CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-814

Statistical Review(s)

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) bid
Indication(s):	Treatment of HIV infection
Applicant:	Boehringer Ingelheim Pharmaceuticals
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Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	**Rafia Bhore, Ph.D.**
Concurring Reviewers:	Thomas Hammerstrom, Ph.D. Mohammad Huque, Ph.D.
Medical Division:	Division of Antiviral Drug Products (HFD-530)
Clinical Team:	Andrea James, M.D., Primary Medical Reviewer Neville Gibbs, M.D., Medical Reviewer Melisse Baylor, M.D., Medical Reviewer Rosemary Johann-Liang, M.D., Medical Team Leader
Project Manager:	Tanima Sinha, M.S.

Keywords: Time to event, Open-Label Bias, Discontinuations, Informative Censoring, Data Quality Issues, Highly treatment-experienced HIV-infected, 24-week efficacy data

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Collective efficacy data through 24 weeks in two large, multinational, and multicenter Phase 3 clinical trials, RESIST 1 (1182.12) and RESIST 2, in 1159 HIV-infected patients who are highly treatment-experienced with (protease inhibitor) PI-resistant virus, show that APTIVUS™ (tipranavir) given in combination with ritonavir demonstrated efficacy when compared with the control group. The control group in these trials consisted of comparator protease inhibitors (lopinavir, amprenavir, saquinavir or indinavir) pharmacokinetically boosted with ritonavir. Efficacy evaluation was based on the surrogate endpoint of confirmed 1 $\log_{10}$ reduction from baseline in HIV RNA after 24 weeks of treatment. No results were available to make any conclusions to evaluate the effect of tipranavir on the clinical progression of HIV to AIDS.

1.2 Brief Overview of Clinical Studies

This statistical review of APTIVUS™ (tipranavir) NDA 21-814 was based on clinical data from two Phase 3 studies, RESIST 1 and RESIST 2.

The two identically designed RESIST trials, namely, RESIST 1 (1182.12) and RESIST 2 (1182.48) were multi-center, multi-national, randomized and controlled, open-label studies in highly treatment-experienced HIV-infected patients with triple antiretroviral class and dual protease inhibitor (dual PI)–drug regimen experience. The difference between the two studies was that RESIST 1 was conducted in the United States, Canada and Australia, while RESIST 2 was conducted in Europe and Latin America. Tipranavir boosted with ritonavir (TPV/r 500 mg/200 mg bid) was compared with respect to safety and efficacy through 24 weeks of treatment against a control group of protease inhibitors boosted with ritonavir (comparator PI/r or CPI/r included lopinavir, amprenavir, saquinavir or indinavir boosted with ritonavir) where the control PIs were genotypically determined. The studies are ongoing and designed to continue through 96 weeks.

Patients were highly antiretroviral treatment-experienced HIV-infected with triple ARV class (NRTI, NNRTI, and PI) experience and dual-PI regimen experience. Genotypic resistance testing was done at screening in which patients were to have at least one primary PI mutation(s) at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M and were to have no more than two protease mutations 33, 82, 84, or 90.

A total of 1159 patients were randomized equally to either the TPV/r or to the comparator PI/r group and treated through 24 weeks. The randomization was stratified with respect to the pre-selected protease inhibitor (PI) as well as the use of enfuvirtide (T-20). Both

treatment groups (TPV/r versus CPI/r) were to receive optimized background regimen consisting of at least two non-PI drugs based on genotypic resistance testing (i.e., resistance of HIV to drug) prior to randomization. Due to the complex comparator treatment group containing various protease inhibitor drugs with different dosing regimen and varying degrees of resistance profiles of the drugs, the studies had to be designed as open-label trials. Furthermore, the FDA review team strongly recommended the Applicant that the studies be tested for superiority of efficacy of TPV/r versus CPI/r, instead of testing for non-inferiority as originally proposed by the Applicant, because testing for non-inferiority against a control arm of sub-optimal drugs in such an experienced population will be uninterpretable. The RESIST studies included an escape clause whereby patients in the control arm who had a lack of initial virologic response by Week 8 were allowed to discontinue their assigned comparator protease inhibitor and enroll into the roll-over Study 1182.17 where all patients would receive tipranavir (TPV/r).

1.3 Statistical Issues and Findings

Evaluation of the efficacy of tipranavir was based on the collective data through 24 weeks from two open-label Phase 3 clinical studies, RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48), conducted in highly treatment-experienced HIV-infected subjects. The primary efficacy evaluation was based on surrogate endpoint of the proportion of subjects with *confirmed 1 log_{10} reduction in HIV RNA from baseline at Week 24 without evidence of treatment failure.* This primary endpoint was computed using the Time to Loss of Virologic Response algorithm (see FDA Guidance document entitled "Antiretroviral Drugs Using Plasma HIV RNA Measurements—Clinical Considerations for Accelerated and Traditional Approval" on http://www.fda.gov/cder/guidance).

A number of statistical issues were identified and addressed that required re-analysis of the primary efficacy endpoint for assessing the treatment effect. The statistical issues were as follows.

1. The Applicant had planned to evaluate the primary efficacy data for non-inferiority of TPV/r versus the comparator PI/r group. Their null hypothesis was that the proportion of treatment responders at 24 weeks was at least 10% lower in the TPV/r group than in the CPI/r group.

   A non-inferiority analysis would have been possible with the original protocol of RESIST trials for evaluating efficacy of tipranavir as the control arm would have been an active control arm. However, after Protocol Amendment # 2 was introduced, a non-inferiority analysis was unacceptable to the FDA review team, as this amendment allowed the Applicant to enroll a large number of patients in RESIST studies with highly resistant Protease Inhibitor virus to be treated with boosted protease inhibitors. This amendment created a control arm that is sub-optimal and primarily not active. As was recommended previously to the Applicant, the FDA reviewers therefore evaluated the RESIST studies for a superiority analysis of efficacy.

2. The open-label study designs had a potential to introduce bias in efficacy evaluation. Bias could come from multiple sources. Firstly, the studies had an escape clause at Week 8 of the study, which allowed patients in the control group to discontinue their randomized treatment if they did not show an initial virologic response. A large number of patients (17% in TPV/r vs. 47% in CPI/r) in the control group had discontinued treatment before Week 24 and that was attributable mainly to virologic failure. The proportion of initial virologic failures by Week 8 was 35% in TPV/r versus 59% in CPI/r.

   Therefore, the FDA reviewers incorporated this escape clause as a reason for treatment failure into the time-to-event analysis which would provide a correct interpretation of the final primary efficacy endpoint.

3. Other sources of potential open-label bias were: a) post-randomization changes by patients to their assigned background antiretroviral drugs taken in combination with their randomized treatment of TPV/r or CPI/r, b) post-randomization changes to their randomization strata with or without adding enfuviritide (T-20), c) large number of patients with protocol violations (51% in TPV/r and 56% in CPI/r group) in the study, d) potential lack of treatment compliance due to knowledge of treatment group.

   This FDA reviewer has addressed all of these open-label bias issues to evaluate whether the evidence of efficacy of tipranavir is sufficiently robust or not.

4. Finally, the FDA reviewer also evaluated claims made in external publications that tipranavir is superior in efficacy to any of the control protease inhibitor drugs such as lopinavir, amprenavir, saquinavir, or indinavir. Our evaluation was based on the drug resistance profiles of the comparator drugs and the prior exposure to the drugs. As noted before, a substantial proportion of patients (86%) were not susceptible to the comparator drugs because of resistant virus, while tipranavir was a new drug to which the HIV had not yet developed resistance.

Extensive review and evaluation of the efficacy data from the two Phase 3 studies lead us to the following conclusions.

1. RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48) studies were identically designed studies with primary difference being the geographic location where the studies were conducted. RESIST 1 was conducted in the USA (80%), Canada (13%), and Australia (7%) and RESIST 2 was conducted in Europe (85%) and Australia (15%). Both studies are ongoing and are of 96 weeks in duration. This statistical review is based on 24 week efficacy data from both studies.

2. In RESIST 1, a total of 620 patients were randomized and treated with either tipranavir/ritonavir (TPV/r) or comparator PI/ritonavir (CPI/r) given in combination with an optimized background regimen of at least two non-PI antiretroviral drugs. Out of these 84% of patients completed treatment through 24 weeks in TPV/r arm and 54% completed treatment through 24 weeks in the CPI/r arm.

In RESIST 2, a total of 863 patients were randomized and treated with either tipranavir/ritonavir (TPV/r) or comparator PI/ritonavir (CPI/r) given in combination with an optimized background regimen of at least two non-PI antiretroviral drugs. All of these 863 patients were to have completed 16 weeks in the study. However, as previously agreed by FDA, the Applicant provided efficacy data on 539 patients who would complete 24 weeks of the study. Out of these 539 patients, 82% of patients completed treatment through 24 weeks in TPV/r arm and 51% completed treatment through 24 weeks in the CPI/r arm.

3. The demographics of patients both studies were balanced across both treatment groups. In both RESIST studies combined, the mean age of patients was 44 years (range 17 to 80), 88% were male (12% female), 73% were of white origin, 14% of black origin, 1% of Asian origin and 12% patients from France did not report race due to local law.

4. Patients who enrolled in the RESIST trials were in an advanced HIV disease stage with many patients on a failing treatment regimen prior to study entry. Most of the baseline disease characteristics were balanced across the treatment groups in both studies. In both studies combined, the total of 1159 randomized and treated patients had a median baseline plasma HIV RNA of 4.82 (range 2 to 6.8) $\log_{10}$ copies/mL, and median baseline CD4 cell counts of 155 (range 1 to 1893) cells/mm^3. Forty percent (40%) of patients had baseline HIV RNA of >= 100,000 copies/mL, 61% had a baseline CD4 cell count <200 cells/mm^3, and 57% had an AIDS defining Class C event at baseline. In RESIST 1 and RESIST 2, respectively, 10% and 18% patients were either hepatitis B or C positive.

5. The randomization stratification factors in the RESIST studies were the pre-selected comparator protease inhibitors and the pre-determined assignment of enfuvirtide (T-20). These factors were not similar between the two studies. In RESIST 1, the proportion of patients assigned to the protease inhibitor stratum of lopinavir, amprenavir, saquinavir or indinavir, respectively were 61%, 14%, 21%, and 4%. In RESIST 2, the proportion of patients assigned to the protease inhibitor stratum of lopinavir, amprenavir, saquinavir or indinavir, respectively were 38%, 40%, 20%, and 3%. In other words, in RESIST 1 trial patients were most likely to be in the lopinavir stratum while in RESIST 2 the most common strata were lopinavir or amprenavir.

   In RESIST 1, 37% were assigned to receive enfuvirtide while in RESIST 2 only 14% were assigned to receive enfuvirtide.

   In RESIST 1 and RESIST 2, respectively, the proportion of patients evaluated to be possibly resistant or resistant using genotypic testing were 92% and 80% respectively. This difference could be attributed to the use of two different types of assay methods and algorithms (In RESIST 1 TruGene assay was used and in RESIST 2, European sites used Virtual Phenotype while Latin American sites used TruGene assay).

6. The FDA analysis of primary efficacy incorporated the early discontinuations due to lack of initial virologic response at Week 8 as treatment failure. Based on our analysis,

the proportion of treatment responders (confirmed 1 log reduction in HIV RNA from baseline) at Week 24 was 41% in TPV/r and 21% in the CPI/r arm in RESIST 1 study. In RESIST 2, the proportion of treatment responders was 40% in TPV/r group and 14% in the CPI/r group. Treatment differences of 20% in RESIST 1 (95% CI: [12%, 27%]) and 26% in RESIST 2 (95% CI: [19%, 33%]) were statistically significant and in favor of tipranavir/ritonavir. The major source of treatment failures in both studies was due to virologic failure and specifically due to the initial lack of response in many patients at Week 8.

7. Additionally, several sensitivity analyses were conducted by the FDA reviewer to address the many different sources of potential open-label biases such as early escape clause, post-randomization changes to the background antiretroviral regimen, post-randomization changes to the randomization strata of enfuvirtide assignment, numerous protocol violations (in at least 50% of patients), and potential treatment non-compliance. All of the sensitivity analyses were consistent with the FDA results of primary efficacy. These analyses indicated that the treatment effect of tipranavir/ritonavir was statistically significant compared with the comparator protease inhibitors/ritonavir. The treatment benefit due to tipranavir/ritonavir compared with comparator PI/ritonavir is expected to range between 9% and 32% using a pooled confidence interval of 99.875% for both studies combined.

8. In RESIST 1 and RESIST 2 studies combined, among the patients who achieved the primary endpoint (confirmed 1 log reduction from baseline in HIV RNA at Week 24), the proportion of patients with HIV RNA < 400 copies/mL was significantly greater in the TPV/r arm than in the control CPI/r (34% and 15%, respectively). The treatment difference was 19% with a pooled 99.875% confidence interval of (11%, 27%).

   Similarly, for the pooled RESIST studies, the proportion of patients with HIV RNA < 50 copies/mL was significantly greater in the TPV/r arm than in the control CPI/r arm (24% and 10%, respectively). The treatment difference was 14% with a pooled 99.875% confidence interval of (7%, 21%).

9. Among all patients who completed 24 weeks of therapy, the median change from baseline in HIV RNA in patients receiving tipranavir/ritonavir (N=489) versus comparator PI/ritonavir (N=285) was -1.34 and -1.02 log10 copies/mL, respectively. However, among all randomized and treated patients including virologic responders and treatment failures, the median change from baseline in HIV RNA in patients receiving tipranavir/ritonavir (N=582) versus comparator PI/ritonavir (N=577) was -0.8 and -0.25 log10 copies/mL at Week 24, respectively.

   Among all patients who completed 24 weeks of therapy, the median change from baseline in CD4+ cell count in patients receiving tipranavir/ritonavir (N=436) versus comparator PI/ritonavir (N=248) was +40 cells/mm3 and +32 cells/mm3 , respectively. However, among all randomized and treated patients including virologic responders and treatment failures, the median change from baseline in CD4+ cell count in patients receiving tipranavir/ritonavir (N=582) versus comparator PI/ritonavir (N=577) was +34

and +4 cells/mm3 at Week 24, respectively.

10. Several subgroup analyses were conducted on the primary efficacy endpoint (confirmed 1 $\log_{10}$ drop in HIV RNA from baseline at Week 24) based on the use of enfuvirtide (T-20), resistance to pre-selected comparator PIs, baseline HIV RNA, baseline CD4 cell count, gender, race and age. The first two subgroup analyses were based on the randomization strata of enfuvirtide use and resistance to comparator PIs. The second two subgroup analyses were standard subgroup analyses done for HIV drugs based on baseline HIV RNA and baseline CD4 cell counts—both being clinically relevant surrogate endpoints.

    Efficacy of tipranavir/ritonavir was demonstrated regardless of the use of T-20, but the efficacy was significantly greater in both studies when TPV/r was combined with T-20 in the patient population defined in the RESIST trials. When T-20 was combined with TPV/r the additional treatment effect was 32% versus 18% when T-20 was not used.

    Among patients who were not resistant to the comparator protease inhibitors, there was no statistically significant difference between TPV/r and CPI/r groups. However, this does not imply lack of efficacy of tipranavir. Among patients who were possibly resistant or resistant to the control drugs, tipranavir boosted with ritonavir was shown to be better than any of other boosted comparator PIs, implying efficacy of tipranavir.

    Treatment effect was significant and in favor of tipranavir/ritonavir compared with comparator PI/ritonavir in all three subgroups of patients with baseline HIV RNA $\leq$10,000 copies/mL, >10,000 to $\leq$100,000 copies/mL and >100,000 copies/mL. Treatment effect was similar in all three subgroups. However, in both treatment arms, the response rate declined when baseline HIV RNA increased.

    In both RESIST studies combined, the treatment difference between TPV/r and comparator PI/r groups (i.e., treatment benefit) was similar whether patients had baseline CD4 cell count <200 cells/mm^3 or $\geq$200 cells/mm^3. Also note that in both treatment arms, the treatment response was lower when baseline CD4 cell count was <200 cells/mm^3.

    In both RESIST studies, female patients had a numerically higher treatment response rate with TPV/r than CPI/r than male patients (29% treatment difference in females in RESIST 1 and 45% treatment difference in females in RESIST 2).

    In RESIST 1 study, the white patients had a statistically significant treatment benefit with TPV/r compared with CPI/r (24% treatment difference), but the black patients did not have a significant treatment effect with TPV/r (2% treatment difference). However, the treatment effect due to TPV/r was similar between white and black patients in RESIST 2 study. The number of patients of Asian origin was very small in both studies to make any statistical conclusions of efficacy of tipranavir/ritonavir.

    In both studies combined, the median age of patients was 43 years. The treatment effect due to TPV/r compared with CPI/r was statistically significant and in favor of tipranavir whether patients were below 43 years of age or above. In RESIST 1, the treatment effect was similar in both age groups. However, in RESIST 2 study, patients

of age <=43 years had a larger treatment benefit (30%) than patients of age >43 years (19%). The number of patients of age 65 years or more was only 16 in both studies.

11. FDA analysis of a head-to-head comparison was done to compare the treatment effect of boosted tipranavir (TPV/r) with each of the individual control PIs of boosted lopinavir, boosted amprenavir (APV/r), boosted saquinavir (SQV/r) and boosted indinavir (IDV/r). When patients were susceptible and naïve to the control PIs, the treatment difference between TPV/r versus each of LPV/r, and APV/r was small and not statistically significant, implying that tipranavir/ritonavir combination is not superior to the control PIs, LPV/r and APV/r. In the SQV/r strata among patients susceptible and naïve to SQV, the treatment difference between TPV/r and SQV/r was not statistically significant but the confidence intervals were shifted positive in favor of TPV/r. The number of patients in IDV/r strata who were susceptible and naïve to IDV were too small to make a head-to-head comparison.

    Among patients who were experienced or resistant to the comparator protease inhibitors, the control group was sub optimal, and the treatment effect was statistically significant and in favor of TPV/r versus each of LPV/r, APV/r, SQV/r and IDV/r on a head-to-head comparison basis.

2. INTRODUCTION

2.1 Overview

The Applicant submitted New Drug Application (NDA) 21-814, Serial Number 000, for APTIVUS™ (tipranavir, TPV) to the U.S. Food and Drug Administration (FDA) on December 29, 2004. The proposed indication for tipranavir is [

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Tipranavir belongs to the class of antiretroviral drugs that treat HIV infection called *protease inhibitors*. Specifically, tipranavir is a non-peptidic protease inhibitor (PI). APTIVUS™ (tipranavir, TPV) has been initially developed for use in highly ***antiretroviral treatment-experienced HIV-positive patients*** whose treatment options are limited because they have developed resistance to several classes of HIV drugs. Many of these patients have already acquired AIDS (Acquired Immunodeficiency Syndrome).

This NDA contains 24-week data on two identical Phase 3 clinical trials, 1182.12 (RESIST-1) and 1182.48 (RESIST-2), on tipranavir, done in HIV positive, treatment-experienced patients with triple antiretroviral class and dual protease inhibitor [dual PI]-drug regimen experience. In addition, supporting efficacy data for 24 weeks is also provided from a Phase 2 dose-ranging study, Study 1182.52, in a similar patient population who are treatment-experienced in triple antiretroviral classes and dual PI-experience. RESIST-1 and RESIST-2 studies are ongoing larger Phase 3, randomized, controlled, open-label trials designed to examine the safety and efficacy of tipranavir boosted with low-dose ritonavir (TPV/RTV), versus a low-dose ritonavir-boosted comparator protease inhibitor (CPI/RTV) in treatment-experienced patients for up to 96 weeks (~2 years).

The proposed dose for APTIVUS™ (tipranavir, TPV) is 500 mg given in combination with 200 mg ritonavir (RTV), where Norvir™ (ritonavir, RTV) is an FDA-approved protease inhibitor drug used in treating HIV infection.

2.1.1 Clinical Studies Supporting Efficacy Evaluation

Appendix 6.2 shows a table listing the clinical trials submitted by the Applicant to summarize the Integrated Summary of Efficacy and for evaluating the efficacy of tipranavir 500 mg given in combination with 200 mg ritonavir (i.e. TPV/RTV 500 mg/200mg).

2.2 Data Sources

This statistical review is based on data submitted from Studies 1182.12 (RESIST 1), and 1182.48 (RESIST 2).

Note that NDA 21-814 was a hybrid submission with electronic data in CDISC (Clinical Data Interchange Standards Consortium) format and paper submission of the study reports, etc., in the CTD (Common Technical Document) format. The electronic data is stored at the FDA, Center for Drug Evaluation and Research (CDER) internal network directory of \\Cdsesub1\N21814\N_000 .

Statistical Reviewer's Comments:

The Applicant submitted the first set of electronic datasets in the CDISC format on 21-October-2004. This submission contained both, the raw datasets and the Applicant's version of the analysis datasets. The vertical file structure (i.e., "long and skinny" file structure) of the raw datasets made it extremely difficult for reviewers to distinguish between different results for the same outcome measure when different methods were used. Additionally, it was very difficult to locate the needed variables for evaluating efficacy, safety and disposition of patients as well as understanding of the content of data within the electronic submission.

Based on several requests and numerous communications of clarification from the review team, the Applicant electronically submitted the efficacy datasets (raw datasets and analysis datasets) a total of 5 times. The submission dates of the efficacy data were 21-Oct-2004, 24-Nov-2004, 05-Dec-2004, 09-Dec-2004, and finally 29-Dec-2004.

Were there any differences between the 5 Efficacy Submission Sets?

We asked the Applicant to clarify whether there were any changes between the different sets of raw data and analysis data files. Also, what were the database cut off dates for each submission?

In addition, this statistical reviewer requested the Applicant at the face-to-face meeting with FDA review team on November 22, 2004 to provide a master patient file in a horizontal structure that would give the final efficacy results, patient disposition, demographics and baseline disease characteristics for RESIST 1 and RESIST 2 studies.

According to the Applicant, in the referenced 5 sets of submissions, the content of the raw efficacy data had not changed but the format of data structure had changed each time. In the 5 sets of electronic submissions, all the efficacy data files (raw and analysis data) for RESIST 1 contained data through exactly 24 weeks for all patients. For RESIST 2 study, as previously agreed upon by FDA, the Applicant submitted 24 weeks data for a subset of 539 patients out of a total of 863 patients who would have completed 16 weeks in the study. Only the Patient Master Files contained longer-term data through the database cut off dates for respective studies with a minimum of 24 weeks data per patient.

The database cut off date for RESIST 1 was April 01, 2004 and for RESIST 2 it was March 19, 2004. If any patient had reached beyond 24 weeks of treatment then that data was provided in the master patient files. The Applicant is expected to resubmit longer-term efficacy data through 48 weeks for both studies at a later time. (See Table in Appendix 6.3).

Note that this NDA submission contained numerous versions and iterations of the CDISC formatted raw datasets and analysis datasets for each study. The earlier submissions of the CDISC formatted datasets did not format any date variables and were stored as numerous digits of SAS dates. Almost all CDISC files had completely vertical structures. Each file contained variables called SEQ (sequence number) with no explanation provided in the definition files as to what a sequence number meant.

Given that the efficacy (by Rafia Bhore, Ph.D.) and safety review (by Dr. Susan Zhou) involved evaluation of the Phase 2/3 Studies 1182.12 (RESIST 1). 1182.48 (RESIST 2), 1182.52, and 1182.51 there were several versions of different file formats, file structures and ambiguous or fuzzy naming of variable in files. There were 4 Studies, 9 sets of electronic data file, and approximately 25 data files per set. The vertical file structures made it extremely challenging to discern the meaning of the data transferred from Case Report Forms to Raw Data in so many data files.

Therefore, a significant amount of the review time was lost by this Statistical Reviewers in performing data quality checks and understanding of the data, rather than performing statistical analysis.

For this Statistical Review and Evaluation we finally evaluated the electronic datasets from the last submission of 29-December-2004 (see Table in Appendix 6.3).

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Designs

In this section we describe the study designs of the two identically designed Phase 3 RESIST trials, namely Study 1182.12 (RESIST 1) and 1182.48 (RESIST 2).

Figure 1 shows a schematic of the study design of the RESIST (**R**andomized **E**valuation of **S**trategic **I**ntervention in Multi-Drug Re**S**istant Patients with **T**ipranavir) trials. RESIST 1 and RESIST 2 were two identical multi-center and multinational Phase 3 studies with the same study design. The difference between the two studies was that RESIST 1 was planned to be conducted in the United States, Canada, and Australia, while RESIST 2 was to be conducted in Europe and Latin America.

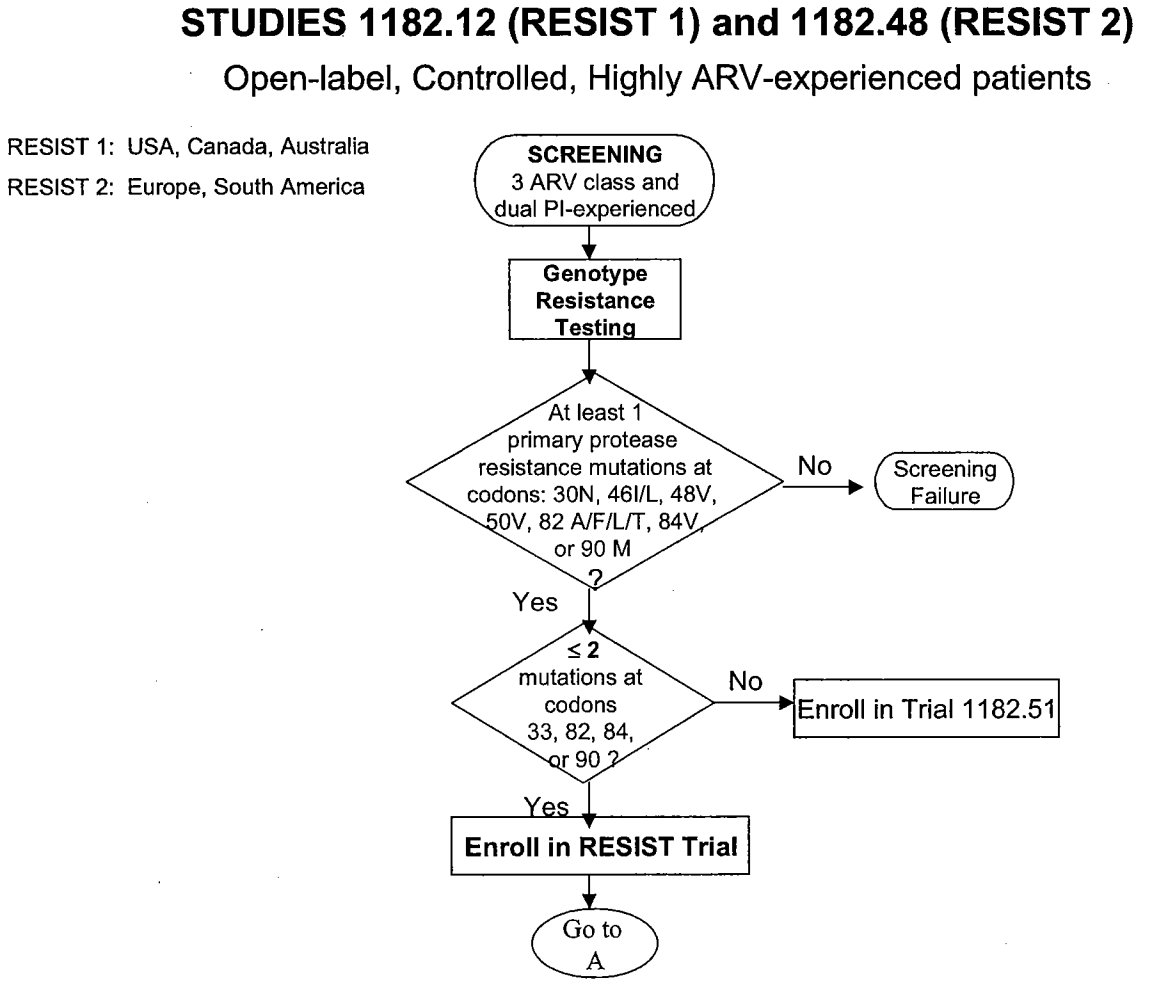
Study 1182.51 was a companion trial to the RESIST trials conducted at majority of the sites RESIST studies would occur. It was designed for multiple drug resistant patients who fail screening for RESIST 1 and 2. Study 1182.51 was a pharmacokinetic and safety study evaluating dual-boosted PI (protease inhibitor) regimens in these patients.

In future, the Applicant will plan to do a comparative Trial 1182.13 (RESIST 3) in these multi-drug resistant patients once the combinations used in Study 1182.51 are shown to be safe and active.

Study 1182.52 was designed and conducted prior to the RESIST trials. It was a double-blind, controlled, dose-ranging study with three dose combinations of TPV/RTV in mg: TPV/RTV 500/100, 500/200, and 750/200 twice daily (b.i.d).

Figure 1:

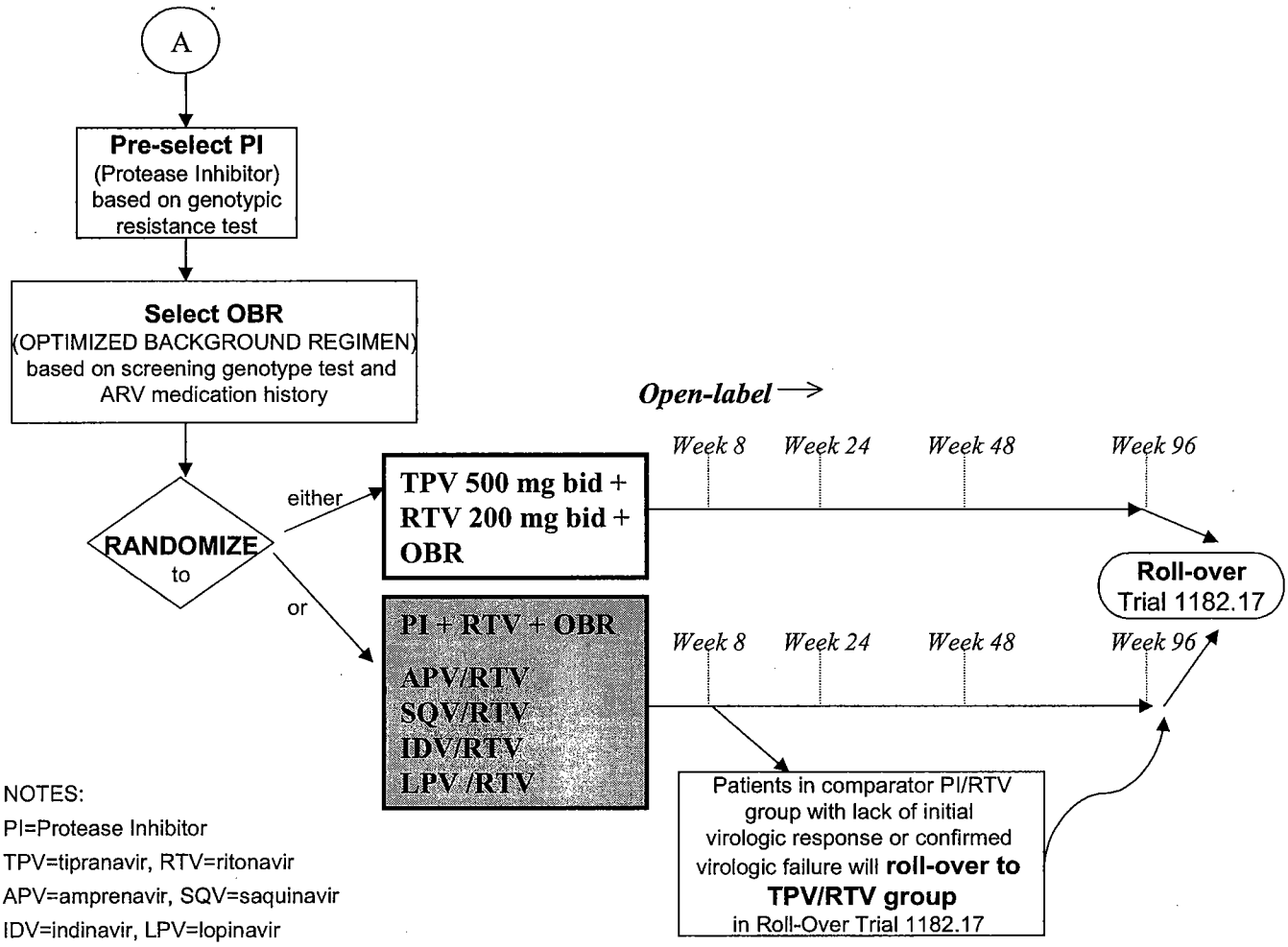
Schematic of RESIST Trials—Study Design



CONTINUED...

Figure 1:

Schematic of RESIST Trials—Study Design (CONTD.)



Source: FDA Statistical Reviewer's depiction of study design and Protocols 1182.12 (RESIST 1) and 1182.48 (RESIST 2), Volume 1.6 of Module 5

3.1.1.1 Study 1182.12 (RESIST-1)— Phase 3, Randomized, Controlled, Open-Label

Following is a description of the original RESIST study protocol dated 8-Nov-2002. The Sponsor, Boehringer Ingelheim (BI), had subsequently amended the protocol 5 additional times. The protocol amendments, reason for change, and dates of protocol amendment are given in Table 25 within Appendix 6.1.

Title of Study 1182.12 (RESIST 1):
"Randomized, open-label, comparative safety and efficacy study of tipranavir boosted with low-dose ritonavir (TPV/RTV) versus genotypically-defined protease inhibitor/ritonavir (PI/RTV) in multiple antiretroviral drug-experienced patients."

Study 1182.12 or RESIST 1 was designed as a Phase 3, randomized and controlled clinical trial. RESIST 1 was conducted at multiple centers in the USA, Canada and Australia while RESIST 2 (Study 1182.48) was conducted at multiple centers in Europe and Latin America.

Duration: The study duration was originally planned to be 48 weeks. Per protocol amendment # 5, the study duration was extended to be **96 weeks**.

Objective:

The study objective was to demonstrate the safety and efficacy of tipranavir (TPV), boosted with ritonavir (TPV/RTV), in comparison to a control group of other protease inhibitors, boosted with ritonavir (PI/RTV) where the control PIs were genotypically determined.

Patient Population:

Patients to be enrolled in the study would be highly antiretroviral treatment-experienced HIV-1 infected patients who are on a PI-based regimen and have plasma HIV-1 RNA >=1,000 copies/mL at study entry. Patients would be triple-ARV class and dual-PI experienced.

Patients must satisfy the following key inclusion/exclusion criteria.

1. Patients must have antiretroviral (ARV) experience in 3 ARV classes (NRTI, NNRTI, PI) with at least 2 PI-based regimens, one of which must be the current regimen. The current PI-based ARV regimen must be taken for at least three months prior to randomization.
2. The genotypic resistance report at screening must indicate both of the following:
   - At least one primary PI mutation(s) [1] at codons 30N, 46 I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M, and
   - no more than two protease mutations 33, 82, 84, or 90.[2]

   If a patient has at least 3 mutations on codons 33, 82, 84, or 90, then they may qualify for the tipranavir companion Trial 1182.51.
3. Patients must have HIV-1 viral load >=1,000 copies/mL at screening.[3] Any CD4+ cell count is acceptable.
4. A prior AIDS defining event is acceptable as long as it has resolved or the patient has been on stable treatment for at least 2 months. (AIDS related complex was acceptable.)
5. Patients whose genotype report demonstrated resistance to all comparator PIs (amprenavir, saquinavir, indinavir, and lopinavir) would be excluded.
6. Patients whose survival was likely to be less than 12 months in the opinion of the investigator because of underlying disease were to be excluded.

[1] A resistance-conferring PI-mutation would indicate that the virus is no longer susceptible to the protease inhibitor drug that the patient is currently taking, implying that the patient's current therapy is sub-optimal to treat HIV infection.
[2] Trial 1182.52 (Dose ranging study) demonstrated that patients with more than 2 mutations on codons 33, 82, 84 or 90 achieved less reduction of viral load and thus warrant more aggressive treatment. Polymorphisms do not count; for example 82 A/F counts as one mutation.
[3] Note: Viral load >=1,000 copies/mL is the lowest limit for virus amplification for genotyping. It is expected that patients failing a current PI-based regimen have higher viral load.

Randomization

Eligible patients would be randomly assigned to one of the 2 following treatment groups.

Randomization to TPV/RTV or comparator PI/RTV group will be *stratified* with respect to the *pre-selected PI.* After protocol amendment # 3 on 17-Mar-2003, the Sponsor will also stratify with respect use of *enfuvirtide (T-20).*[4]

Test Group:	TPV 500 mg b.i.d. + RTV 200 mg b.i.d. + OBR[§] (n=247 planned in RESIST 1)
Control Group(s):	Pre-selected PI[†] + low-dose RTV[‡] + OBR (n=247 planned in RESIST 1) (i.e. LPV/RTV + OBR, or APV/RTV + OBR, or IDV/RTV + OBR, or SQV/RTV + OBR)

[†] PI = Protease Inhibitor: The PIs could be lopinavir (LPV), amprenavir (APV), indinavir (IDV), or saquinavir (SQV).
‡ 100-200 mg, according to product label or published recommendations
[§]OBR = Optimized Background Regimen contains antiretrovirals (ARVs) that are not protease inhibitors.

The comparator protease inhibitor (PI) is to be selected by the physician based on genotyping results and must be boosted with 100-200 mg RTV b.i.d. An HIV-resistance consultant panel will be in place to review choice of PI in selected cases.[5] In cases in which lopinavir is available to the patient according to the genotype resistance report and the patient had no prior lopinavir exposure, lopinavir should be pre-selected even if another PI is reported as having the same level of resistance.

The protease inhibitors (PIs) in the control group will be lopinavir, amprenavir, indinavir, or saquinavir (LPV, APV, IDV, or SQV).

Once the PI is pre-selected for each patient and the patients are eligible, patients entering the trial will be centrally randomized to either TPV/RTV or PI/RTV.

Taking both, genotype results and ARV medication history into consideration, the investigator will identify at least **two** non-PI ARVs for the patient to start taking at the time of randomization. These 2 drugs will be the Optimized Background Regimen. It is understood that these background ARV medications may either be new or be recycled

[4] Note that enfuvirtide (T-20, ENF) is a new drug belonging to the new class of antiretroviral drugs called Fusion Inhibitors. T-20 (ENF) is an injectable drug and offers a new treatment option to patients who are resistant to the older drug classes of protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), such patients enrolled in the RESIST trials. Also, these patients are not resistant to T-20. Therefore, T-20 is expected to contribute to the efficacy endpoint of reducing HIV viral load.
[5] Selected cases include those in which an investigator wishes to recommend a PI reported as possibly resistant or resistant, and a PI with no evidence of resistance is available to the patient. The consultant panel must review the rationale for such a recommendation (i.e., based on adverse event profile or patient history) and comment.