CLINICAL REVIEW

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Submission Number	005, 000, 000
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Reviewer Name	Yodit Belew, M.D.
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Established Name	Tipranavir
(Proposed) Trade Name	APTIVUS
Therapeutic Class	Protease Inhibitor
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Priority Designation	P
Formulation	Oral Capsule Oral Solution
Dosing Regimen	Twice daily (BID)
Indication	Treatment of HIV-1 Infection
Intended Population	Pediatric Population 2 -<18 years of Age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The supplement to NDA 21-814 (SE1) containing data from the pediatric clinical trial supports the indication for use of Aptivus (tipranavir, TPV) co-administered with ritonavir in combination with other antiretroviral drugs for the treatment of HIV infection in treatment experienced subjects 2 to 18 years of age. This reviewer recommends the approval of this supplemental NDA (sNDA). Tipranavir co-administered with ritonavir, in combination with other drugs, resulted in reduction in HIV-1 viral load and increases in CD4 cell counts over the 48 week study period across all ages.

No deficiencies were identified in this sNDA that would preclude the approval of this submission. Tipranavir/ritonavir (TPV/r) was studied in one phase 1/2a, open-label, randomized study. Children were stratified according to age (2 - <6 years, 6 - <12 years, and 12 - 18 years) and randomized to one of two doses of tipranavir/ritonavir, with background antiretroviral (ARV) therapy. In addition, the Applicant submitted bioavailability study of TPV oral solution formulation to the TPV capsule formulation at steady state under fasted and fed condition.

Two doses of tipranavir/ritonavir were studied in this phase 1/2a study. Equal number of subjects received either the high dose (375/150mg/m^2, n=55) or the low dose (290/115mg/m^2, n=55). No differences in response rate could be identified in the youngest age group (2 to < 6 years) based on the dose of tipranavir/ritonavir given; the proportion of subjects with viral load <400 copies/mL was 70% in both low and high dose groups. However, for the older children (6 to <18 years), those who had received the higher dose of tipranavir/ritonavir, especially those with ≥ 5 baseline tipranavir associated mutations, were more likely to achieve HIV RNA < 400 copies/mL if given high dose tipranavir vs. low dose tipranavir (i.e. 40% vs. 11%, respectively).

The Applicant demonstrated an acceptable safety profile for tipranavir co-administered with ritonavir in combination with other antiretroviral drugs. While adverse events were common (95%) and 55% of the events were considered possibly drug related, significantly less were serious in nature (25%) or required discontinuation of study drug (16%). Many of the adverse events were related to common childhood illnesses or conditions. Clinically significant laboratory abnormalities were also relatively uncommon and rarely led to treatment discontinuation. The frequency of serious adverse events, adverse events leading to discontinuation, protocol defined significant adverse events and rash were similar between the two tipranavir dose groups.

Differences were noted between the two doses of tipranavir administered. Hepatic adverse events (including laboratory toxicities) were reported slightly more frequently in the tipranavir high dose group. An exposure-safety relationship was demonstrated for hepatic adverse events (i.e. there was a positive correlation between subjects with higher Cmax and hepatic adverse events). Although bleeding adverse events were reported more frequently in the high dose group, no exposure-safety relationship was established for bleeding adverse events.

Despite increased incidences of hepatic and bleeding adverse events with the higher dose of tipranavir, this reviewer recommends the approval of the higher dose for all pediatric age population (2 to 18 years old). The older age group (6-18 years) will likely be more treatment experienced and harbor HIV-1 virus with multiple mutations. The efficacy of the higher dose was clearly better than the lower dose for this subpopulation of subjects who have multiple tipranavir mutation. Therefore, for the older age group, the benefit of 375/150mg/m^2 dose outweighs the potential increased risks. In addition, all the AIDS defining illnesses were reported in the 6-18 years group who received 290/115 mg/m^2 dose.

Based on study results from this clinical trial, it would be appropriate to recommend the 290 mg/m2/115 mg/m2 dose for the 2 to <6 years age group. However, even for this age group, treatment response was better with the high dose tipranavir when analyzed by baseline mutations (although the difference was not as robust as seen in the older age group). Keeping in mind the labeled indication for APTIVUS is for treatment experienced subjects who are resistant to more than one protease inhibitor, in clinical practice, the most likely subjects (even in the 2 to <6 years old age group) who will be prescribed APTIVUS are those with no alternative optimized treatment regimen. These subjects will likely have more baseline resistance than what was seen in the subjects enrolled in this clinical trial. Therefore, it is reasonable to maximize response by recommending 375mg/m^2/150mg/m^2 twice daily.

Understanding the risk/benefit of tipranavir, an option to dose reduce to tipranavir/ritonavir 290/115 mg/m^2 (low dose studied) should be available for patients experiencing toxicity or intolerability while receiving the high dose. However, a dose reduction is not appropriate for patients with multiple baseline PI mutations.

Using data from subjects enrolled in study 1182.14, dosing by body weight has been calculated. Tipranavir/ritonavir 290/115mg/m^2 reasonably matched 12/5mg/kg and Tipranavir/ritonavir 375/150mg/m^2 reasonably matched 14/6mg/kg. Both dosing calculations will be included in the label.

Similar to many other pediatric studies which evaluate safety and effectiveness of ARVs, this study was not powered for true statistical analysis of safety or efficacy. Descriptive statistical methods were used to describe the findings.

1.2 Risk Benefit Assessment

Virologic and immunologic activity was demonstrated in all age groups. More children receiving the high dose achieved and maintained HIV RNA < 400 and < 50 copies/mL compared to children receiving the low dose. The virologic activity of the high dose group is further demonstrated in patients with multiple baseline mutations. The observed risks for tipranavir are well known and the type and rate of adverse events were similar to adults with few exceptions. Tipranavir/ritonavir in combination with other antiretroviral drugs has been shown to be effective in treating HIV-1 infected treatment experienced adults. The previous risks identified with the use of tipranavir/ritonavir in adults include hepatotoxicity (namely grade 3/4 ALT

and/or AST elevations) and intracranial hemorrhage (ICH) (fatal and non-fatal). Both risks are displayed as boxed warning in the current tipranavir label.

At Week 48 in the adult trials (RESIST studies), 10.3% of subjects on the TPV/r arm compared to 2.9% on the CPI/r arm developed treatment emergent grade 3/4 ALT and/or AST elevations. Similar to adults, there were 7 (7%) pediatric subjects with grade 3/4 laboratory toxicity for ALT and/or AST during the 48 week study period. Although subjects who received the higher dose of tipranavir had a 37% higher tipranavir exposure when compared to adults, no increased risk of hepatotoxicity was observed in the pediatric trial when compared to the adult patient populations.

At the time of the ICH risk identification, the pediatric study was already ongoing. A number of steps have been taken to evaluate, understand and communicate risk of ICH. All bleeding adverse events in the pediatric study have been assessed. No clinical bleeding patterns have been identified. Overall, similar number of pediatric subjects reported to have bleeding adverse event (7%) compared to adults (6%). No ICH was reported in the pediatric study. The most common cause for bleeding was epistaxis (3.5%), which is historically more common in the pediatric population than adults. When bleeding adverse event was analyzed without epistaxis, the proportion of pediatric subjects with bleeding AEs was (3.5%). In addition, no treatment related serious adverse event was identified during the trial. Furthermore, a post-marketing study, Study U07-3477 (Tipranavir Freeze Study), has been conducted to asses the effect of tipranavir (capsule and solution) on coagulation factors both in adults and children. The result of the study did not show a clinically significant change in vitamin K dependent coagulation factors or an increase in PT/PTT at end of tipranavir therapy when compared to baseline values.

There are currently limited protease inhibitors available for use in pediatric subjects. Tipranavir would provide an alternative treatment option for HIV-1 infected treatment experienced pediatric subjects with resistance to more than one protease inhibitor. Given no apparent increase in clinically significant adverse events, including hepatotoxicity and bleeding events, the virologic and immunologic benefit demonstrated in all age groups outweighs the observed and potential risks. Furthermore, the Freeze study did not demonstrate a clinically meaningful change in coagulation time and no ICH occurred during the pediatric study (up to 100 weeks of treatment).

Of note, the DSMB responsible for review of this pediatric study recommended the high dose, despite the higher incidence of hepatic adverse events in the high dose group, as the benefit of successful treatment of HIV-1 infection outweighed the adverse event risks.

I also concur with the CMC and Clinical Pharmacology review and support approval for the oral formulation. The Applicant has provided sufficient data to demonstrate the relative bioavailability at steady state for the capsule and oral solution formulations. In addition, the exposure-response data in children further support the oral solution approval.

1.3 Recommendations for Postmarketing Risk Management Activities

The Applicant will continue to follow pediatric subjects who have enrolled into the study until tipranavir becomes available on the market. In addition, the Applicant will submit periodic safety reports for review.

No additional postmarketing risk management activities are planned.

1.4 Recommendations for other Post Marketing Study Commitments

No additional pediatric post marketing study commitments will be sought. The current submission fulfills the Pediatric Written Request and in fact, exclusivity was granted. The current submission also fulfills all Post Marketing Commitments (PMC). No additional studies are needed at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Established name: Tipranavir (TPV)
Trade name: APTIVUS
Chemical: $C_{31}H_{33}F_3N_2O_5S$
Class: Protease Inhibitor
Proposed indication: Treatment of HIV-1 infection in treatment experienced pediatric population age 2 to <18 years of age.

Dose and regimen:

- By Body Surface Area (BSA)
  - Pediatric patients: 375mg/m^2 with 150mg/m^2 ritonavir orally twice daily, not to exceed adult maximum of 500mg/200mg TPV/RTV.
- By Body Weight (BW)
  - Pediatric patients: 14mg/kg with 6mg/kg ritonavir orally twice daily, not to exceed adult maximum of 500mg/200mg TPV/RTV
- Subjects may be prescribed a lower dose 290mg/m2 tipranavir with 150mg/m2 ritonavir (12mg/kg tipranavir with 5mg/kg ritonavir) if they are unable to tolerate the higher dose or develop toxicities, provided that they do not have multiple protease inhibitors associated mutations.

Dosage form: 250mg capsule
100mg/ml solution

Tipranavir (TPV) is a non-peptidic protease inhibitor (PI) that is a sulfonamide and belongs to the class of 4-hydroy-5,6-dihydro-2-pyrones. Tipranavir was first approved in 2005 under accelerated approval program (21 CFR 314.510 Subpart H) for treatment of HIV-1 in treatment experienced adults with ongoing viremia and limited therapeutic options.

2.2 Tables of Currently Available Treatments for Proposed Indications

Protease inhibitors have become the mainstay of highly active antiretroviral therapy when given in combination with nucleoside reverse transcriptase inhibitors (NRTIs). Combination

antiretroviral drug therapy is now the standard of care. Despite the great progress in treatment of HIV infection, a number of challenges remain, including the development of resistance to currently existing drugs and the significant adverse effects associated with these drugs. A need for new drugs with improved resistance profiles and better tolerability and toxicity profiles remains critical.

Table 1: Currently approved pediatric ARV drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT or ZDV)	Retrovir®
	Didanosine (ddI)	Videx®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Nevirapine	Viramune®
	Efavirenz	Sustiva®
PI	Ritonavir	Norvir®
	Nelfinavir	Viracept®
	Fosamprenavir	Lexiva®
	Lopinavir/ritonavir fixed dose combination	Kaletra®
	Atazanavir	Reyataz®
Fusion Inhibitor	Enfuvirtide (T20)	Fuzeon®

2.3 Availability of Proposed Active Ingredient in the United States

Tipranavir is currently marketed in the United States under the trade name Aptivus. The proposed API for the treatment of HIV-1 infected pediatric subjects remains the same as the approved tipranavir. The same capsule formulation that is currently on market will be accessed by pediatric subjects who were at least 12 years of age and reached a tipranavir/ritonavir 500/200 mg dose. For those < 12 years of age or unable to swallow capsules, oral solution formulation will be available. It is not anticipated that there will be any difficulty accessing the proposed pediatric formulation (100mg/ml).

2.4 Important Safety Issues with Consideration to Related Drugs

General safety issues associated with PIs include side effects such as hyperglycemia and diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, hemolytic anemia and bleeding diathesis in hemophiliac subjects. PIs also have potential for multiple drug-drug interactions, especially when boosted with ritonavir. Section 7 further discusses the adverse events associated with tipranavir when administered to the pediatric population.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Tipranavir was first submitted to the Agency under IND 51,979 in 1996. A phase 2 clinical development in adult HIV-1 infected subjects had been ongoing since 2000. After review of phase 2 studies, the dose 500/200 mg was agreed upon at the end of phase 2 meeting held on December 17, 2002. Based on data from phase 3 comparative studies in treatment-experienced adult subjects [Trial 1182.12 (RESIST-1) and 1182.48 (RESIST-2)] tipranavir capsules were granted accelerated approval by the FDA in June 2005. The traditional approval of tipranavir occurred in October 2007.

At the time of the accelerated approval, among the postmarketing commitments (PMC) and Pediatric Research Equity Act (PREA) requirements were to conduct study(ies) in pediatric subjects with HIV-1 infection:

- "Assess two alternative doses of either tipranavir/ritonavir liquid formulation or capsules in addition to safety, in ARV naive and experienced children and adolescents between 2 and 18 years of age."
  The protocol for this requirement was submitted in August 2003. The final report was required for submission on June 30th, 2006.

- "Evaluate dose requirements and safety in pediatric subjects age 2 weeks to 2 years with HIV-1 infection (after review of 48 week data from the 2 to 18 year old children in trial 1182.14 with the FDA)."
  The protocol submission for this requirement was due on September 30th, 2006.

In addition to PREA requirements, a Pediatric Written Request (PWR) was also issued in December 2006, which required the study to be conducted in pediatric subjects (treatment naïve or experienced) from 2 weeks of age to <18years.

The PWR was later amended for the following reasons:

- As tipranavir was not indicated for treatment of naïve adults, treatment naïve pediatric subjects were also excluded from the study(ies).
- Children less than 2 years of age are highly unlikely to be treatment experienced, harboring PI resistant HIV-1 virus and failing their current HAART. Therefore, this population was also excluded.
- The due date of the amended study(ies) was changed to December 31, 2007.

In accordance with the amended PWR, study requirements under PREA were also amended to reflect enrollment of study subjects who are treatment experienced and at least two years of age.

The currently submitted pediatric study fulfills all the requirements stated under PREA and PWR. The Applicant has submitted a 48 week safety and efficacy data. In addition, the current submission contains up to 100 week of safety data.

Please refer to Appendix (sections 9.1 and 9.4) for review of the complete PWR and PREA.

2.6 Other Relevant Background Information

Preclinical studies results in rodents (U06-3728) showed that TPV induced time-related changes in coagulation parameters (notably decrease in vitamin K-dependent factors VII and IX and increase in aPTT) and inhibited arachidonic acid-induced platelet aggregation. At the time of the accelerated approval (24 week data) no consistent pattern of bleeding events were noted and no increase in PT/PTT associated with tipranavir was noted. Furthermore, during the traditional approval, no statistically significant differences in bleeding between tipranavir and CPI/r treatment groups from the combined RESIST trials were noted.

The label reflected these findings and states that caution is recommended when prescribing TPV to subjects who may be at risk for increased bleeding or who are receiving medications known to increase the risk of bleeding.

In March 2006 two cases of intracranial hemorrhage (ICH) were reported to Boehringer Ingelheim (BI) which led to a review of ICH cases reported among subjects treated with tipranavir. Thirteen subjects treated with tipranavir were identified across BI's clinical development program. In 8 of the 13 subjects, the ICH resulted in fatality. No abnormalities of the coagulation pathways were observed in subjects in general or preceding the development of ICH. This finding led to product labeling update to note TPV has been associated with reports of both fatal and non-fatal intracranial hemorrhage and routine measurement of coagulation parameters is not currently indicated in the management of subjects receiving TPV/r.

Because tipranavir oral solution contains vitamin E and vitamin E is known to affect Vitamin K-related coagulation factors in rats, a study (06R241) was conducted in rats to evaluate any potential interactions between TPV, vitamin E and vitamin K-related coagulation pathways. In February 2007, results of this study showed co-administration of TPV and vitamin E led to a synergistic effect of vitamin E and tipranavir on coagulation factors and bleeding events. Please refer to Dr. Anita Bigger's Pharmacology-Toxicology review for further detail.

A retrospective clinical study (Freeze Study) was also conducted to asses the effect of tipranavir (and vitamin E) on coagulation factors in both. The results from this study are discussed in this review (section 7.4.5).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Because of Good Clinical Practice (GCP) issues identified in one of the study sites, DSI audits were requested by the review team. Two sites were chosen for investigation based on the number of subjects enrolled. Result of the DSI inspection did not reveal irregularities with regards to the conduction of the clinical trials.

3.2 Compliance with Good Clinical Practices

The Applicant states that the study was conducted according to accepted ethical standards based on the principles established by the Declaration of Helsinki.
A copy of a sample Informed Consent Form is included in the submission.

Good Clinical Practice (GCP) issues were identified at one of the sites that study 1182.14 was conducted. A site located in Latin America (Mexico) had enrolled 5 subjects into the study. Among the GCP compliance issues identified were (a) investigator filling out ICF, although signed by parent or guardian, and (b) omission of study visits and required baseline testing such as CXR and ECG. Although the 5 subjects from the Mexican site were included in BI's safety and efficacy analysis, this reviewer excluded the 5 subjects from the FDA analyses. Despite exclusion of these 5 subjects, the pediatric development program included enough subjects (>100) with at least 24 week safety and efficacy data (as required by PWR).

3.3 Financial Disclosures

The Applicant submitted financial disclosure information and this was reviewed in the original NDA package. Updated financial disclosure information was submitted with this pediatric study report.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No issues have been identified. Please refer to the CMC review for full detail.

4.2 Clinical Microbiology

Please see Dr. Lisa Naegar's Clinical Microbiology Review for detail. In summary, older pediatric subjects (especially those older than 12 years) had more baseline protease inhibitor mutations present compared to the younger subjects. Overall, response to therapy was influenced by the number of baseline protease inhibitor mutations present, regardless of age. In addition, for subjects with 5 or more baseline protease inhibitor mutations, which was observed in the older age group, response to treatment was better for children in the high dose tipranavir (375mg/m2) group compared to treatment response in the low dose tipranavir group. This finding was among the key factors that led to the recommendation of the high dose for approval (and labeling). As discussed previously, a dose reduction (to 290mg/m2) will be allowed for subjects who are not able to tolerate tipranavir or develop treatment limiting toxicities, provided that they do not have multiple protease inhibitor mutations present.

4.3 Preclinical Pharmacology/Toxicology

Please refer to Dr. Anita Bigger's Preclinical Pharmacology/Toxicology review which was completed with the traditional NDA approval. No new Preclinical Pharmacology/Toxicology data was submitted with this sNDA. However, Dr. Bigger was instrumental in assessing the amount of vitamin E present in the oral solution of tipranavir and has reviewed the current pediatric submission with regards to the potential daily exposure of vitamin E for pediatric subjects. Vitamin E was shown to significantly increase the effects of tipranavir on coagulation parameters and bleeding events in rats. This finding was not observed in adult and pediatric subjects who were enrolled in tipranavir clinical trials. A retrospective study was conducted to evaluate the effect of tipranavir oral solution (and capsule) on coagulation factors and parameters. No clinically significant or meaningful changes were observed (please see Section 7.4.5 Special Safety Studies). However, given the preclinical findings, information on vitamin E regarding the preclinical findings has been included in the label. In addition, limitation on the maximum daily intake of vitamin E has also been included in the label.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Tipranavir (TPV) is an HIV-1 protease inhibitor that inhibits the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

4.4.2 Pharmacodynamics

Please refer to Dr. Pravin Jadhav's and Dr Joo Yeon Lee's Pharmacometrics review of this sNDA. Briefly, the pharmacometrics review focused on three main questions:

1. Is there an exposure-virologic success relationship for TPV?

Genotypic Inhibitory Quotient (GIQ), calculated by dividing geometric mean TPV plasma trough concentration (Cmin) by number of TPV related mutations, was found to be one of the major predictors of virologic success (proportion of subjects with viral load below 400 copies/mL and 50 copies/mL) at week 48. The virologic success at week 48 increased with higher TPV exposure.

2. Is there exposure-safety relationship for TPV?

The analysis of safety and exposure conducted, focused on rash, bleeding and liver enzyme tests (LFT). There was no apparent relationship shown between rash or bleeding and exposure, but LFT seemed to increase as exposure increases.

3. What is the appropriate dose of TPV based on exposure-virologic success and exposure-safety relationship?

The low dose (290/115mg/m^2) reasonably matched exposures to that of adult's approved dose (500/200mg/m^2). The high dose resulted in a 37% increase in TPV exposures compared to

adults. Overall, more children achieved HIV RNA < 400 copies/mL in the high dose group compared to low dose group. The benefit of the higher dose was observed in children who had more baseline protease inhibitor mutations. Therefore, the higher dose (375/150 mg/m^2) is recommended for all children. The BSA dosing was converted to mg/kg. The final recommendations for dose selections are as follows:

> Tipranavir/ritonavir: 14/6 mg per kilogram twice daily or 375/150 mg/m^2 twice daily, not to exceed adult 500/200 mg twice daily.

4.4.3 Pharmacokinetics

Please refer to Dr. Derek Zhang's Clinical Pharmacology review of this sNDA. Briefly, among the pediatric subjects enrolled in this study, steady state plasma tipranavir trough concentrations were obtained 10 to 14 hours following study drug administration. The geometric mean tipranavir trough concentrations evaluated among 50 subjects taking 290mg/m2/115mg/m2 and 375 mg/m2/150 mg/m2 BID were between 47 and 61 uM.
Below is a table summarizing PK parameters.

Table 2: Pharmacokinetic Parameters[a] of tipranavir/ritonavir 375 mg/m^2/150 mg/m^2 for HIV-1 Positive Pediatric Patients by Age*

Parameter	2 to <6 years (n=12)	6 to <12 years (n=8)	12 to 18 years (n=6)
Cp_{trough} (μM)	59.6 ± 23.6	66.3 ± 12.5	53.3 ± 32.4
C_{max} (μM)	135 ± 44	151 ± 32	138 ± 52
T_{max} (h)	2.5	2.6	2.7
AUC_{0-12h} (μM•h)	1190 ± 332	1354 ± 256	1194 ± 517
CL/F (L/h)	0.34	0.45	0.99
V (L)	4.0	4.7	5.3
$t_{1/2}$ (h)	8.1	7.1	5.2

[a] Population pharmacokinetic parameters reported as mean ± standard deviation
* Source: Study 1132.14

5 Sources of Clinical Data

This submission contains data from a single randomized pediatric study, Study 1182.14. The study was conducted by the Applicant and utilized 24 principal investigators in 9 countries. In addition, safety data from the Expanded Access/Emergency Use Program and from a post-marketing surveillance program was reviewed. This submission also contains review of the retrospective coagulation study (Freeze Study) which evaluated the effect of tipranavir (and vitamin E) on coagulation factors and parameters.

This submission contains electronic materials documenting the study results and BI's conclusions regarding Study 1182.14, 48-Week Report. An additional study report has also been submitted which contains a 100 week safety data. In addition, copies of the CRTs and CRFs have been submitted for reviewer's aid. Datasets (as SAS transport files) of demographic, safety and efficacy data has also been submitted.

5.1 Tables of Clinical Studies

Table 3 summarizes the studies included in this review. Table 4 summarizes the subjects enrolled in Study 1182.14 by country and site.

Table 3: Studies conducted in support of this submission

Study Name	Type of Study	Number of Subjects Enrolled	Number of subjects with ≥ 24 week data
1182.14	A phase 1/2a randomized open-label pediatric study	110*	92
1182.67, 1182.58, 1182.16	Expanded Access Program/Emergency Use Program	17	10
1182.48, 1182.33	RESIST Trials- pivotal adult trials	8	8
U07-3162	Freeze Study- a retrospective coagulation study	44	N/A

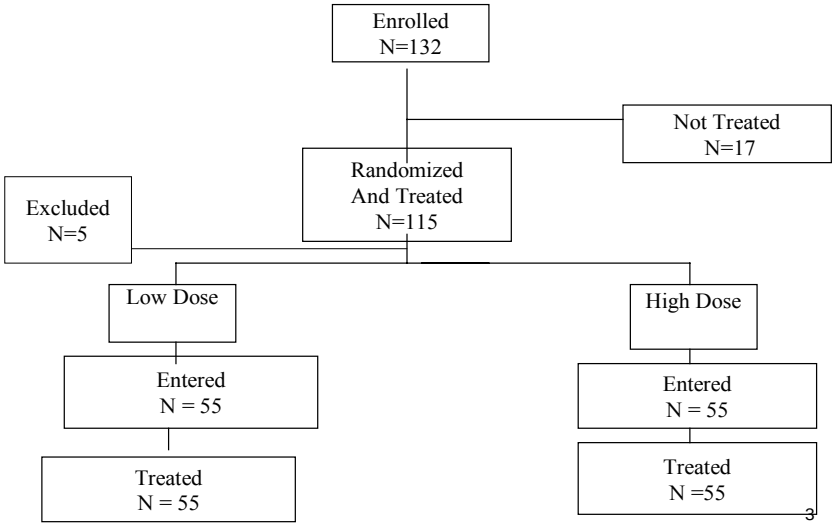
* This number reflects total number of subjects after exclusion of the 5 subjects.

Table 4: Subjects enrolled in study 1182.14

Country	Number of Sites Enrolling	Number of Subjects Enrolled			Number Prematurely Discontinued
		Naïve	Experienced	Total	
Argentina	1	2	19	21	2
Brazil	2	0	19	19	4
Mexico*	1		5	5	1
United States	9	1	31	32	10
Canada	2	0	9	9	2
France	3	0	4	4	1
Germany	3	0	7	7	2
Italy	2	0	10	10	3
Spain	2	0	8	8	1

*This reviewer has excluded subjects from this site from analysis

Figure 1: Patients Disposition



5.2 Review Strategy

Study 1182.14 was reviewed for safety, tolerability, pharmacokinetics and efficacy. The Applicant's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. Dr. Thomas Hammerstrom performed the statistical analysis confirming the primary endpoint and some secondary endpoints in this pediatric trial. This clinical reviewer evaluated study design, patient demographics, adverse events and laboratory safety monitoring data and reviewed the efficacy and safety results using the JMP Statistical software.

In addition to study 1182.14, safety data from Expanded Access Program/Emergency Use Program, the RESIST Trials as well as the post-marketing safety data are included in the safety section of this review.

Please note that for all tables and figures that were not created by this reviewer, a foot note has been included to describe the source of the data. If the table or figure is created by this reviewer, no foot note is included.

5.3 Discussion of Individual Studies

Study 1182.14 is the pivotal study conducted in pediatric subjects. This study supports the approval of tipranavir co-administered with ritonavir in combination with other antiretroviral drugs in HIV-1 infected treatment-experienced pediatric subjects infected who are resistant to more than one protease inhibitor. Data from the other studies such as the Expanded Access Program are included in the safety section of this review to increase robustness of safety data on the use of tipranavir in pediatric subjects.

Study1182.14: A Phase I/IIA study of safety, tolerability, and pharmacokinetics of tipranavir in combination with ritonavir in HIV-1 infected children. This was an International, multi-center, open-label, randomized study. The trial was designed and performed in collaboration with the Pediatric AIDS Clinical Trials Group (PACTG). The primary objective was to determine the pharmacokinetic, safety and tolerability profile of tipranavir oral solution and gel capsule across the age range studied. The secondary objective was to determine dose of TPV/r in HIV infected children (2 to 18 years) required for an equivalent systemic exposure of TPV/r 500/200 mg. Two formulations (oral solution and capsule) were used. The initial pediatric TPV/r doses selected for this trial were 290 mg/m2 TPV + 115 mg/m2 RTV b.i.d and 375 mg/m2 TPV + 150 mg/m2 RTV b.i.d. Tipranavir/ritonavir 290/115 mg/m2 was allometrically scaled by body surface area to the 500/200 mg adult dose (BSA 1.73 m2). The higher dose (375/150 mg/m2), projected to be a 30% increase in the adult dose was selected to account for potential increase in metabolism and clearance of the drug in pediatric subjects. Both doses were administered during the study period. Children were enrolled regardless of their HIV genotype status, stratified according to their age into three cohorts (2 to <6 years, 6 to <12 years, and 12 to 18 years), and randomized to one of two doses of TPV/r: low dose group, TPV 290 mg/m2 + RTV 115 mg/m2 b.i.d. and high dose group, TPV 375 mg/m2 + RTV 150 mg/m2 b.i.d. Children >12 years were permitted to switch from TPV oral solution to an equivalent dose of TPV capsules after four weeks of therapy (Note: switching to capsule was not randomized).

The study design incorporated pharmacokinetic (PK) endpoints for dose optimization. Pharmacokinetic (PK) sampling was performed on a subset of subjects at week 2 and for those adolescents switching to TPV capsules again at week 6. In addition, an interim analysis of PK, safety and efficacy data was assessed on 52 subjects at week 4.

Additional Studies: Prospective clinical data was submitted from the Expanded Access Program (EAP)/Emergency Use Program (EUP) (1182.58, 1182.67, 1182.16), and clinical trials 1182.48 and 1182.33. In total, there were 25 pediatric subjects from these trials, 18 of which had data for at least 24 weeks of treatment.

Freeze Study: This retrospective study selected baseline and serial stored frozen plasma samples from Trial 1182.14 and the RESIST trials for evaluation of Vitamin K dependent coagulation factor levels. A total of 44 pediatric subjects provided data for this study.

6 Review of Efficacy

Efficacy Summary

Study 1182.14 was an open-label, randomized study. Children and adolescents were stratified according to age (2 to <6 years, 6 to <12 years and 12 to 18 years) and randomized to one of two doses of tipranavir/ritonavir with background ARV therapy chosen by their local investigator. After analysis of intensive PK sampling performed on a subset of subjects at Week 2 and for those adolescents switching to tipranavir capsules again at Week 6, an interim 4 week analysis (using PK, safety and efficacy data) was performed to determine the tipranavir dose required for

an adult-equivalent systemic exposure. Tipranavir/ritonavir 290/115 mg/m2 matched the adult exposure. An initial recommendation by an outside study monitoring board (DSMB), after review of the 4 week interim data, was to switch all subjects to the low dose. However, prior to implementation of the recommendation to switch, efficacy data from later weeks showed the high dose to have a better efficacy profile when compared to the low dose. The DSMB recommended subjects continue on high dose (if assigned to high dose group) and recommended all subjects in the low dose group receive the high dose after completion of 48 week study period, after which time subjects had the option of participating in an optional long-term safety study.

Tipranavir capsule and oral solution co-administered with ritonavir exhibited good antiretroviral activity when used in combination with at least 2 antiretroviral drugs over the 48 weeks of the study period. Overall, 43% of study subjects achieved and sustained an HIV RNA level < 400 copies/mL and 33% reached an HIV RNA level < 50 copies/mL over the 48 weeks study period. The overall treatment response was slightly higher in the high dose group when compared to the low dose group (46% vs. 40%). However the difference increased when the two groups were compared for durability of treatment effect at 96 weeks (high dose: 36% vs. low dose: 27%). The difference is even greater when comparing viral load <50copies/mL at 96 weeks (high dose: 31% vs. low dose: 16%). For the 2 to < 6 year old age group, no significant differences in response rates could be identified based on tipranavir dose administered (375/150 or 290/115mg/m2). But children 6 years of age and older had different treatment response based on the dose group they were assigned. More specifically, those with baseline tipranavir mutations $\geq$ 5 who received low dose tipranavir (290 mg/m2) had lower responses compared to those with <5 tipranavir mutations. Table 5 summarizer treatment responses by dose group at Week 48 and 96 and compares Dr. Hammerstrom's (statistical reviewer) findings with the Applicant's. Table 6 summarizes treatment responses by dose group and age.

Significant increases in CD4 cell counts and declines in mean log change in HIV RNA levels were also noted in all patient groups analyzed.

Table 5: Proportion of subjects with HIV RNA < 400 copies/mL (<50 copies/mL)

	Low Dose tipranavir/ritonavir 290 mg/m^2/115 mg/m^2			High Dose tipranavir/ritonavir 375 mg/m^2/150 mg/m^2		
	Number of success	Number of failures	Percent success	Number of success	Number of failures	Percent success
<400 (50) (at week 48)	22(17)	33 (38)	40% (31%)	25 (19)	30 (36)	46% (35%)
<400 (<50) (at week 96)	15(9)	40(46)	27% (16%)	20(17)	35(38)	36% (31%)
Applicant's Results						
<400 (50) (at week 48)	23(20)	35(38)	40% (34%)	26(18)	31(39)	46% (32%)

Table 6: Proportion of subjects with HIV RNA < 400 copies/mL (<50 copies/mL) by age and dose (48 weeks)

	2-<6 years N =20	6 - < 12 years N=38	12-18 years N=52
APTIVUS/ritonavir dose of 290 mg/m^2/115 mg/m^2	n=10 70% (53.8%)	n=19 36.8% (31.6%)	n=26 30.8% (23.1%)
APTIVUS/ritonavir dose regimens: 375 mg/m^2/150 mg/m^2	n= 10 70% (41.7%)	n=19 50% (38.9%)	n=26 33.3% (29.6%)

6.1 Indication

APTIVUS, co-administered with ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected subjects who are treatment-experienced. This indication is based on analyses of plasma HIV-1 RNA levels from study 1182.14.

6.1.1 Methods

For a detailed review of efficacy, please refer to Dr. Tom Hammerstrom's Statistical review.

For assessment of virologic response, the following endpoints were used:

- Proportion of subjects reaching and maintaining a viral load <400 copies/mL at Week 48 (primary efficacy endpoint)
- Time to treatment failure. Time to treatment failure is defined as the time of the first occurrence of:
  - Loss of virologic response, defined as the last measurement before a viral load rebound to >400 copies/mL followed by a confirmatory value or loss to follow-up.
  - Study discontinuation if due to an adverse event(s) or lack of efficacy.
  - Introduction of a new ARV drug to the existing treatment regimen if it is not solely related to either toxicity or intolerance clearly attributable to a background drug.
  - Subjects who never achieve a confirmed viral load <400 RNA copies/mL are considered failures at time zero.
  - Subjects who were lost to follow-up while they showed virologic response (viral load <400 RNA copies/mL) are considered failures at their last visit.

Efficacy data were evaluated at 48 and 96 week timepoints. The analysis compared treatment response between the two dose groups as well as among the 3 age groups.
This reviewer included all subjects who were randomized and received at least one dose of the study drug in the efficacy analysis. If a patient had a missing efficacy parameter value (i.e. viral load < 400c/mL or <50c/mL), the patient was considered a failure. In addition, if rebound was immediately preceded by consecutive missing values, the patient was considered a failure.

In addition to virologic parameters, resistance parameters, immunologic parameters (CD4+ cell count and percentage), and compliance were also assessed as part of efficacy evaluation.

6.1.2 Demographics

Demographics and baseline characteristics were balanced between the two tipranavir dose groups. The 110 randomized pediatric subjects had a median age of 11.7 years (range 2 -18), and were 57% male, 68% white, 30% black, and 2% Asian. The median baseline plasma HIV-1 RNA was 4.7 (range 3.0 to 6.8) log10 copies/mL and median baseline CD4+ cell count was 379 (range 2 to 2578) cells/mm3. Overall, 37% of subjects had a baseline HIV-1 RNA of >100,000 copies/mL; 29% had a baseline CD4+ cell count ≤ 200 cells/mm3, and 48% had experienced a prior AIDS defining Class C event at baseline. Subjects had prior exposure to a median of 4 NRTIs, 1 NNRTI, and 2 PIs. Table 7 summarizes the demographics.

Table 7: Demographics

	TPV/r low dose	TPV/r high dose	Total
	N (%)	N (%)	N (%)
Total Treated	55 (100.0)	55(100.0)	110 (100.0)
Age group			
2 to <6	10 (18)	10 (18)	20 (18)
6 to <12	19 (34)	19 (34)	38 (34)
12 to 18	26 (47)	26 (47)	52 (47)
Weight (Kg)			
mean	34.4	35.6	35
min	12	11	11
med	33	32	32
max	72	91	91
Gender			
Male	30 (55)	33 (60)	63 (57)
Female	25 (46)	22 (42)	47(43)
Race			
White	45 (82)	33 (60)	78 (71)
Black	13 (24)	20 (36)	33 (30)
Asian	0 (0.0)	2 (4)	2 (2)
Ethnicity			
Hispanic/Latino	32 (58)	24 (44)	58(53.0)
Mixed race	3 (5.2)	2 (4)	5 (5)
Unknown	20 (36)	29 (53)	49 (45)

Baseline HIV Characteristics

Overall, the median baseline HIV RNA count was 4.7 $\log_{10}$ copies/mL, while CD4 counts and percentage were 379 cells/mm^3 and 20%, respectively. These values were comparable between the two treatment groups. However, as expected the baseline median

values for CD4+ cell counts were highest in the 2 to <6 age group (795 cells/mm3) and lowest in oldest age group (318 cells/mm3). Vertical transmission was the most common cause for acquisition of HIV infection (93%, 102/110). In the oldest age group (12 to 18 years) other risk factors for acquiring HIV were identified, including blood transfusion and sexual contacts. There were more subjects with CDC classification clinical category C in the youngest age group compared to the older age groups. Table 8 summarizes the findings.

Table 8: CDC Classification Clinical Category C

Age	Low Dose	High Dose	Total
2 to <6	80% (8/10)	70% (7/12)	75% (15/20)
6 to 12	43.5% (10/23)	47.8% (11/23)	45.6% (21/46)
13 to 18	54.5% (12/22)	31.8% (7/22)	43.2% (19/44)

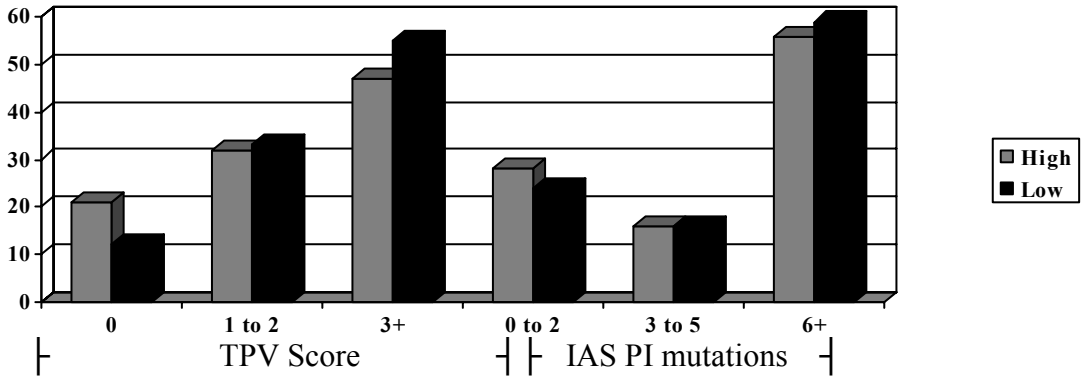
Previous Antiretroviral Treatment History

The oldest age group (12-18) had the most previous ART treatment history (median = 10). The median number of previously used ART was 8 in the 6 to <12 age group and 3 in the 2 to < 6 age group. There were 3 subjects enrolled in the study with no previous ART history (ages 3 years old, 9 years old and 17 years old). The 3 year old received low dose while the other two subjects were randomized to the high dose group.

Baseline HIV Resistance

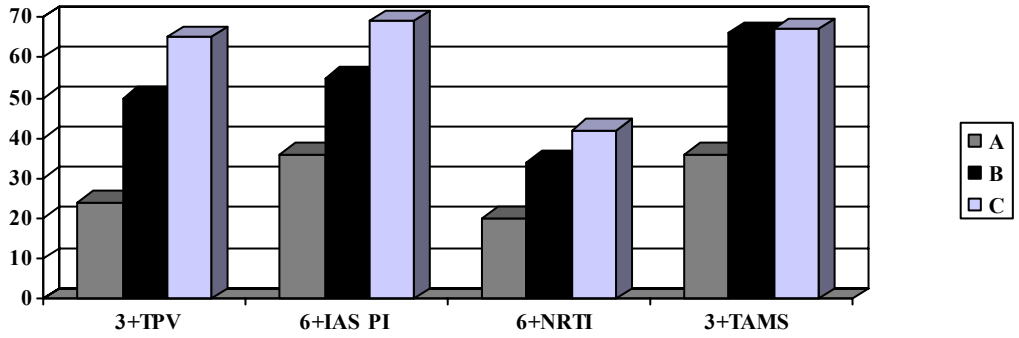
Please refer to Dr. Lisa Naegar's Microbiology Review for further detail.
In summary, both treatment arms had similar baseline PI resistance (Figure 2). When baseline mutation is assessed by age group the number of mutations increase with age in both treatment groups (figure 3). As subjects grow older and duration of ART exposure increases, more mutations are expected to accumulate; therefore, reduced susceptibility to treatment.

Figure 2: Baseline PI Mutations by Dose Group



(Source: Dr. Naegar's review)

Figure 3: Prevalence of Mutations by Age



Source: Dr. Naegar's review
A= 2-<6 years; B= 6-<12 years; C=12-18 years

6.1.3 Patient Disposition

Eighty three (75%) completed the 48 week period and 25% discontinued prematurely. Of the subjects who discontinued prematurely, 9 (8%) discontinued due to virologic failure, and 11 (10%) discontinued due to adverse reactions. Table 9 summarizes subjects' enrollment and disposition.

Table 9: Patient Disposition

	TPV/r low dose	TPV/r high dose	Total
	N (%)	N (%)	N (%)
Total screened			132
Not entered/randomized			22
Total randomized	55	55	110
Total treated	55 (100)	55 (100)	110
Total completed at Week 48	41 (70.7)	47 (82.5)	88 (76.5)
Total prematurely discontinued	17 (29.3)	10 (17.5)	27 (23.5)
Reason for premature discontinuation			
Adverse event	5 (8.6)	4 (7.0)	9 (8)
Non-adherence	4 (6.9)	2 (3.5)	6 (5.2)
Consent withdrawn	1 (1.7)	1 (1.8)	2 (1.7)
Virologic failure	6 (10)	3 (5)	9(7.8)
Other (RTV intolerance)	1(1.7)	0	1(1)

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the assessment of safety and tolerability of tipranavir. Adverse events reported by subjects and changes in laboratory measurements were graded according to severity.

The DAIDS standardized Toxicity Table for Grading Severity of Pediatric (>3 months) Adverse Experiences was used for grading. Please refer to Section 7.3 (safety analysis).

6.1.5 Analysis of Secondary Endpoint(s)

Treatment Response

Overall, the proportion of subjects with protocol defined treatment response was similar between the two groups [22 (40%) subjects in the low dose and 25 (46%) subjects in the high dose]. Out of the 47 subjects with treatment response, 12 (26%) [7(15%) in the low dose group and 5 (11%) in the high dose group] had treatment failure during the open label, expanded treatment option period beyond the 48 week study period.

Table 10: Treatment Response (48 weeks)

	Low Dose tipranavir/ritonavir 290 mg/m^2/115 mg/m^2			High Dose tipranavir/ritonavir 375 mg/m^2/150 mg/m^2		
	Number of success	Number of failures	Percent success	Number of success	Number of failures	Percent success
<400 (50) (at week 48)	22(17)	33 (38)	40% (31%)	25 (19)	30 (36)	46% (35%)
<400 (<50) (at week 96)	15(9)	40(46)	27% (16%)	20(17)	35(38)	36% (31%)

Reasons for Treatment Failure

The most common reasons for treatment failure in the high dose group were discontinuation due to adverse events (7%) and virologic failure (5%). For the low dose group, proportion of subjects who discontinued due to adverse events was 9% and 11% discontinued due to virologic failure. The overall antiviral benefit of the high dose is apparent here, as more than double the proportion of subjects discontinued due to virologic failure in the low dose group. Table 11 summarizes the results.

Table 11: Reasons for Treatment Failure (48 weeks)

	Total N=110	
Reasons for failure	Low Dose N=55	High Dose N=55
AEs	5(9%)	4 (7%)
Virologic Failure	6(11%)	3(5%)
Consent w/d	1(2%)	1(2%)
Non-adherence	4(7%)	2(4%)
Other		
Could not tolerate taste (ritonavir)	1	
Completed study but did not continue beyond the 48 the week	5	1

6.1.6 Other Endpoints

Key secondary analysis endpoints also included determination of TPV and ritonavir pharmacokinetic parameters at steady-state (C_{max}, Cp_0, Cp_{10h}, Cp_{12h}, AUC_{0-10h}, AUC_{0-12h}, t_{max}, CL, V, $t_{1/2}$) and relative bioavailability of TPV liquid and capsules formulations.

M.O. Comment: Please refer to Clinical Pharmacology Review by Dr. Zheng for detailed discussion.

6.1.7 Subanalysis

Analysis by Age

Efficacy of tipranavir was analyzed based on the 3 stratified age group (2-<6 years, 6- <12 years, and 12-18 years). When analyzed by age group, high dose tipranavir does not appear to give any additional efficacy benefit over the low dose group for the 2 - < 6 year group. However, children 6 years of age and older appears to have benefited from the high dose, when treatment response is measured using viral load <50 copies/ml. Table 12 summarizes treatment response based on age and dose given. Note that subjects in the 2 to <6 years old age group did not have as many baseline tipranavir associated mutations compared to the older subjects, which may have contributed to apparent lack of difference in treatment response between the high and low dose groups (see analysis below based on baseline mutations).

Table 12: Proportion of subjects with HIV RNA < 400 copies/mL (<50 copies/mL) by age and dose

	Low Dose tipranavir/ritonavir 290 mg/m^2/115 mg/m^2			High Dose tipranavir/ritonavir 375 mg/m^2/150 mg/m^2		
<400 (50) (at week 48)	Number of success	Number of failures	Percent success	Number of success	Number of failures	Percent success
2 to <6 years	7 (7)	3(6)	70% (54%)	7 (5)	3(7)	70% (42%)
6 to <12 years	7 (6)	12(13)	37% (32%)	9(7)	9(11)	50% (39%)
12 to 18 years	8 (6)	18(20)	31% (23%)	9(8)	18(19)	33% (30%)

The Applicant's analysis (table 13) slightly differs from this reviewer's (and Dr. Hammerstrom's) analysis, see table 12.

Table 13: Proportion of subjects with HIV RNA < 400 copies/mL (<50 copies/mL) *

<400 (50) (at week 48)	Low Dose tipranavir/ritonavir 290 mg/m^2/115 mg/m^2	High Dose tipranavir/ritonavir 375 mg/m^2/150 mg/m^2
	Percent success	Percent success
2 to <6 years	77% (54%)	67% (50%)
6 to <12 years	32% (32%)	42% (42%)
12 to 18 years	27% (27%)	39% (23%)

*Sponsor's analysis

The reasons for treatment failure are summarized by age group and dose in table 11. The highest number of subjects who prematurely discontinued the study is in the 12 to 18 year old group.

Virologic failure was also most common reason for discontinuation among those in the oldest age group who received the low dose. This is most likely due to history of previous treatment with ARV and high degree of baseline resistance.

Table 14: Reasons for Failure by Age and Dose

	Age						Total	
	2-6 (n=25)		7-11 (n=38)		12-18 (n=52)		110	
Reasons for D/C study 48 wk analysis	Low	High	Low	High	Low	High	Low	High
AE			2	2	3	2	5	4
Virologic Failure	1		1	1	4	2	6	3
Consent w/d					1	1	1	1
Non-adherence			2		2	2	4	2
Other								
Could not tol. taste					1		1	
Completed study but not cont w/ >48 wk							5	1

Analysis by Baseline Resistance

The number of tipranavir associated mutations for the two dose groups is summarized in table 15. The proportion of subjects with treatment response (viral load <400 copies/mL) was highest in the youngest age group (2 - < 6 years) compared to the older age groups (6-18 years) regardless of the number of baseline resistance mutations (table 16).

Overall, for subjects with 5 or more tipranavir resistance-associated mutations at baseline, the proportion of subjects who responded to treatment (viral load <400 copies/mL) was higher in the high dose group compared the low dose group [42% (5/12) vs.7% (1/15)]. Furthermore, within the oldest age group (12 to 18 years) for those with ≥5 tipranavir PI mutations at baseline, the proportion of subjects who responded to treatment (viral load <400 copies/mL) was higher in the high dose group compared to the low dose group, [40% (4/10) vs. 11% (1/9)] (table 16). Please refer to Dr. Naegar's review for full detail.

Table 15: Number of tipranavir associated mutations*

Dose	High	Low
#TPV Mutations		
0	4/12 (33%)	6/7 (86%)
1	10/13 (77%)	2/8 (25%)
2	2/5 (40%)	5/11 (45%)
3	4/8 (50%)	4/8 (50%)
4	1/7 (14%)	4/9 (44%)
5	2/5 (40%)	1/6 (17%)
≥6	3/7 (43%)	0/9 (0%)

*Source: Dr. Naegar's review

Table 16: Treatment response based on key tipranavir mutations and tipranavir associated mutations by dose group and age*

TPV Dose	APTIVUS/ritonavir dose regimen: 375 mg/m^2/150 mg/m^2				APTIVUS/ritonavir dose regimen: 290 mg/m^2/115 mg/m^2			
Age	ALL	2 to <6	6 to <12	12 to 18	ALL	2 to <6	6 to <12	12 to 18
Key TPV mutations								
0	50% (11/22)	71% (5/7)	63% (5/8)	14% (1/7)	53% (10/19)	88% (7/8)	0/4	43% (3/7)
1	77% (10/13)	75% (3/4)	100% (5/5)	50% (2/5)	38% (6/16)	50% (2/4)	33% (3/9)	33% (1/3)
2	11% (1/9)	0/1	0/3	20% (1/5)	36% (4/11)	-	50% (1/2)	33% (3/9)
3	25% (3/12)	-	0/3	33% (3/9)	17% (2/12)	0/1	50% (2/4)	0/7
4	1/1			1/1				
≥2	23% (5/22)	0/1	0/6	33% (5/15)	26% (6/23)	0/1	50% (3/6)	19% (3/16)
	High Dose				Low Dose			
Age	ALL	2 to <6	6 to <12	12 to 18	ALL	2 to <6	6 to <12	12 to 18
TPV-associated mutations								
0-1	14/25 (56%)	5/7 (71%)	7/10 (70%)	2/8 (25%)	8/15 (53%)	5/6 (83%)	0/2	3/7 (43%)
2-4	7/20 (35%)	2/4 (50%)	3/8 (38%)	2/8 (25%)	13/28 (46%)	4/6 (67%)	6/12 (50%)	3/10 (30%)
≥5	5/12 (42%)	1/1	0/1	4/10 (40%)	1/15 (7%)	0/1	0/5	1/9 (11%)

* Source: Dr. Naegar's review

Analysis by Exposure

The low dose tipranavir demonstrated a pharmacokinetic profile similar to the adult marketed dose of 500/200 mg bid. Response rates were similar between doses for subjects with 0-3 TPV associated mutations. However for subjects with 4 or more TPV-associated mutations at baseline, the proportion of subjects who responded to treatment (viral load <400 copies/mL) was higher in the high dose group compared the low dose group [42% (5/12) vs.7% (1/15)].

Trough concentrations were collected in subjects throughout the trial (i.e. 48 and 100 week period). Troughs were collected between 10 and 14 hours after the prior reported dose time. Overall, a clear exposure-effectiveness relationship was demonstrated with trough concentration and virologic response.

Genotypic inhibitory quotient (GIQ) is defined as the tipranavir trough level divided by the number of tipranavir mutations. In general, subjects in the tipranavir high dose group had a

higher GIQ, see table 17. GIQ was a strong predictor of efficacy. The proportion of subjects with virologic response increased as GIQ increased. Virologic response increased from no response in the lowest GIQ quartile to 73% response in the fourth quartile (table 17).

Table 17: Median and range for GIQ

	Low Dose	High Dose	Total
All	12.3 (0.6-163)	19.0 (0.8-215)	13.7(0.6-215)
2-<6	24.4 (9-162)	43.2 (7-215)	24.4(7-215)
6 to <12	8.7 (1.6-76)	33.3(0.8-83)	11(0.8-83)
12 to <18	10 (06-122)	11.5(0.9-98)	10.5 (0.6-122)

Source: Table 15.1.4.2:1

Table 18: Virologic response at Week 48 based on GIQ quartiles

GIQ quartiles	<400 copies/mL n (%) N	<50 copies/mL n (%) N
Q1 (0.56 - 7.19)	2 (8.0) 25	1 (4.0) 25
Q2 (7.23 – 13.50)	13 (52.0) 25	11 (44.0) 25
Q3 (13.68 – 38.61)	15 (57.7) 26	13 (50.0) 26
Q4 (39.29 − 215.38)	17 (68.0) 25	14 (56.0) 25

Source: Tables 15.2.7: 3, 15.2.10: 3, 15.2.13: 3

Analysis by Medication Adherence

Overall, adherence was better in the high-dose group. The reason for this finding is unclear. The difference was most striking for the 6 to <12 years old group where the proportion of subjects with 95-120% adherence was 47% for the high dose group and 16% for the low dose group. This finding may partially explain the discrepancy of treatment response for this age group (and for the 12-18 years old group), where more subjects in the high dose group had successful treatment response compared to low dose group. Table 19 summarizes these findings.

Table 19: Proportion of subjects with 95%-120% TPV adherence at Week 48

	TPV/r low dose	TPV/r high dose
	N (%)	N (%)
Week 48	N= 58	N=57
All	18 (31)	26(46)
2 to <6 years	10/13 (77)	8/12(67)
6 to <12 years	3/19 (16)	9/19(47)
12 to 18 years	5/26 (19)	9/26 (35)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose selection for the three age groups, including possible dose reduction was based on the following results:

The 290 mg/m^2/115 mg/m^2 twice daily regimen provided tipranavir plasma concentrations similar to those obtained in adults receiving 500/200 mg twice-daily. The 375 mg/m^2/150 mg/m^2 twice daily regimen provided tipranavir plasma concentrations 37% higher than those obtained in adults receiving 500/200 mg twice-daily.

The HIV RNA results were similar for children 2- <6 years of age receiving either 290 mg/m^2/115 mg/m^2 or 375 mg/m^2/150 mg/m^2 twice daily. Based on study results from this clinical trial, it would be appropriate to recommend the 290 mg/m2/115 mg/m2 dose for this age group. However, even for this age group, treatment response was better with the high dose tipranavir when analyzed by baseline mutations (although the difference was not as robust as seen in the older age group). Keeping in mind the labeled indication for APTIVUS is treatment experienced subjects who are resistant to more than one protease inhibitor, in clinical practice, the most likely subjects (even in the 2 to <6 years old age group) who will be prescribed APTIVUS are those with no alternative optimized treatment regimen. These subjects will likely have more baseline resistance than what was seen in the subjects enrolled in this clinical trial. Therefore, it is reasonable to maximize response by recommending 375mg/m^2/150mg/m^2 twice daily. Those who develop intolerance or toxicity may be able to be prescribed the lower dose, provided that they do not have multiple protease inhibitors associated mutations.

Unlike the 2- <6 year age group, a greater proportion of pediatric subjects 6-18 years of age receiving APTIVUS/ritonavir 375 mg/m^2/150 mg/m^2 achieved HIV RNA <400 copies/mL at 48 weeks, compared to those receiving APTIVUS/ritonavir 290 mg/m^2/115 mg/m^2. A greater proportion of subjects 6-18 years of age with multiple baseline resistance substitutions receiving APTIVUS/ritonavir 375 mg/m^2/150 mg/m^2 achieved HIV RNA <400 copies/mL at 48 weeks when compared to subjects receiving APTIVUS/ritonavir 290 mg/m^2/115 mg/m^2.

In summary, the recommended dose for all age groups is:

Tipranavir/ritonavir: 375 mg/m^2/150 mg/m^2 twice daily, not to exceed adult maximum dose 500/200 mg twice daily

An equivalent dose has also been calculated using the body weight dosing calculation (i.e. mg/kg). This alternative dosing method allows for dosing based on mg rather than age. This dosing methodology may allow for less overexposure of subjects who may be underweight for age. The following is the dose recommendation using mg/kg calculations:

Tipranavir/ritonavir: 14/6mg/kg twice daily, not to exceed adult maximum dose 500/200 mg twice daily.

For subjects without multiple baseline mutations, lower dose of tipranavir/ritonavir (12/5 mg/kg or 290 mg/m^2/115 mg/m^2) may be considered if intolerance or toxicity develops. A dose reduction in subjects with multiple baseline protease inhibitor mutations is not recommended.

One additional finding that supports the recommendation of the 375 mg/m^2/150 mg/m^2 twice daily dosing is the number of subjects who developed AIDS defining illness during study period- all subjects were in the low dose group (please see Section 7.3.5)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The treatment effect was more durable in the high dose group compared to the low dose group. As illustrated previously, at the 96 week treatment period, 27% of the subjects who received low dose tipranavir had maintained a treatment response (viral load <400c/mL) whereas 36% of subjects who received high dose had treatment response. The difference in response is greater at Week 96 when comparing viral load < 50 copies/mL - the proportion of subjects with treatment response was 16% in the low dose group and 31% in the high dose group.

Overall, 6 (5%) subjects had AIDS defining illness during the treatment period. All of these subjects received the 290 mg/m^2/115 mg/m^2 dose (see section 7.3.4 for details). This finding further supports the recommended dose of tipranavir, where despite a slight increase in adverse events, the benefits from tipranavir/ritonavir 375 mg/ m^2/150 mg/m^2 outweigh the observed and potential risks.

6.1.10 Additional Efficacy Issues/Analyses

In summary, tipranavir was shown to be effective as treatment for HIV-1 infection in treatment experienced pediatric subjects 2 years of age and older. More specifically, the higher dose tipranavir studied (379 mg/ m^2/150 mg/m^2) appears to have advantage for certain subpopulations, including those with high tipranavir associated baseline mutations. This was clearly demonstrated by analysis of treatment response by baseline mutation and GIQ score. In addition, the overall number of subjects who discontinued treatment due to virologic failure was twice as many in the low dose group compared to the high dose group. The durability (96 weeks) of treatment effect (particularly viral load <50 copies/mL) was also higher for the high dose group. Finally, no patient who received high dose tipranavir developed AIDS defining illnesses during the treatment period.

The efficacy of tipranavir demonstrated in this pediatric trial was comparable (or slightly higher) to the adult RESIST trials. At week 48, the proportion of adults subjects with HIV RNA <400 copies/mL was 30%; the proportion of subjects with viral load <50 copies/mL was 23%.

The extrapolation of efficacy for antiretroviral drugs like tipranavir is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)[4] DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease (Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468), noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in HIV-infected adults.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and HIV RNA viral load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been shown to lower HIV RNA, improve CD4 counts (or percentage) and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

7 Review of Safety

Safety Summary

Overall, tipranavir co-administered with ritonavir in combination with other antiretroviral drugs was safe and tolerable when administered to pediatric subjects 2 to 18 years of age. The types of adverse events reported were similar to adults but the frequency was lower in pediatric subjects, although vomiting and rash (all grades, all causality) were more frequent in pediatric subjects. When the high and low dose tipranavir are compared, the overall adverse events profile was similar for the two groups. However, the number of subjects with hepatic adverse events (i.e. increased ALT) and bleeding adverse event was higher in the high dose group. An exposure-safety relationship was shown for hepatic adverse events; in contrast no exposure-safety relationship was established for bleeding adverse events. Of note in the statistical design of study 1182.14- this study was not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in adverse event incidences. Descriptive statistics were applied to describe the observed findings. Caution should be exercised when interpreting these results.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The safety profile of tipranavir has already been established in adults with adequate number of subjects.

Study 1182.14 was the pivotal pediatric study conducted to assess safety and efficacy of tipranavir in pediatric subjects. The population of ongoing Study 1182.14, which is currently ongoing, includes HIV-1 infected pediatric subjects who were 2 to 18 years of age at the time of randomization. With exception of 3 subjects, all were treatment experienced. The primary objective of this study was to assess the safety and tolerability of tipranavir co-administered with ritonavir in combination with other ARV drugs. The first patient was randomized into the study on February 18th, 2004. The last patient completed 48 weeks of treatment on October 13th, 2005. The initial treatment period was for 48 weeks, after which subjects could continue in the Optional Safety Extension (OSE). The last patient completed 100 weeks of treatment on

September 29th, 2006. OSE will continue until tipranavir becomes available on market for pediatric subjects.

This submission also contains safety results on pediatric subjects from the adult RESIST studies, emergency use studies and expanded access programs. Safety data has also been submitted from Global Drug Safety database (ARISg) to support approval of tipranavir in pediatric subjects with HIV-1 infection. Three cases reported to the FDA's Adverse Events Reporting System (AERS) are also included.

In total, these studies provide an adequate number of pediatric subjects who were exposed to tipranavir during its clinical development.

7.1.2 Adequacy of Data

The data submitted support safety and tolerability of tipranavir co-administered with ritonavir in combination with other ARVs. The PWR required a minimum of 100 patients followed for safety at the to-be-marketed dose or higher for 24 weeks. The submitted data are adequate with regards to number of subjects exposed to tipranavir and duration of exposure. The data were submitted by SAS transport file for analysis using JMP software. Adverse events were depicted using MedDRA preferred terms. All adverse events were graded using DAIDS standardized Toxicity Table for Grading Severity of Pediatric (>3 months of age) Adverse Events. All adverse events were also noted as drug related if considered to be related to study drugs.

No studies will be conducted on pediatric subjects less than 2 years of age or in pediatric subjects who are treatment naïve. This decision was based on the intended population tipranavir is approved for -treatment-experienced HIV-infected subjects. A favorable risk/benefit assessment was not established for treatment-naïve adults; therefore, a treatment-naïve indication will not be sought. Please refer to October 2007 traditional approval review by Dr. Kirk Chan-Tack for details.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Study 1182.14 is a descriptive study. No formal statistical analysis was performed. In addition, this submission contains safety data from additional supportive studies (expanded access program/emergency use program and RESIST trials).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A minimum of 100 pediatric subjects with 24 week safety data was requested by the Division. The Applicant has submitted safety data on 114 pediatric subjects with at least 24 week safety data. In addition, 83 subjects from Trial 1182.14 have at least 48 weeks of treatment and 73 subjects have at least 100 weeks of treatment. Table 20 summarizes the number of subjects from each study.

In all the safety sections below, safety data beyond the 48 week study period were included when available. Unless specifically stated, all discussions and tables below reflect safety data inclusive of 100 weeks. Please note that for premature treatment discontinuation analysis and Grade 3/4 ALT elevations analysis, both the 48 week data and the 100 week data has been presented.

Table 20: Pediatric Trials with Safety Data

All Pediatric Subjects, Regardless of Duration of TPV/r Treatment		Pediatric Subjects Receiving TPV/r Treatment for ≥24 Weeks
Trial Number	Total Number of Subjects	Total Number of Subjects
1182.14	110	92
1182.33	3	3
1182.48	5	5
1182.58, 1182.67 and 1182.16 (EAP/EUP)	17	10
ARISg	10	4
Total Number of Subjects:	145	114

7.2.2 Explorations for Dose Response

During the pediatric development plan, 2 doses were selected for study. The first dose, tipranavir/ritonavir dose 290/115 mg/m2 was allometrically scaled by body surface area to the 500/200 mg adult dose (BSA 1.73 m2). A higher dose (375/150 mg/m2), projected to be a 30% increase in the adult dose was selected to account for potential increase in metabolism and clearance of the drug in pediatric subjects. Both doses were administered during the study period. A dose response relationship has been explored both for safety and efficacy. With higher dose, there appears to be an improved efficacy response (see Section 6). Similarly, there is a slight increase in adverse events with the higher dose or exposure, specifically an increase in hepatic adverse events. However, the hepatic adverse event trend was noted only in the oldest age group (see Section 7.5.1 below).

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the original and the traditional review of tipranavir for detail. No new animal and/or in vitro testing was submitted with this sNDA.

7.2.4 Routine Clinical Testing

Protocol defined routine clinical and laboratory testing were conducted during the trial. These tests were adequate. Subjects were evaluated for adverse events and laboratory tests were performed at appropriate frequencies (weeks 2, 4, 6, and 8). After study Week 8, routine assessments were conducted every 4 weeks. Pre-specified adequate monitoring plans were also in place for hepatic adverse events.

7.2.5 Metabolic, Clearance, and Interaction Workup

Adequate studies of metabolism, clearance and drug-drug interactions for tipranavir have already been conducted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

During the study period, cholesterol, triglycerides, and glucose were followed to monitor for protease inhibitor class adverse effects. In addition, tipranavir specific adverse events noted in adults (namely hepatic adverse events and bleeding adverse events) were also monitored.

7.3 Major Safety Results

7.3.1 Deaths

Study 1182.14
No deaths occurred during the 48 week study period. However, during the optional extended treatment period, 2 deaths were reported. Both deaths were not related to treatment drug.

The cause of death for one patient was gastrointestinal bleeding. This was a 17 year old male who was on treatment with tipranavir for 22 months. The subjects discontinued study drug due to poor compliance. One day after discontinuation, he presented with epigastric pain, oral candidiasis and wasting syndrome. He was hospitalized and found to have hepato-splenomegaly, oral candidiasis, wasting, and diffuse abdominal pain with peritoneal reaction. On radiographic studies, an enlarged spleen and pancreas head, dilated hepatic biliary ducts, free liquid in peritoneal cavity and retroperitoneal lymphadenopathy were noted. Patient was also coagulopathic and received fresh plasma and platelets transfusions. The patient did not have hepatic failure. The cause of coagulopathy was believed to be due to gastrointestinal lymphoma or alternatively due to malnutrition, wasting, advanced HIV disease and vitamin K deficiency. The investigator and clinical monitor believed there was no causal relationship between the event the trial drug. This reviewer is in agreement with the investigator and clinical monitor. Given the multiple medical complications, especially the gastrointestinal lymphoma and the advanced HIV disease, it is most likely that the gastrointestinal bleeding is related to the subject's medical condition and unlikely related to study drug. Tipranavir has been shown to have effect on coagulation parameters in pre-clinical studies. Therefore tipranavir's contribution to coagulopathy cannot be excluded with full certainty.

The cause of death for the second patient was renal failure secondary to B-cell lymphoma. Patient was a 10 year old male who had completed the study trial (48 weeks). He presented approximately 5 months later with B-cell lymphoma and renal failure. He received chemotherapy and dialysis but died due to complication of B-cell lymphoma (tumor lysis) and AIDS. The cause of death was judged not to be related to the study drug.

EAP/EUP (CPDb and ARISg)
There were 2 deaths reported in pediatric subjects from EAP/EUP, neither of which were deemed related to the study drug.

One patient died due to acute respiratory distress. This patient was known to have recurrent cerebral toxoplasmosis. Another patient died from sepsis and septic shock; this patient had underlying medical conditions including cryptococcosis and atypical mycobacterial infection.

7.3.2 Nonfatal and Fatal Serious Adverse Events (SAEs)

Study 1182.14

Serious adverse events (SAE) were reported by 27 (25%) subjects during the 48 week study period. The number of subjects with SAE remained at 25% even beyond the 48 week period. The number of SAEs was similar between the high and low dose group and between the comparative age groups. In fact, for the 2 to <6 and 12 to 18 years old age groups, slightly more SAEs were reported in the low dose group.

Hospitalization was the most common reason for qualifying an adverse event as a serious adverse event (SAE). The majority of SAE reports were considered not related to study drug.

Table 21: Serious Adverse Events

	Age						Total	
Number of subjects with Serious AE	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		110	
	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose
	3 (30)	2 (20)	6 (36)	6 (36)	6 (23)	4 (15)	15 (27)	12 (22)

Infection and Infestation was the most frequently reported SAE, followed by Gastrointestinal disorders. Among the notable SAEs reported in the two groups include:

High Dose	Low Dose
Abdominal pain	Abdominal pain
Bloody Diarrhea	Diarrhea
Nausea	GI bleed
Vomiting	LFT increase
Bruise	Thrombocytopenia

PT increase	TTP
Pneumonia	Anemia
Esophageal Candidiasis	Pneumonia
Neutropenia	Esophageal Candidiasis
Urticaria	Psychiatric
ARF	

The number of subjects with SAEs was similar to the adult trials. Through Week 48 of the RESIST studies, a total of 156 subjects (21%) in the TPV/r arm reported serious adverse events. Infections and Infestations (9%) and Gastrointestinal Disorders (4%) were the two most common MedDRA System Organ Classes reported.

EUP/EAP and clinical trials other than 1182.14 (CPDb and ARISg)
Serious adverse events were reported for 10 subjects. Infection was the most frequent SAE reported. Two subjects had hepatic adverse event- hepatic failure and cytolytic hepatitis.

7.3.3 Dropouts and/or Discontinuations

During the 48 week treatment period, 9(8%) subjects discontinued trial due to AE (9% in the low dose and 7% in the high dose group). There were no discontinuations due to AE in the youngest age group, 4 subjects in the 6 to <12 age group and 5 subjects in the 12 to 18 age group. The most common reason for discontinuation was GI (5%) and hepatic (4%) related adverse events. Three subjects in the low dose group discontinued due to elevation in GGT; while the GGT events were graded as severe, none were serious or considered clinically significant. One patient in the high dose group discontinued due to increased ALT. The ALT increase was severe and significant (protocol defined). Table 22 summarizes the events. All were considered to be related to study drug.

M.O. Comment: When grading severity of an adverse event (excluding laboratory toxicities), the Sponsor did not use numbering system (i.e. Grades 1, 2, 3, 4). Adverse events were described as mild (which was equivalent to Grade 1), moderate (equivalent to Grade 2), or severe (equivalent to Grades 3 and 4).

Table 22: Adverse events leading to discontinuation of study drug (48 Week)*

Patient	Age/ Gender	Group	Preferred term	Onset day	Intensity	Study drug related	Serious	Treatment duration
1086	10/F	TPV/r low	Abdominal pain upper	1	Mild	Yes	No	13
1213	17/M	TPV/r low	Retching	1	Moderate	Yes	No	1
1213	17/M	TPV/r low	Vomiting	1	Moderate	Yes	No	1
3924	13/F	TPV/r low	GGT increased	83	severe	Yes	No	90
3925	14/M	TPV/r low	GGT increased	10	severe	Yes	No	45
3927	11/M	TPV/r low	GGT Severe	29	severe	Yes	No	168
5401	15/M	TPV/r high	ALT increased	31	severe	Yes	Significant	63
1054	11/M	TPV/r high	Abdominal pain	5	Moderate	Yes	Serious	5
1054	11/M	TPV/r high	Nausea	5	Severe	Yes	Serious	5
1054	11/M	TPV/r high	Vomiting	5	Mild	Yes	No	5
1211	14/F	TPV/r high	Abdominal discomfort	1	Moderate	Yes	No	9
1211	14/F	TPV/r high	Retching	1	Moderate	Yes	No	9
5505	10/F	TPV/r high	Urticaria	11	Moderate	Yes	Serious	15

Source: Listing 15.4.2: 1 and Appendix 16.2, Listing 7.1.2

At the 48 week analysis of the adult RESIST trials, the number of GI and hepatic adverse events leading to discontinuation are summarized in the table below. In total, 13% of the subjects discontinued due to adverse events, 5% with GI disorders and 0.5%- 2.7% with hepatic related adverse events. The proportions of subjects with these adverse events are similar to the pediatric subjects.

Table 23: AE leading to treatment discontinuation (RESIST Studies)*

Total # of subjects with AE leading to treatment discontinuation, n (%)	99 (13.2)
Gastrointestinal disorders	39 (5.2)
Nausea	12 (1.6)
Vomiting	11 (1.5)
Diarrhea	14 (1.9)
Abdominal pain	4 (0.5)
Pancreatitis	4 (0.5)
Investigations	26 (3.5)
Liver function analyses	20 (2.7)
ALT increased	7 (0.9)
AST increased	3 (0.4)
Hepatic enzymes increased	4 (0.5)

* Source: Dr. Kirk Chan-Tacks Traditional NDA review (sNDA 21-814)

The number of pediatric subjects who discontinued study drug increase when subjects were followed beyond the 48 week period- with discontinuation reported in 18% in the low dose group and 15% in the high dose group. The proportion of subjects who interrupted treatment or

discontinued treatment due to AEs was comparable between the two dose groups. When compared by age and treatment group, discontinuation was most frequent in the 12 to 18 years old group who received the low dose. This result should be interpreted with caution as the results were from the optional long-term safety follow-up study period.

Table 24: Treatment interruption/discontinuation due to AE (≥ 48 weeks)

AGE								
	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		Total =110	
	Low (10)	High (10)	Low (19)	High (19)	Low (26)	High (26)	Low (55)	High (55)
Interr due to AE	2 (20)	1 (10)	6 (33)	4 (21)	3 (12)	6 (24)	11(20)	11(20)
Discontinue to AE	0	2 (20)	4 (22)	2 (11)	6 (24)	2 (8)	10 (18)	8 (15)

7.3.4 Significant Adverse Events

The study protocol had 5 predefined significant adverse events. These events do not meet criteria for SAE, but are reported in the same manner as SAEs. The protocol defined significant AEs include:

- Any Grade 4 non-serious adverse event
- DAIDS Pediatric Toxicity Grade 3 or 4 hemoglobin
- DAIDS Pediatric Toxicity Grade 3 or 4 bilirubin
- DAIDS Pediatric Toxicity Grade 3 or 4 AST or ALT
- DAIDS Pediatric Toxicity Grade 3 or 4 lipase

Table 25 summarizes significant AEs reported during the study period. Overall, the events were similar between the two dose groups. However, increased ALT adverse events occurred slightly more in the high dose group when compared to the low dose group (9% vs. 4%, respectively). Most of these subjects were in the 12 to 18 year group. Of note, the patient with hyperbilirubinemia had discontinued the study drug and started atazanavir at the time of the event.

Table 25: Protocol Defined Significant AEs (48 Weeks)

Number (%) of Subjects			
	TPV/r low dose	TPV/r high dose	Total
Number of subjects	55	55	110
Total with significant adverse event	5 (9)	6 (11)	11(10)
Pancreatitis	1 (2)	0 (0)	1 (1)
Hyperbilirubinemia	1 (2)	0 (0)	1 (1)
Alanine aminotransferase increased	2 (4)	5 (9)	7 (6)
Hyperamylasemia	1 (2)	1 (2)	2 (2)
Increased GGT	1 (2)	1 (2)	2 (2)

Source data: Table 12.2.3.4: 1 (U06-3397-01)

No increased severe adverse events were noted with administration of high dose tipranavir. Slightly more moderate AEs were seen with the high dose (65%) when compared to the low dose (51%).

Table 26: Severity of AEs

	AGE						Total	
Number of subjects with AEs	2- <6		6-<12		12-<18			
	Low	High	Low	High	Low	High	Low	High
Moderate	4 (40)	6 (60)	8 (42)	13 (68)	16 (62)	17 (65)	28 (51)	36(65)
Severe	1 (10)	2 (20)	8 (42)	6 (32)	10 (38)	6 (23)	19(35)	14(25)

Table 27: Description of Severe AEs

Number of subjects with AEs	Low Dose	High Dose	Total
Increased GGT	5(9%)	4(7%)	9(8%)
Nausea		1(2%)	1(<1%)
Increased ALT	2(4%)	2(4%)	4(4%)
Increased LFT	1(2%)		1(<1%)
Anemia	1(2%)		1(<1%)

As summarized in table 27 above, number of severe hepatic adverse events was comparable between the two dose groups.

7.3.5 Submission Specific Primary Safety Concerns

Bleeding AEs

Bleeding events were selected as special interest due to intracranial hemorrhage (ICH) events (fatal and non-fatal) reported with use of tipranavir in adult subjects. ICH is now included in the Box Warning, in the package insert. Many of these subjects with ICH had other medical conditions or were receiving concomitant medications that may have caused or contributed to these events. In addition, no pattern of abnormal coagulation parameters has been elicited in these subjects in general. Bleeding adverse events (including ICH) were evaluated when the 48 week adult (RESIST) studies were submitted. More subjects experienced on-treatment adverse events of bleeding/hemorrhage in the TPV/r group when compared to the CPI/r group [41(6%) vs. 27(4%)]. Please refer to the traditional NDA (21-814) review for detail.

In vitro experiments have shown tipranavir to inhibit human platelet aggregation at levels consistent with exposures observed in subjects receiving tipranavir/ritonavir. Additionally, preclinical studies in rats have shown tipranavir to induce dose-dependent changes in coagulation parameters (increase in prothrombin time, increase in activated partial thromboplastin time, and a decrease in some vitamin K dependent factors). In some rats, these changes led to bleeding and death. In addition, co-administration of tipranavir with vitamin E in the form of TPGS (d-alpha-

tocopherol polyethylene glycol 1000 succinate) resulted in a significant increase in effects on coagulation parameters, bleeding events, and death.

Given this background, bleeding was selected as a special interest adverse event during the analysis of the pediatric study. Bleeding events were evaluated for the 48 week period. Eight subjects 8 (7%) had bleeding events that occurred during the 48 weeks. This finding is similar to the adult study (RESIST) where 6% of the subjects were reported to have bleeding AEs. The type of bleeding AEs for 4(3.5%) of these subjects was epistaxis.

The most common cause for bleeding in the pediatric subjects was epistaxis, which is historically more common in the pediatric population than in adults. When bleeding adverse events were analyzed without epistaxis, the proportion of pediatric subjects with bleeding AEs decreases to 3.5%.

Bleeding events were also evaluated for the 100 week study period. Overall, 13 (12%) experienced bleeding related adverse events. The most common type of bleeding AE was epistaxis (4.5%). One patient had a fatal adverse event (see Section 7.3.1). The bleeding was not considered to be drug related. No patient had a serious bleeding adverse event considered drug related. No ICH was reported in the pediatric study.

One additional patient is included along with the 13 subjects with bleeding adverse events (see table 38, Section 9.4). This patient had thrombocytopenia, which was thought to be unrelated to study drug. The event was present prior to initiation of therapy. Although thrombocytopenia is a risk factor for bleeding (therefore included in the list), this patient did not experience a true bleeding event.

When bleeding adverse events were compared based on dose, slightly more subjects reported bleeding AEs in the high dose group (15%) compared to low dose group (9%) (see table 38, Section 9.4). Overall, the types of AEs were similar between the two groups. In addition, the most serious (fatal) AEs occurred in the low dose group. More events were noted in the oral solution (OS) group (69%) when compared to capsule group (31%). However, most children were also taking the solution formulation during the trial.

Table 28: Any Bleeding-related AEs

	Age						Total	
	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		110	
	Low	High	Low	High	Low	High	Low	High
Bleeding	0	0	1 (5)	4 (21)	4 (15)	4 (15)	5 (9)	8 (15)
Bleeding (OS)	0	0	1 (100)	4 (100)	3 (75)	1(25)		
Bleeding (Cap)	0	0	0	0	1(25)	3 (75)		

A retrospective study on effect of tipranavir and vitamin E on coagulation was conducted using frozen plasma samples from subjects who were enrolled and treated in Study 1182.14. In summary, no clinically significant change was seen on PT and PTT or vitamin K dependent

coagulation factors when comparing baseline to during treatment period, regardless of the formulation (OS vs. Cap) administered. Please refer to Section 7.4.5 for details.

GI and Hepatic AEs (selected)

Within the MedDRA System Organ Classes, group of adverse events were selected for analysis. These included: Nausea, vomiting, diarrhea, abdominal pain, hepato-, investigation, LFT, ALT, AST, GGT, and bilirubin. Table 29 summarizes AEs by severity (moderate and severe) and treatment groups. Overall, the moderate and severe hepatic and GI AEs were similar between the two groups.

Table 29: Moderate and severe GI and hepatic adverse events

Number of Subjects with Moderate and Severe AEs	Low N=55	High Dose N=55	Total N=110
Abdominal Pain	2 (4%)	2(4%)	4 (4%)
Nausea	4(7%)	2(4%)	6(5%)
vomiting	5(9%)	5(9%)	10(5%)
diarrhea	3(5%)	4(7%)	7(6%)
↑GGT	6(11%)	6(11%)	12(11%)
LFT	1(2%)		1(1%)
↑ALT	3(5%)	4(7%)	7(6%)
Bilirubin	1(2%)	1(2%)	2(2%)
Pancreatitis	1(2%)		1(1%)
↑ Amylase	1(2%)		1(1%)

Table 30 summarizes the AEs across the age groups and by dose of tipranavir given.

While more subjects in the low dose group experienced increased GGT, more subjects in the high dose group experienced increased ALT and/or AST and vomiting (see table 29). Older subjects (12-18 years) who received high dose tipranavir were the primary factors for increasing the incidence of ALT/AST abnormality. Also this is the age group who benefits the most from having high dose tipranavir because they are most likely to have multiple baseline resistance mutations (please see Section 6.1.7 for discussion on resistance and efficacy outcome).

Table 30: Number (%) of Subjects GI and Hepatic AEs

	Age						Total	
	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		110	
	Low	High	Low	High	Low	High	Low	High
Nausea	1 (10)	0	2 (11)	4 (21)	7 (27)	7 (27)	10(18)	11(18)
Vomiting	4(40)	6 (60)	6 (32)	6 (32)	9(35)	14 (54)	19(35)	26(47)
Abdominal pain	0	1	4 (21)	7 (37)	6(23)	5(19)	10(18)	13(24)
Diarrhea	4 (40)	4 (40)	6 (32)	7 (32)	5(19)	7(27)	15(27)	18(33)

Investigation	0	0	0	0	1(4)	0	1(2)	0
↑LFT	0	0	1 (5)	0	0	0	1(2)	0
↑GGT	1(8)	1	2 (11)	2(11)	4(15)	3 (12)	7(13)	6(11)
↑Bilirubin	0	0	0	0	1(4)	1 (4)	1(2)	1(2)
↑ALT	0	0	2	0	1(4)	4(15)	3(5)	4(7)
↑AST	0	0	0	1(5)	0	1(4)	0	2(4)
Cholelithiasis	0	0	0	0	0	1(4)	0	1(2)
Hepatomegaly	1(8)	0	0	0	0	0	1(2)	0
Steatorrhea	0	0	1(5)	0	0	0	1(2)	0
Pancreatitis	1(8)	0	1 (5)	0	0	0	2(4)	0
↑ Amylase	0	0	1(5)	0	0	0	1(2)	0

Rash

Within the MedDRA System Organ Classes for Skin and Soft Tussue, selected adverse events have been included to compare proportion of subjects with rash in each age group and dose group. Specifically, terminologies such as rash, erythema, papular, macular, maculo-papular, urticaria, drug rash, hypersensitivity, swelling, pruritic rash and pruritis were selected. Overall the number of subjects with rash was 23 (21%). This adverse event appears to occur more frequently in children compared to adult studies (12%). The occurrence of rash was similar between the high and low dose groups (20% in high dose group and 22% in low dose group). Most of the events occurred in subjects 6 to 18 years of age, particularly in the low dose group. One patient from high dose group discontinued study drug due to urticaria. This event was also classified as serious. More subjects in the high dose group experienced moderate rash. Overall, 5(5%) subjects had moderate rash, 4 of whom received the high dose tipranavir. The type of moderate rash were drug rash (2 subjects in the high dose group), maculo-papular rash (1 subject in the high dose group), urticaria (1 subject in the high dose group), and pruritic rash (1 subject in the low dose group). Out of the 4 subjects in the high dose group, two required treatment interruption and one discontinued. The one subject with moderate rash from the low dose group did not have treatment interruption or discontinuation.

Table 31: Number (%) of Subjects Developing Rash (pooled analysis)

	Age						Total	
	2-<5 (n=20)		6-<12 (n=38)		12-18 (n=52)		110	
	Low	High	Low	High	Low	High	Low(55)	High (55)
Rash	0	1(10)	6(32)	4(21)	6(23)	6(23)	12(22)	11 (20)

AIDS Defining Illnesses

Overall, 6 subjects had AIDS defining illness during the study period. All were in the low dose group, age 6-18.

Table 32: AIDS defining illness during treatment period

	Age						Total	
	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		110	
	Low	High	Low	High	Low	High	Low(55)	High (55)
Total (6 subj)							6 (11)	0
PNA			1		1		2 (4)	
Eso. Candidia.^			2				2 (4)	
Herpes Simplex^			1				1 (2)	
MTB			1				1 (2)	
Lymphoma*					1		1 (2)	
Wasting synd.*					1		1 (2)	
Isosporiasis*					1		1 (2)	

^ One subject with multiple AIDS defining illnesses; * one subject w/ multiple AIDS defining illnesses.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The number of subjects with any AEs was similar between the two dose groups and between the comparative age group.

Table 33: Adverse Events

Number of subjects with any AE	Age							
	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		Total =110	
	Low (n=10)	High (n=10)	Low (n=19)	High (n=19)	Low (n=26)	High (n=26)	Low (n=55)	High (n=55)
	8(80)	9 (90)	19 (100)	19 (100)	26(100)	25(96)	53(96)	53(96)

The most frequently system Organ Class (SOC) adverse events were similar to adults, with GI and Infection and Infestations being most common. The most frequent AEs (all causes and severity) were gastrointestinal, vomiting (38%), diarrhea (28%), and nausea (20%). Cough (31%) and pyrexia (31%) were also among the most frequently reported AEs.

Table 34: Number (%) of Subjects with AEs (all causes and severity)

	Age						Total	
	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		N= 115	
	Low	High	Low	High	Low	High	Low	High
Vomiting	4(40)	6(60)	6(32)	6(32)	8(31)	12(46)	18(33)	24(44)
Diarrhea	4(40)	3(30)	5 (26)	7 (37)	5 (19)	7 (27)	14(24)	17(31)
Nausea	1 (10)	1 (10)	2 (11)	4 (21)	7 (27)	7(27)	10(18)	12(23)
Abdominal pain	0	0	2 (11)	4(21)	6 (23)	2 (8)	8(15)	6 (11)
GGT	1(10)	1(10)	2(11)	3(16)	4 (15)	3 (12)	7(13)	7 (13)
Pneumonia	2(20)	4 (40)	1(5)	1(5)	2(8)	2(8)	5(9)	7(13)

Oral Candidiasis	0	0	2(11)	1(5)	5 (19)	2 (8)	7(13)	3(5)
Pyrexia	3 (30)	5 (50)	6 (32)	5 (26)	9 (35)	6 (23)	18(33)	16 (29)
Cough	1 (10)	4(40)	5 (26)	7 (37)	7 (27)	10 (39)	13(24)	21(38)
Otitis media	4(40)	3 (30)	1(5)	5(26)	2(8)	1(4)	7(13)	9(16)
headache	0	1 (10)	4 (21)	4(21)	5 (19)	2(11)	9 (16)	7(13)

7.4.2 Laboratory Findings

Chemistry

DAIDS Grade 2-4 laboratory adverse events are summarized in tables 35a and 35b. Increase in ALT (Grade 3 and/or 4) was reported more frequently in the high dose group (11% vs. 5%), particularly in the 12 to 18 years age group. The number of subjects with a grade 4 increase in GGT was also slightly higher in the high dose group (5% vs. 2%).

During the 48 weeks study period, 7 subjects (7%) experienced Grade 3/4 ALT increase. As observed during the 100 weeks study period, the proportion of patients with Grade 3/4 ALT elevation was higher in the high dose group 5 (9%) when compared to the low dose group 2(4%). Of note, only one subject (high dose group) had Grade 4 increase in ALT. The number of subjects with Grade 3 amylase elevation was also similar between the 48 weeks and 100 weeks study period (7% vs. 8%, respectively). Overall, during the 48 week period 8 subjects had Grade 3 increase in amylase; the proportion was higher in the high dose group 6 (11%) when compared to the low dose group 2(4%). No subject had Grade 4 amylase increase during the 48 week period. Table 34a summarizes the 100 week chemistry laboratory data.

When compared to the adult RESIST studies, the overall number of subjects with Grade 3 and/or 4 increase in ALT is similar (11% in adults vs. 8 % in pediatrics).

Table 35a: Chemistry Laboratory (during treatment)

	Age						Total	
Number of subjects with AEs	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		110	
	Low	High	Low	High	Low	High	Low	High
GGT								
G2-4	3(30)	2(20)	9(47)	6(32)	10(38)	5(10)	22(40)	13(24)
G3-4	1(10)	1(10)	3(16)	2(11)	3(12)	2(8)	7 (12)	5 (9)
G2	3(30)	2(20)	9(47)	6(32)	10(38)	5(10)	22(40)	13(24)
G3	1(10)	1(10)	3(16)	2(11)	3(12)	2(8)	7 (12)	5(9)
G4	0	1(10)	0	0	1(4)	2(8)	1 (2)	3(5)
T. Bilirubin (G2-4)	0	0	0	0	0	0	0	0
ALT								
G2-4	0	0	2(11)	4(40)	2(8)	5(19)	4(7)	9(16)
G3-4	0	0	2(11)	2(11)	1(4)	4(15)	3 (5)	6 (11)
G2		0	2(11)	4(21)	2(8)	4(15)	4(7)	8(15)

G3	0	0	2(11)	2(11)	1(4)	4(15)	3 (5)	6 (11)
G4	0	0	0	1(5)	0	1(4)	0	2 (4)
AST								
G2-4	0	0	2(11)	1(5)	1(4)	4(15)	3(5)	5 (9)
G3-4	0	0	0	0	0	0	0	0
G2	0	0	2(11)	1(5)	1(4)	4(15)	3(5)	5(9)
G3	0	0	0	0	0	0	0	0
G4	0	0	0	0	0	0	0	0
AMYLASE								
G2-4	4(40)	3(30)	7(37)	6(32)	6(23)	8(31)	17(31)	17(31)
G3-4	0	1(10)	2(11)	2(11)	2(8)	2(8)	4 (7)	5 (9)
G2	4(40)	3(30)	6(32)	6(32)	5(19)	8(31)	15(27)	17(31)
G3	0	1(10)	1(5)	2(11)	1(4)	2(8)	2(5)	5 (9)
G4	0	0	1(5)	0	1(4)	0	2(5)	0
LIPASE G2-4	0	0	0	0	0	0	0	0
CPK								
G2-4	1(10)	1(10)	1(5)	0	6(23)	7(27)	8 (15)	8 (15)
G3-4	1(10)	1(10)	1(5)	0	6(23)	7(27)	8 (15)	8 (15)
G2	0	0	0	0	0	0	0	0
G3	1(10)	1(10)	1(5)	0	6(23)	7(27)	8 (15)	8 (15)
G4	0	0	0	0	0	0	0	0

Table 35b: Chemistry Laboratory (during and post treatment)

	Age						Total	
Number of subjects with AEs	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		110	
	Low	High	Low	High	Low	High	Low	High
GGT								
G2-4	3(30)	2(20)	9(47)	6(32)	11(42)	5(19)	23 (42)	13 (24)
G3-4	1(10)	1(10)	3(16)	2(11)	3(12)	2(8)	7 (12)	5 (9)
G2	3(30)	2(20)	9(47)	6 (32)	11(42)	5(19)	23 (42)	13(24)
G3	1(10)	1(10)	3(16)	2(11)	3(12)	2(8)	7 (12)	5(9)
G4	0	1(10)	0	0	2(8)	2(8)	2 (3)	3(5)
T. Bilirubin								
G2-4	0	0	0	0	1(4)	1(4)	1(2)	1(2)
G3-4	0	0	0	0	1(4)	1(4)	1(2)	1(2)
G2	0	0	0	0	1(4)	0	1(2)	0
G3	0	0	0	0	1(4)	1(4)	1(1)	1(1)
G4	0	0	0	0	0	0	0	0
ALT								

G2-4	0	1(10)	2(11)	4(21)	3(16)	5(19)	5(9)	9(16)
G3-4	0	1(10)	2(11)	1(5)	1(4)	4(15)	3 (5)	6 (11)
G2	0	0	2(11)	4(21)	3(16)	4(15)	5(9)	8(15)
G3	0	1(10)	2(11)	2(11)	1(4)	4(15)	3 (5)	7 (13)
G4	0	0	0	1(5)	0	1(4)	0	2 (4)
AST								
G2-4		0	2(11)	1(5)	2(8)	4(15)	4(7)	5(9)
G3-4	0	0	0	0	0	0	0	0
G3	0	0	0	0	0	0	0	0
G4	0	0	0	0	0	0	0	0
AMYLASE								
G2-4	5(50)	3(30)	7(37)	7(37)	7(27)	8(31)	19(35)	18(33)
G3-4	0	2(20)	2(11)	2(11)	1(4)	2(8)	3 (5)	6 (11)
G2	5(50)	3(30)	6(32)	7(37)	6(23)	8(31)	17(31)	18(33)
G3	0	1(10)	1(5)	2(11)	1(4)	2(8)	2(5)	5 (9)
G4	0	0	1(5)	0	1(4)	0	2(5)	0
LIPASE (G2-4)								
G2-4	0	0	0	0	0	0	0	0
G3-4	0	0	0	0	0	0	0	0
CPK								
G2-4	1(10)	2(20)	1(5)	0	6(23)	7(27)	8 (15)	8 (15)
G3-4	1(10)	2(20)	1(5)	0	6(23)	7(27)	8 (15)	8 (15)
G2	0	0	0	0	0	0	0	0
G3	1(10)	1(10)	1(5)	0	6(23)	7(27)	8 (15)	8 (15)
G4	0	0	0	0	0	0	0	0

Coagulation and Platelet

Only one patient experienced DAIDS Grade 3 increase in PT. Most other AEs were grade 1 or 2.

Table 36: Coagulation parameters and platelet

	Age						Total	
	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		110	
	Low	High	Low	High	Low	High	Low	High
PTT	0	0	0	2(11)	0	0	0	2 (4)
G1	0	0	0	2(11)	0	0	0	2(4)
G2	0	0	0	0	0	0	0	0
G3	0	0	0	0	0	0	0	0
G4	0	0	0	0	0	0	0	0
PT	0	0	0	1(5)	0	0	0	1(2)

G1	0	0	0	1(5)	0	0	0	1(2)
G2	0	0	0	0	0	0	0	0
G3	0	0	0	1(5)	0	0	0	1(2)
G4	0	0	0	0	0	0	0	0
PLATELET	0	0	0	1(5)	1(4)	0	1(2)	1(2)
G1	0	0	0	0	0	0	0	0
G2	0	0	0	1(5)	1(4)	0	1(2)	1(2)
G3	0	0	0	0	0	0	0	0
G4	0	0	0	0	0	0	0	0

Hematology
Two subjects in the low dose group had DAIDS Grade 3 or 4 neutropenia. The remaining abnormalities were Grade 1 and/or 2. One of the subject (8 years old, white male) had neutropenia at the time the study drug was initiated and continued to have neutropenia when the dataset was locked. The subject continued with study drug. The other patient (15 years old, white male) developed neutropenia one day after starting treatment. After 50 days, neutropenia recovered. This subject discontinued treatment drug due to adverse event (neutropenia).

Table 37: Hematology

	Age						Total	
	2-6 (n=20)		7-11 (n=38)		12-18 (n=52)		110	
	Low	High	Low	High	Low	High	Low	High
WBC (<3.0)	1	0	11	2	27	3	39 (70)	5 (9)
Lymph % (<15.0)	0	1	0	2	3	3	4 (7)	6 (11)
Hgb (G3/4)	0	0	0	0	0	0	0	0

7.4.3 Vital Signs

Baseline vital signs were collected for all randomized subjects. Physical examinations and vital signs collection were performed at each study visit. These data were not provided for analysis. However, if any abnormalities were observed, they were recorded as adverse events and captured in the AEs datasets.

7.4.4 Electrocardiograms (ECGs)

Please refer to the original NDA review (Section 7.1.9)

7.4.5 Special Safety Studies

Freeze Study
This retrospective study selected baseline and serial stored frozen plasma samples from

Trial 1182.14 and the RESIST trials for evaluation of Vitamin K dependent coagulation factor levels. Serial plasma samples were selected for randomly chosen subjects in these trials for Vitamin K-dependent coagulation factor determination. The retrospective laboratory trial had two primary objectives:

1. To investigate whether there is an effect of the formulation of TPV/r (oral solution versus soft gel capsule) on Vitamin K-dependent coagulation factors in the pediatric Trial 1182.14.

2. To investigate whether there is a TPV/r effect on Vitamin K-dependent coagulation factors in comparison to an active PI control treatment in the RESIST trials.

Because of the observed effect of TPV/Vitamin E-TPGS on the levels of Vitamin K dependent coagulation factors in rats, this study focused on specific Vitamin K-dependent clotting factors (II, VII). Functional levels of Factors VII and II were also measured. To explore whether TPV/Vitamin E-TPGS has a more global effect on the synthesis of these clotting factors, Factor VII antigen levels and the ecarin clotting times were determined. Factor VII antigen provides an index of total Factor VII levels and measures both non-functional and functional forms. Likewise, the ecarin clotting time also measures both non-functional and functional forms of Factor II.

All eligible subjects from the oldest age group (12 to 18 years old) were selected for the sampling for the tipranavir oral solution (OS) group. Specifically, in the 12-18 year age group, 14 subjects using OS and 18 subjects using TPV capsules had samples selected for coagulation factor analyses. To achieve the overall target of 25 subjects per formulation, additional subjects from the middle age group (11 in 6 to <12 year age group using OS and 1 patient using capsules) were selected for coagulation factor analyses. No additional subjects received capsules in this group. Overall, 25 subjects using OS and 19 subjects using TPV capsules had samples included for coagulation factor analyses. Among these subjects, most used the TPV/r high dose: 56.0% (14 of 25) using the OS formulation and 73.7% (14 of 19) using the capsule formulation

Geometric mean on-treatment values were calculated for each of the Vitamin K-dependent coagulation factors (V, ECT II, PT, and aPTT). The percent change from baseline for these variables was calculated, and a t-test was applied.

Minor changes in coagulation factor levels and coagulation times were observed when comparing the OS formulation with capsules. Average on-treatment Factor II levels were decreased by 3.8% from baseline in children receiving the OS compared with an increase of 0.6% for capsules. Average on-treatment functional Factor VII levels were decreased by 4.1% from baseline for the OS compared with an increase of 3.4% for capsules. Factor V levels were unaffected. None of the changes were statistically significant or considered clinically important.

Coagulation times were shorter on-treatment relative to baseline in both treatment formulation groups. No subjects had PT or aPTT outside of the normal range at any time during the study except for one subject, who is also referred in the bleeding AEs section (7.4.2) and table 38.

This was a 9 year old subject who was randomized to the high dose group. Baseline PT and aPTT values for this patient were normal. At Week 48 of treatment, abnormal prolongations of coagulation times were reported through routine central laboratory testing. No actions were taken at that time in the clinical management of the patient with regard to this laboratory abnormality. More than one year later (Week 112 of study), the patient was noted to have bruising reportedly secondary to mild trauma and bruising on the arm reportedly secondary to insect bites. Ultimate investigation for the cause of prolongation of PT/PTT included speculation that the severe Vitamin K deficiency was due to partly malnutrition but could not be well characterized in the context of the post-study analyses and limited plasma samples.

7.4.6 Immunogenicity

Please refer to the original NDA (Section 7.1.10) for further detail. Tipranavir is a protease inhibitor and is not expected to have an immunogenic effect.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As discussed previously, the pharmacometrics team has done a formal analysis on exposure-safety relationship for tipranavir. The analysis of safety and exposure was focused on rash, bleeding and liver enzyme tests (ALT, AST, GGT) and alkaline phosphastase and bilirubin. No apparent relationship was shown between rash or bleeding and exposure, but liver enzymes seemed to increase as exposure increases. Liver enzymes were analyzed from adverse event as well as lab dataset. The proportion of subjects with ≥ grade 2 (ALT, AST, GGT) increased from 16% in the lowest quartile (median Cmin=14uM) to 53.8% in the highest quartile (median Cmin= 74uM).

7.5.2 Time Dependency for Adverse Events

7.5.3 Drug-Demographic Interactions

This sNDA evaluated use of tipranavir in the pediatric population. The study was stratified by age (2 to <6, 6 to <12, 12 to 18 years). Clearance of tipranavir appears to be highest in the youngest age group. Despite some pharmacokinetic profile difference between the youngest and older age groups, the overall safety profile was similar among the three age groups. In general, hepatic adverse events were most common in the oldest age group.

7.5.4 Drug-Disease Interactions

Tipranavir was not administered as a monotherapy. Therefore it is difficult to assess drug-disease interaction. Overall, similar to adults, administration of tipranavir in combination with low dose ritonavir and other ART appears to have decreased the HIV-1 viral load in the host. In addition, CD4+ cell count and percentage have improved across all age groups after initiation of treatment with tipranavir co administered with ritonavir in combination with other ART.

7.5.5 Drug-Drug Interactions

It is expected that the same types of drug interactions will be observed in pediatric subjects as those that have been observed in adult subjects taking tipranavir/ritonavir. Drug-Drug interactions are included in the label.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

The applicant conducted a mouse study to evaluate the carcinogenic potential of tipranavir with ritonavir co-administration. The carcinogenicity study was adequate, and the study was positive in male and female mice. The Non-Clinical Toxicology section of the label has been updated to reflect the results of the carcinogenicity study.

7.6.2 Human Reproduction and Pregnancy Data

Tipranavir is classified as category C. Please refer to Section 7.1.14 of the original review for additional details. There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1 infection. The current recommendation is tipranavir/ritonavir should be used during pregnancy only if the benefits outweigh the risks to the fetus. To monitor fetal outcomes of pregnant women exposed to tipranavir, healthcare providers are encouraged to register subjects with the Antiretroviral Pregnancy Registry.

7.6.3 Pediatrics and Effect on Growth

The Applicant did not conduct formal assessments on the effects of tipranavir on growth and development. No specific adverse event profile has been identified which would have major impact on growth and development of pediatric subjects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no withdrawal or abuse potential with tipranavir. There is no information on overdoses in pediatric subjects.

7.7 Additional Submissions

Not Applicable

8 Postmarketing Experience

Spontaneous reports were available for 6 children. Most children had concomitant medications while reporting the adverse events. These cases consisted of the following:

• "An 18-year-old HIV-infected male who experienced increased liver enzymes, diarrhea, cough, and wheezing after taking TPV/r capsules (concomitant medications included ENF and EFV);
• An 18-year-old mentally deranged male who reported nausea, vomiting, and stomach ache after taking TPV/r capsules, which were obtained after breaking into a drug supply;
• An 18-year-old HIV-infected female who experienced mental status changes and inability to swallow TPV/r capsules after taking TPV/r capsules (concomitant medications included ENF, 3TC, ZDV, and TDF);
•A 13-year-old HIV-infected male who experienced nausea and localized skin reaction after taking ENF while receiving therapy with TPV/r (concomitant medications included 3TC, ZDV, and TDF);
•A 16-year-old HIV-infected male who experienced vomiting, abdominal pain, hepatitis, and icterus while on treatment with TPV/r (concomitant medications included Kaletra, Zerit, Epivir and Truvada);
• A 12-year-old male who experienced rash while receiving TPV/r; no data were provided regarding HIV-infection status for this patient."

Adverse Event Reporting System (AERS)

Three cases have been captured using the passive FDA adverse event monitoring system AERS.

- A 16 year old male enrolled in an Open-Label Safety Study (BI 1182.58) to evaluate the safety of tipranavir. Concomitant medications included Fuzeon, Trizivir and Videx. Eight months after starting study drug, the patient developed an acute event with nystagmus, photophobia and strabismus. After 8-10 hours, the event resolved spontaneously. No action was taken regarding study drug.
- One report of pregnancy with delivery of live infant.
- A 16 year old male with HIV/hepatitis C co-infection since birth who commenced Truvada, Norvir, Kaletra and tipranavir. The patient developed elevated ALT (1488 IU/L) AST (540 IU/L), GGT (227 IU/L), bilirubin (139 uM) and alkaline phosphatase (266 IU/L) followed by dark urine, vomiting and cephalgia. All ART were discontinued and patient's laboratory values began to slowly improve.

9 Appendices

9.1 Literature Review/References

1. NDA (Traditional)
   sNDA 21-814
   SN 003
   SC SE7
   Reviewer: Kirk M. Chan-Tack, MD
   Approved: October 04, 2007

2. NDA (Accelerated)
   NDA 21-814
   SN 000
   SC N
   Reviewer: Andrea N. James, MD
   Approved: 6/22/2005

3. Pharmacology-Toxicology Review
   NDA 21-814
   IND 51979
   Dr. Anita Bigger, PhD

4. TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.— (i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric subjects, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric subjects, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

5. Pediatric Written Request (PWR)
See Section 9.4 (Attachment 1)

6. Postmarketing Commitment (PMC) Pediatric Research Equity Act (PREA)

Commitment Number 3

Commitment Required Under	Pediatric Research Equity Act
Original Projected Completion Date	06/30/2006
Commitment Description	Assess pharmacokinetics, safety and antiviral activity in two alternative doses of either tipranavir/ritonavir liquid formulation or capsules in addition to safety, in antiretroviral naive and experienced children and adolescents between 2 and 18 years of age.
Current Status	submitted

9.2 Labeling Recommendations

Pages 52 through 53 redacted for the following reasons:
- -

9.3 Advisory Committee Meeting

Not Applicable

9.4 Tables and Attachments

Table 38: Tabular listing of Bleeding AEs

HIGH DOSE

AGE (Y)	Diagnosis	Onest		Dur. (D)	Drug Related		Serious	Grade	Dose	Outcome
*7.87	Ear haemorrhage	362		85	N			Mild	Continued OS	Recovered
9.54*	Contusion	782		17	N		Disabl	Severe	Interrupted OS	Recovered
	Coag time prolonged	783		19	N		Disabl	Severe	Interrupted	Not yet Recovered
9.80	Epistaxis **(D)**	280			N			Mild	Continued OS	Recovered
11.92	Epistaxis	522		186	N	No		Mild	Continued OS	Recovered
12.44	Haematochezia	254		16	N			Mild	Continued CAP	Recovered
12.75	Contusion	597			N			Mild	Continued OS	Recovered
14.98	Gingival bleeding	85	1	54	Y	No	No	Mild	Continued CAP	Recovered
	Gingival bleeding	251		30	N	No	No	Mild	Continued	Recovered
	Gingival bleeding	435		380	Y	No	No	Mild	Continued	
16.56	Dysmenorrhoea	60	1	6	N	No		Moderate	Continued CAP	Recovered

* event occurred post 48 week study period
** sampled for freeze study

LOW DOSE

AGE	Diagnosis	Onset		Dur.	Drug Related		Serious	Grade	Dose	Outcome
8.64	Epistaxis	63		24	N		No	Mild	Continued OS	Recovered
	Epistaxis	118		37	N			Mild	Continued	Recovered
	Epistaxis	169		17	N			Mild	Continued	Recovered
	Haematoma	363		55	N			Mild	Continued	Recovered
15.10	Menorrhagia	336		30	Y		No	Mild	Continued CAP	Recovered
	Haematoma	334		28	N	No		Mild	Continued	Recovered
15.51	GI haemorrhage	809			N	No	Fatal	Severe	NA OS	Fatal
15.99	Thrombocytopenia	205		620	N	No	Req hosp	Severe	Continued OS	Not Yet Recovered
16.08	Epistaxis	213			N			Mild	Continued OS	Recovered
	Haematoma	589		31	N	No		Mild	Continued	Recovered
16.89	Epistaxis	93	2	1	N			Mild	Continued OS	Recovered

* event occurred post 48 week study period

4		No
		No
		No

Attachment 1: Pediatric Written Request

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 51,979

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Charles Mazzarella
Senior Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Mr. Mazzarella:

Reference is made to your correspondence dated August 31, 2006 requesting changes to FDA's Written Request for pediatric studies for tipranavir. We have reviewed your questions and we are amending the Written Request to:

• extend the timeframe for submitting study reports

• modify the sections "Type of studies" and "Age groups in which studies will be performed"

For clarity, the full text of the Written Request, as amended, follows.

Type of study:
Multiple-dose pharmacokinetic, safety, and activity study of tipranavir in combination with low dose ritonavir together with other antiretroviral agents in HIV-infected treatment-experienced pediatric patients.

The objective of this study will be to determine the pharmacokinetic and safety profile of tipranavir across the age range studied, identify an appropriate dose for use in HIV-infected treatment experienced pediatric patients, and evaluate the activity of this dose (or doses) in treatment.

Indication to be studied:
Treatment of HIV-1 infection.

Age group in which study will be performed:
HIV-infected treatment-experienced pediatric patients from 2 to 18 years.

Drug Information
• Dosage form: age-appropriate formulation
• Route of administration: oral
• Regimen: to be determined by development program

Use an age-appropriate formulation in the study described above. If the study you conduct in response to this Written Request demonstrates this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

Development of a commercially-marketable formulation is preferable. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients acceptable to the Agency. If you conduct the requested study using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the study should be characterized, and if necessary, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug **specific safety concerns:**
Based on available toxicity information with your product, please provide safety data including assessment of gastrointestinal symptoms, rash (including Stevens-Johnson syndrome, elevated liver transaminase levels, metabolic disturbances, intracranial and other bleeding disorders, and any other parameters pertinent to use in the pediatric population.

Safety of tipranavir should be studied in an adequate number of pediatric patients to characterize adverse events across the age range. Approximately 100 patients with at least 24 weeks safety data is required.

Statistical information, including power of study and statistical assessments:
Descriptive analyses of multiple-dose pharmacokinetic, safety, and activity data in HIV-infected pediatric patients.

A minimum number of pediatric patients (as stated below) should complete the pharmacokinetic studies conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

2 years to < 6 years: 12

6 years to < 12 years: 8

12 years to 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients must be approximately evenly distributed across the age range studied.

Study Endpoints:

Pharmacokinetics
Parameters such as Cmax, Cmin, Tmax, t1/2, AUC and apparent oral clearance.

Safety and tolerability
HIV-infected pediatric patients should be followed for safety for a minimum of 24 weeks at the recommended dose or any higher doses studied during pediatric development. In addition, please also submit plans for long-term safety in HIV-infected pediatric patients who have received tipranavir.

Activity
Assessment of changes in plasma HIV RNA levels and CD4 cell counts.

Resistance
Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving tipranavir, particularly from those who experience loss of virologic response.

Labeling that may result from the study:
Information regarding dosing, safety, and activity in HIV-infected pediatric population.

Format of reports to be submitted:
You must submit a full study report not previously submitted to the Agency addressing the issues outlined in this request with full analyses, assessment, and interpretation. In addition, the report is to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity one of the following designations should be used: Hispanic/Latino or not Hispanic/Latino.

Timeframe for submitting reports of the studies:
Report of the above study must be submitted to the Agency on or before December 31, 2007. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:
As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this

Written Request you must notify the Agency of your intent to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, Dissemination of Pediatric Information, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. The type of response to the Written Request (complete or partial);
2. The status of the supplement (withdrawn after the supplement has been filed or pending);
3. The action taken (i.e., approval, approvable, not approvable); or
4. The exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability. If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in

the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, please contact Jaewon Hong, Pharm.D., Regulatory Project Manager, at (301)796-2013.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yodit Belew
6/23/2008 05:26:47 PM
MEDICAL OFFICER

Kimberly Struble
6/23/2008 05:33:01 PM
MEDICAL OFFICER