |
| D60        | 205        | 198        | 49        | 67         | 43         | 39        | 0.0615        |
| H69        | 239        | 203        | 46        | 33         | 38         | 54        | 0.2340        |
| G73        | 187        | 179        | 49        | 85         | 62         | 42        | 0.1673        |
| T74        | 236        | 199        | 46        | 36         | 42         | 54        | 0.1869        |
| V82        | 110        | 92         | 46        | 162        | 149        | 48        | 0.5999        |
| N83        | 265        | 235        | 47        | 7          | 6          | 46        | 0.9519        |
| I84        | 181        | 177        | 49        | 91         | 64         | 41        | 0.0894        |
| N88        | 265        | 238        | 47        | 7          | 3          | 30        | 0.2773        |
| L89        | 217        | 202        | 48        | 55         | 39         | 41        | 0.2380        |
| L90        | 118        | 113        | 49        | 154        | 128        | 45        | 0.4257        |

1. NA-no virologic response (N) and absence of mutation (A); YA-with virologic response (Y) and absence of mutation (A); NP-no virologic response (N) and presence of mutation (P); YP- with virologic response (Y) and presence of mutation (P); %\_A and %\_P – percentage of virologic responders among those mutations were absent or present; and P value- by the Chi-square test.

Table 64: RESIST Trials (TPV/r Arm: without T-20): Viral Responder and PI Mutations<sup>1</sup>

| Mutation | NA  | YA  | %_A | NP  | YP  | %_P | P value |
|----------|-----|-----|-----|-----|-----|-----|---------|
| L10      | 22  | 23  | 51  | 199 | 125 | 39  | 0.1080  |
| I13      | 135 | 115 | 46  | 86  | 33  | 28  | 0.0008  |
| K20      | 72  | 71  | 50  | 149 | 77  | 34  | 0.0029  |
| D30      | 219 | 142 | 39  | 2   | 6   | 75  | 0.0418  |
| V32      | 187 | 136 | 42  | 34  | 12  | 26  | 0.0381  |
| L33      | 174 | 119 | 41  | 47  | 29  | 38  | 0.6970  |
| E34      | 197 | 138 | 41  | 24  | 10  | 29  | 0.1817  |
| E36      | 112 | 91  | 45  | 109 | 57  | 34  | 0.0408  |
| M36      | 73  | 88  | 55  | 148 | 60  | 29  | 0.0001  |
| K45      | 214 | 144 | 40  | 7   | 4   | 36  | 0.7970  |
| M46      | 63  | 46  | 42  | 158 | 102 | 39  | 0.5952  |
| I47      | 170 | 137 | 45  | 51  | 11  | 18  | 0.0001  |
| G48      | 196 | 117 | 37  | 25  | 31  | 55  | 0.0115  |
| I50      | 210 | 137 | 39  | 11  | 11  | 50  | 0.3290  |
| F53      | 184 | 123 | 40  | 37  | 25  | 40  | 0.9699  |
| I54      | 39  | 51  | 57  | 182 | 97  | 35  | 0.0002  |
| Q58      | 183 | 134 | 42  | 38  | 14  | 27  | 0.0363  |
| D60      | 166 | 124 | 43  | 55  | 24  | 30  | 0.0466  |
| H69      | 192 | 123 | 39  | 29  | 25  | 46  | 0.3153  |
| G73      | 156 | 113 | 42  | 65  | 35  | 35  | 0.2222  |
| T74      | 193 | 124 | 39  | 28  | 24  | 46  | 0.3372  |
| V82      | 89  | 58  | 39  | 132 | 90  | 41  | 0.8351  |
| N83      | 215 | 146 | 40  | 6   | 2   | 25  | 0.3780  |
| I84      | 150 | 116 | 44  | 71  | 32  | 31  | 0.0275  |
| N88      | 216 | 145 | 40  | 5   | 3   | 38  | 0.8790  |
| L89      | 184 | 127 | 41  | 37  | 21  | 36  | 0.5090  |
| L90      | 98  | 70  | 42  | 123 | 78  | 39  | 0.5766  |

1. **NA**-no virologic response (N) and absence of mutation (A);  
**YA**-with virologic response (Y) and absence of mutation (A);  
**NP**-no virologic response (N) and presence of mutation (P);  
**YP**- with virologic response (Y) and presence of mutation (P);  
**%\_A** – percentage of virologic responders among those mutations were absent;  
**%\_P**– percentage of virologic responders among those mutations were present; and  
**P value**- by the Chi-square test.



Table 65: RESIST Trials (TPV/r Arm with T-20): % Viral Responder and PI Mutations<sup>1</sup>

| Mutation | NA | YA | % A | NP | YP | % P | P value |
|----------|----|----|-----|----|----|-----|---------|
| L10      | 0  | 4  | 100 | 51 | 89 | 64  | 0.1331  |
| I13      | 34 | 56 | 62  | 17 | 37 | 69  | 0.4444  |
| K20      | 13 | 35 | 73  | 38 | 58 | 60  | 0.1393  |
| D30      | 50 | 91 | 65  | 1  | 2  | 67  | 0.9392  |
| V32      | 40 | 76 | 66  | 11 | 17 | 61  | 0.6334  |
| L33      | 36 | 65 | 64  | 15 | 28 | 65  | 0.9305  |
| E34      | 46 | 84 | 65  | 5  | 9  | 64  | 0.9804  |
| E36      | 26 | 54 | 68  | 25 | 39 | 61  | 0.4132  |
| M36      | 13 | 29 | 69  | 38 | 64 | 63  | 0.4723  |
| K45      | 51 | 91 | 64  | 0  | 2  | 100 | 0.2916  |
| M46      | 10 | 17 | 63  | 41 | 76 | 65  | 0.8452  |
| I47      | 38 | 75 | 66  | 13 | 18 | 58  | 0.3916  |
| G48      | 46 | 74 | 62  | 5  | 19 | 79  | 0.1018  |
| I50      | 47 | 85 | 64  | 4  | 8  | 67  | 0.8748  |
| F53      | 45 | 72 | 62  | 6  | 21 | 78  | 0.1118  |
| I54      | 8  | 17 | 68  | 43 | 76 | 64  | 0.6944  |
| Q58      | 43 | 79 | 65  | 8  | 14 | 64  | 0.9196  |
| D60      | 39 | 74 | 65  | 12 | 19 | 61  | 0.6652  |
| H69      | 47 | 80 | 63  | 4  | 13 | 76  | 0.2752  |
| G73      | 31 | 66 | 68  | 20 | 27 | 57  | 0.2126  |
| T74      | 43 | 75 | 64  | 8  | 18 | 69  | 0.5841  |
| V82      | 21 | 34 | 62  | 30 | 59 | 66  | 0.5855  |
| N83      | 50 | 89 | 64  | 1  | 4  | 80  | 0.4632  |
| I84      | 31 | 61 | 66  | 20 | 32 | 62  | 0.5657  |
| N88      | 49 | 93 | 65  | 2  | 0  | 100 | 0.0545  |
| L89      | 33 | 75 | 69  | 18 | 18 | 50  | 0.0346  |
| L90      | 20 | 43 | 68  | 31 | 50 | 62  | 0.4167  |

1. NA -no virologic responders (N) and absence of mutation (A); YA-with virologic responders (Y) and absence of mutation (A); NP-no virologic responders (N) and presence of mutation (P); YP- with VR (Y) and presence of mutation (P); %\_A – percentage of virologic responders among those mutations were absent; %\_P– percentage of virologic responders among those mutations were present; and P value- by the Chi-square test.

Table 66: RESIST Trials (TPV/r Arm): Correlations between Two Baseline PI Mutation Pair<sup>1</sup>

|     | I13    | K20    | E36    | M36    | I47    | G48    | I54    | #sig <sup>2</sup> |
|-----|--------|--------|--------|--------|--------|--------|--------|-------------------|
| I13 |        | 0.0001 | 0.0005 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 6                 |
| K20 | 0.0005 |        | 0.0001 | 0.2393 | 0.0001 | 0.0001 | 0.0001 | 5                 |
| E36 | 0.0001 | 0.0001 |        | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 6                 |
| M36 | 0.0001 | 0.2393 | 0.0001 |        | 0.0001 | 0.0001 | 0.0001 | 5                 |
| I47 | 0.0001 | 0.0001 | 0.0001 | 0.0001 |        | 0.3144 | 0.0001 | 5                 |
| G48 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.3144 |        | 0.0001 | 5                 |
| I54 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 |        | 6                 |

1. P-values by McNemar's Test of Marginal Homogeneity;
2. #sig- number of rejections in testing marginal homogeneity between the two PI mutation locations.

Table 67: RESIST Trials: Gender Comparisons of DAIDS Grade 3 or 4 Toxicities

|           |         | CPI/r |        |       | TPV/r |        |       |
|-----------|---------|-------|--------|-------|-------|--------|-------|
|           |         | n     | #      | %     | n     | #      | %     |
| 1182_0012 |         |       |        |       |       |        |       |
| Grade ¾   | Female  | 22    | 4      | 18.18 | 32    | 10     | 31.25 |
|           | Male    | 284   | 58     | 20.42 | 276   | 113    | 40.94 |
|           | p-value |       | 0.8011 |       |       | 0.2893 |       |
| LFT       | Female  |       | 2      | 9.09  |       | 6      | 18.75 |
|           | Male    |       | 21     | 7.39  |       | 62     | 22.46 |
|           | p-value |       | 0.7712 |       |       | 0.6316 |       |
| Grade 4   | Female  |       | 3      | 13.64 |       | 3      | 9.38  |
|           | Male    |       | 21     | 7.39  |       | 49     | 17.75 |
|           | p-value |       | 0.2941 |       |       | 0.2310 |       |
| 1182_0048 |         |       |        |       |       |        |       |
| Grade ¾   | Female  | 62    | 9      | 14.52 | 83    | 22     | 26.51 |
|           | Male    | 360   | 70     | 19.44 | 347   | 129    | 37.18 |
|           | p-value |       | 0.3582 |       |       | 0.0673 |       |
| LFT       | Female  |       | 3      | 4.84  |       | 15     | 18.07 |
|           | Male    |       | 27     | 7.50  |       | 73     | 21.04 |
|           | p-value |       | 0.4513 |       |       | 0.5465 |       |
| Grade 4   | Female  |       | 3      | 4.84  |       | 4      | 4.82  |
|           | Male    |       | 22     | 6.11  |       | 49     | 14.12 |
|           | p-value |       | 0.6951 |       |       | 0.0206 |       |

Table 68: RESIST Trials: Summary of DAIDS Grade 3 or 4 Elevations

|   |          | CPI/r      |      | TPV/r      |      |
|---|----------|------------|------|------------|------|
|   |          | # subjects | %    | # subjects | %    |
| Grade 3 or 4 elevations <sup>1</sup>                  | RESIST 1 | 62         | 20.3 | 123        | 39.9 |
|   | RESIST 2 | 79         | 18.7 | 151        | 35.1 |
|   | total    | 141        | 19.4 | 274        | 37.1 |
| Grade 3 or 4 elevations in liver enzymes <sup>2</sup> | RESIST 1 | 23         | 7.5  | 68         | 22.1 |
|   | RESIST 2 | 30         | 7.1  | 88         | 20.5 |
|   | total    | 53         | 7.3  | 156        | 21.1 |
| Grade 4 elevations <sup>1</sup>                       | RESIST 1 | 24         | 8.2  | 52         | 16.9 |
|   | RESIST 2 | 25         | 5.7  | 53         | 12.3 |
|   | total    | 47         | 6.5  | 105        | 14.2 |

1. In ten selected lab parameters: platelets, hemoglobin, white blood cell count, AST, ALT, Gamma GT, total bilirubin, total cholesterol, triglycerides and creatinine.
2. AST, ALT, Gamma GT and total bilirubin.

Figure 48: RESIST Trials: Time to First LDL Abnormality

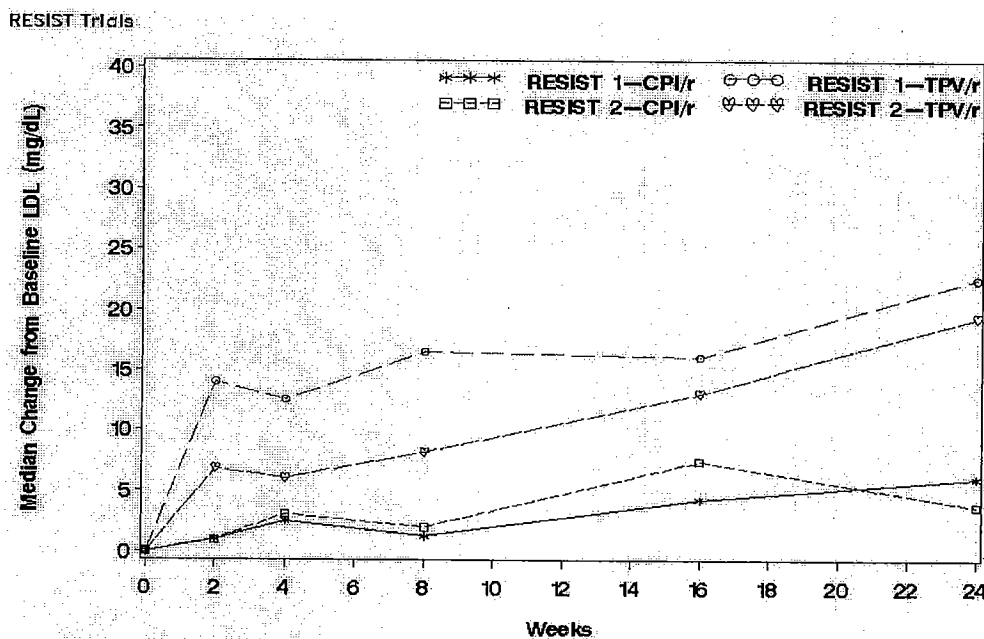


Figure 49: RESIST Trials: Median Change From Baseline LDL (mg/dL)

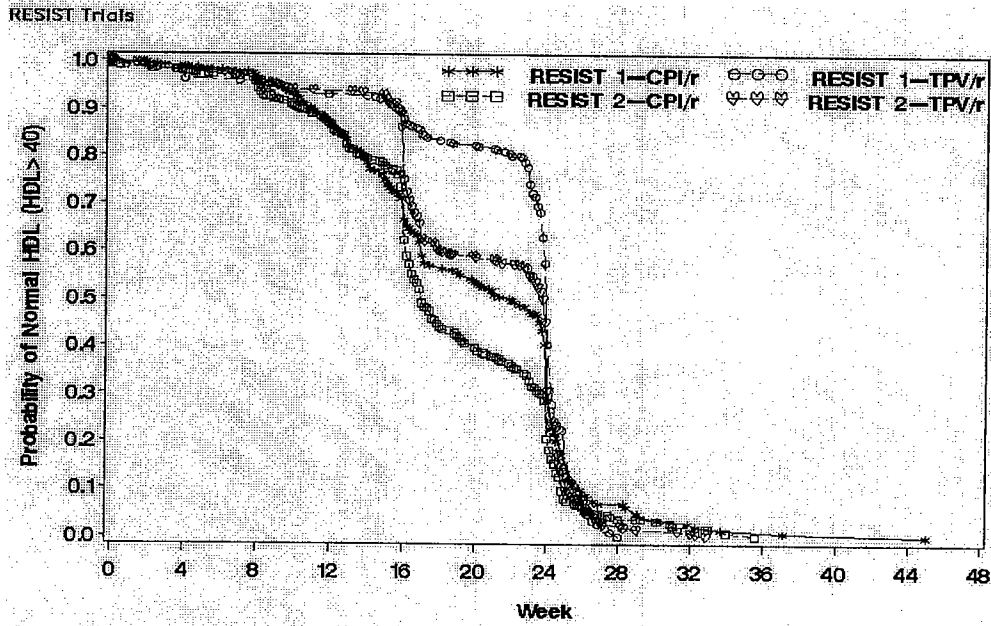


Figure 50: RESIST Trials: Time to First HDL Abnormality

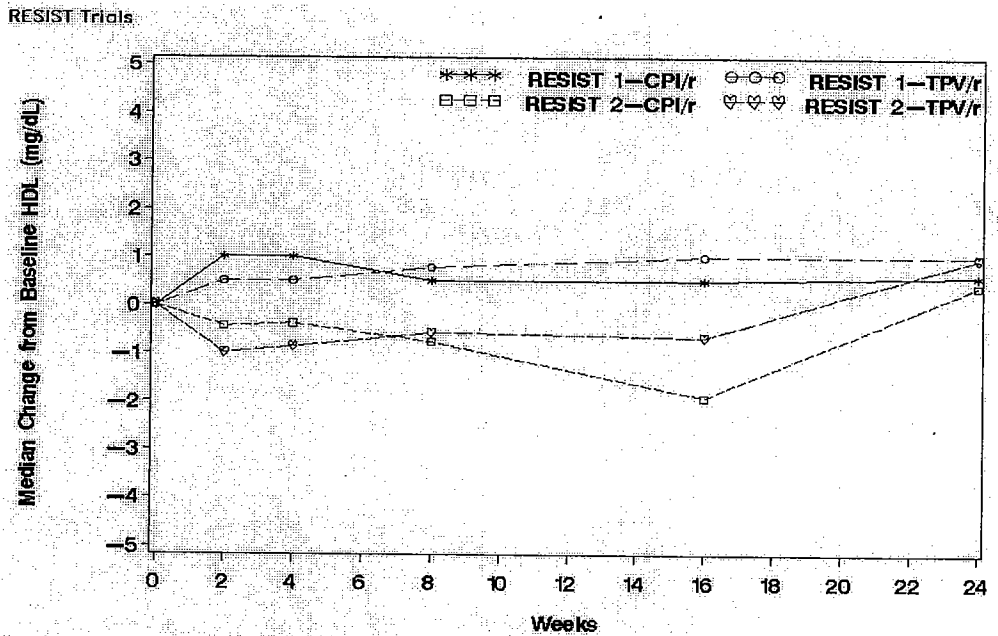


Figure 51: RESIST Trials: Median Change From Baseline HDL (mg/dL)

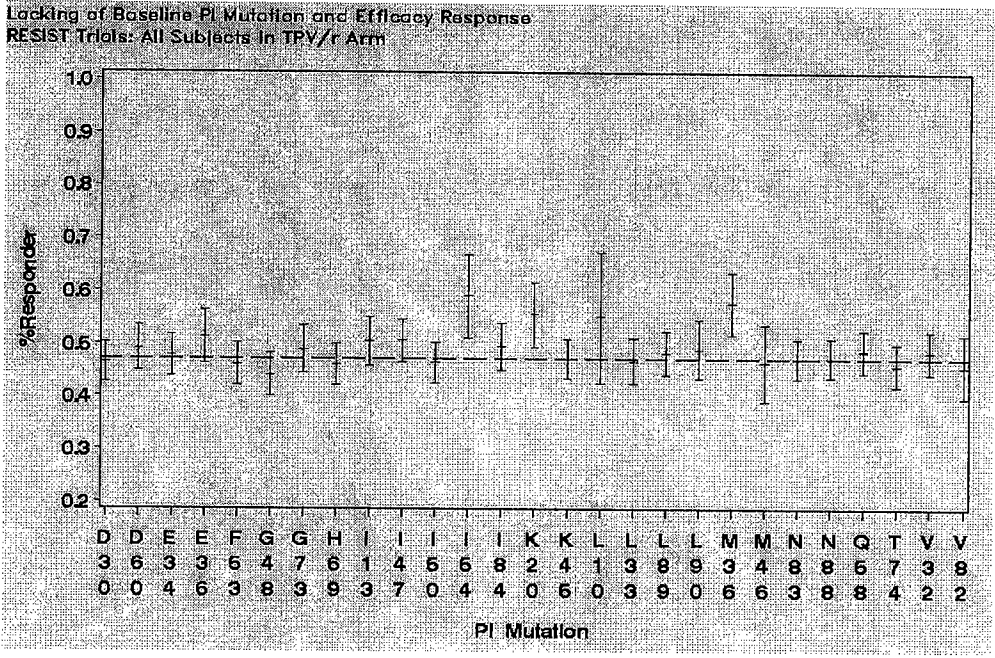


Figure 52: TPV/r Arm in RESIST Trials: % Virological Responders and Lacking PI Mutations

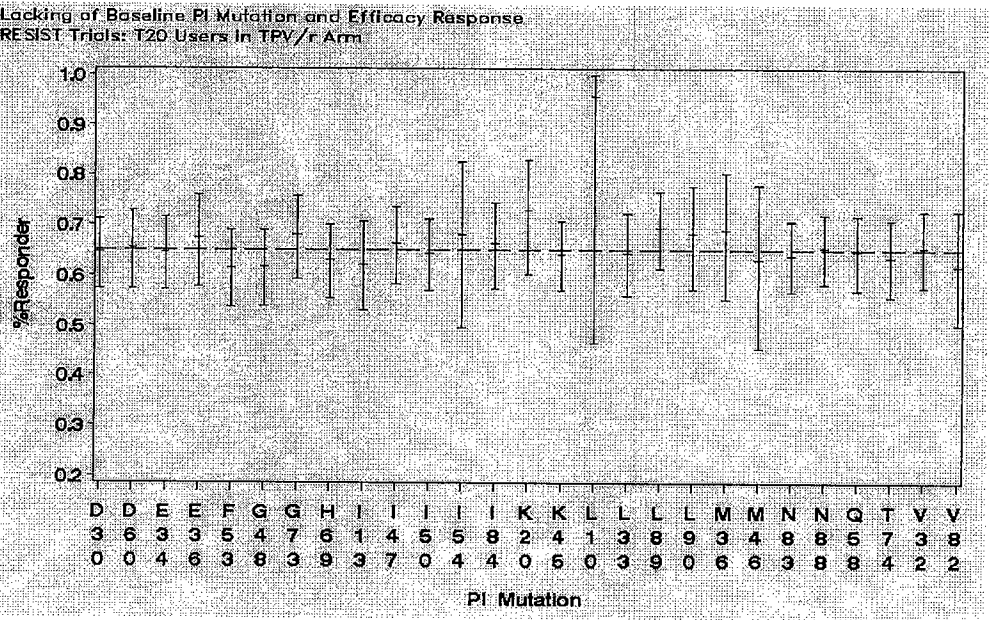


Figure 53: Virological Responder and Lacking PI Mutations among T-20 Users

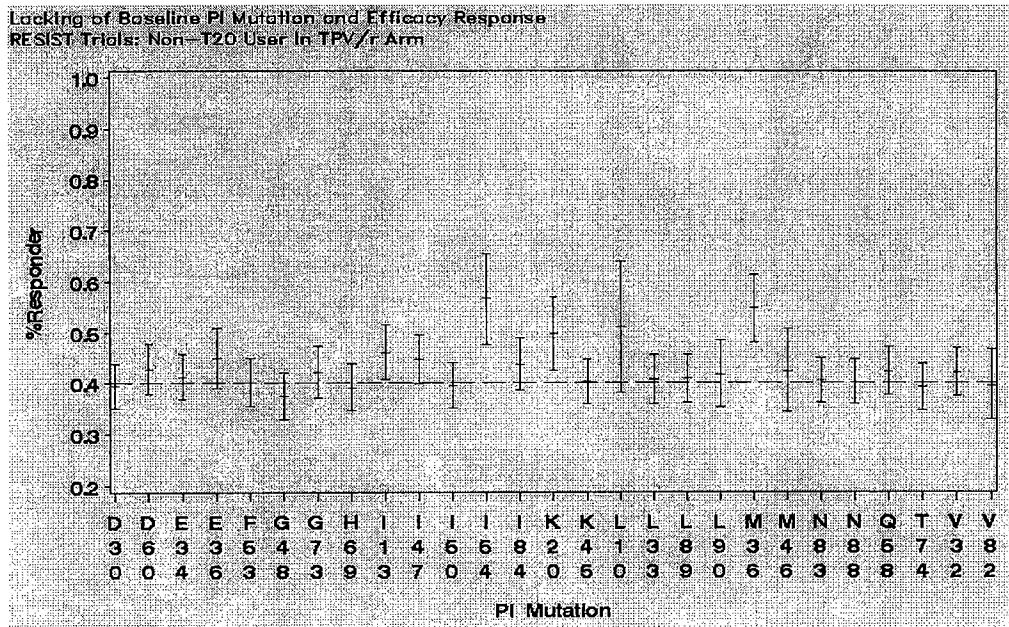


Figure 54: Virological Responders and Lacking PI Mutations Among Non-T-20 Users

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