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
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Review Priority:	Priority review
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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 α=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 (α'=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 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.

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.

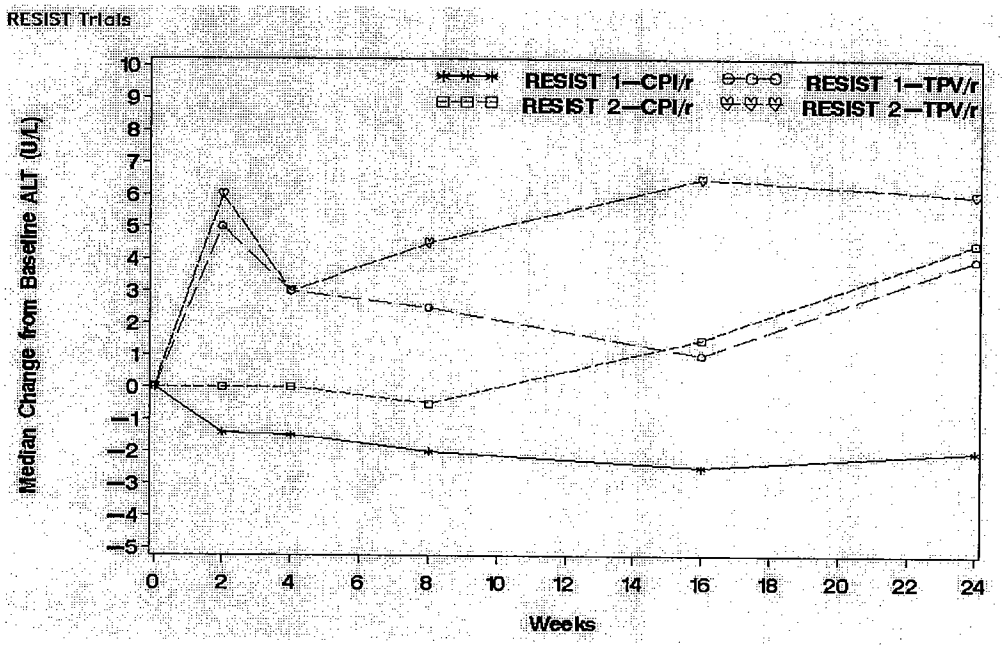

Figure 9: RESIST Trials: Median Change From Baseline ALT (U/L)

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

		CPI/r		TPV/r	
		# subjects	%	# subjects	%
Grade 3 or 4 elevations[1]	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[2]	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[1]	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 $\log_{10}$ 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 affect by the baseline PI mutations among subjects using T-20 with TPV/r.

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[1]

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

		0004	0012	0048	0051	0052
Grade	**Gamma GT**					
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
	ALT					
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
	AST					
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
	Total Bilirubin					
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[1]

	0004	0012	0048	0051	0052
HGB	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
WBC	10.8	10.7	10.7,13.2	10.7	10.5
PLTCT	400	394,400	394,400	394,400	415
SGPT	48,52	32,34,35,43	34,35,43	34,35,43	40
SGOT	36,42,59	34,36	34,36,40	34,36	40
GGT	45,65,73	49,50,61	49,50,51,61	49,50,61	60,65
TBILI	1.29,1.30	1.2,1.23	1.2,1.23	1.2,1.23	1.2,1.23
CHOL	199,199.15,200	218-352, n=17	218-352, n=17	235-320, n=16	199,199.15
TRIGL	198.4,199.99,200	144-327, n=16	124-327, n=22	176-327, n=16	149,149.20
CRE	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 1st Rx	Planned Time Window	Time Window[1] 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.

Table 5: 1182_0012 and 1182_0048: Time Window

Visit	Week	Lower Limit of Visit Window	Day	Upper Limit of Visit 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.