CLINICAL REVIEW

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Established Name	Nevirapine
(Proposed) Trade Name	VIRAMUNE
Therapeutic Class	Non-nucleoside reverse transcriptase
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Priority Designation	P
Formulation	Oral Tablet Oral Suspension
Dosing Regimen	BID
Indication	Treatment of HIV-1 Infection
Intended Population	Pediatric population---- days - <16 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Viramune is currently approved for use in children 2 months and older with HIV-1 infection. This supplement to NDAs 20-636 and 20-933 contains analyses of data from multiple pediatric clinical trials in support of broadening the indication for use of Viramune (nevirapine) in pediatric patients to 15 days through 16 years of age. In addition, data from Study 1100.1368, a Phase 2 study, was submitted in support of a body surface area (BSA) based calculation as a method to determine pediatric doses.

This reviewer recommends the approval of this supplemental NDA (sNDA). No deficiencies were identified in this sNDA that would preclude approval. Adequate data to support identification of a dose for pediatric patients from 15 days to 2 months was submitted with the supplement. In addition, BSA-based dosing of nevirapine, in combination with 3TC and AZT, had a safety profile similar to that observed with weight-based dosing and showed activity in reducing HIV-1 viral load and increasing CD4 cell counts over the 48-week study period. Because BSA-based dosing displayed greater antiviral activity than weight-based dosing in Study 1100.1368, as reflected by greater numbers of subjects achieving and maintaining viral loads < 400 copies/mL and because weight-based dosing has inconsistent lead-in dosing strategies, BSA-based calculation of pediatric doses replaced the previous weight-based calculation in the nevirapine package insert.

When nevirapine was studied for initial pediatric approval (i.e. multiple dose study (BI 1100.882; ACTG 180)), nevirapine suspension or tablets (240 or 400mg/m^2/day were administered to 37 patients (age range 2 months to 15 years). The majority of patients received 120mg/m^2/day for 4 weeks followed by 120mg/m^2/BID (patients >9 years) or 200mg/m^2/BID (patients <9 years). The dose increase for the younger age group was due to increased apparent clearance (when normalized by body weight) of nevirapine in the younger age group. Upon approval, the dosing recommendation was converted to mg/kg for ease of calculation. The pharmacokinetic analysis suggested that either approach could be used in pediatric patients to mimic the nevirapine average concentration in adults taking 200 mg BID.

As stated above, data from one Phase 2, open-label, randomized study was submitted to support inclusion of BSA-based dosing calculation in the nevirapine package insert. In this study, children were stratified according to age (2 months to <2 years, 2 - <6 years, 6 - <12 years, and 12 - 18 years) and randomized to one of two doses of nevirapine. The study was conducted to provide additional activity data for nevirapine when used in combination with other ARV drugs in children with HIV-1 infection.

Two dosing strategies for nevirapine were evaluated in this study. Similar number of patients received either the dose calculated by body weight (BW) (mg/kg, n=57), or the dose calculated by body surface area (BSA) (mg/m^2, n=66). The dose administered for the BW group is the currently approved dose (4 mg/kg/day for the first 14 days followed by 4mg/kg bid or 7mg/kg

bid, depending on age). The dose administered for the BSA group was 150mg/m^2/day for the first 14 days followed by 150mg/m^2/bid, regardless of age. The proportion of patients who responded to therapy was higher in the BSA group (56%) compared to BW group (42%). The difference was largest in the youngest age group, 3 months to <2 years, where 56% of the patients in the BSA dose group had virologic response as compared to 29% of patients in the BW group. Importantly, the difference observed in this age group may be due to dosing differences between the BW and the BSA dosing regimen in the first 14 days of therapy. The currently approved nevirapine pediatric weight-based (BW) dosing regimen is based on age:

- Children younger than 8 years: 4 mg/kg once daily for the first 14 days followed by 7mg/kg twice daily
- Children 8 years and older: 4mg/kg once daily for the first 14 days followed by 4mg/kg twice daily

The dose given during the first 14 days for the younger age groups is 25% of the maintenance dose. In contrast, with the 150mg/m^2 BSA dosing regimen, all subjects received 50% of the maintenance dose during the first 14 days. This apparent lower lead-in dose in the BW dosing regimen in subjects less than 8 years of age may have contributed to the decreased viral response, particularly because the youngest age group tends to have the highest viral load and the highest apparent clearance. No PK samples were available from the lead-in dose period to compare the exposures (troughs) between the two dosing regimens.

In addition, in the BW group, as subjects reach their 8th birthday, a dose reduction is required- from 7mg/kg BID to 4mg/kg BID. In contrast, no dose adjustment is required when nevirapine is administered using BSA-based calculation; all subjects, regardless of age, receive 150mg/m^2 BID. This may have impacted the proportion of subjects (6 to <12 years) who responded to treatment (52% for BSA vs. 38% for BW). However, troughs were similar between the two dosing groups during the maintenance period.

The Sponsor demonstrated an acceptable safety profile for nevirapine in combination with other antiretroviral drugs. While adverse events (AEs) were reported by most (98%), fewer patients (31%) experienced serious adverse events and significantly fewer patients (11%) had AEs considered possibly drug related or discontinued (8%) study drug due to AEs. 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 adverse events and adverse events leading to discontinuation were similar between the two groups. Serious and severe adverse events were reported more frequently in the BW group.

Based on current information about nevirapine-related adverse events, rash and hepatic AEs were submission specific safety concerns. Both are described in a box warning in the current nevirapine label. In addition, neutropenia was reported as one of the common AEs observed in previous pediatric studies. In the submitted pediatric study, rash and neutropenia were reported in more subjects in the BSA group [45% BSA vs. 30% BW for rash (all causes and severity); 12% BSA vs. 5% BW for neutropenia]; however, the proportion of patients with hepatotoxicity was slightly higher in the BW group (5%) compared to BSA group (0%).

To support dosing in pediatric patients less than 2 months of age, a study review was submitted on pharmacokinetic and safety of nevirapine in this age group. This summary contained a pediatric study conducted by Pediatrics AIDS Clinical Trial Group (PACTG) to produce data for pediatric population <2 months of age. This study submission contained pharmacokinetic (PK) datasets for review by the FDA. Safety information in a summary format was submitted. No new drug-related safety issues were identified from this study summary. Neutropenia was the most common adverse event reported.

Similar to many other pediatric studies that 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. The number of subjects in each age group is also small, making interpretation of the results difficult. Therefore, study results should be interpreted with caution.

1.2 Risk Benefit Assessment

Despite the increased incidence of rash and neutropenia observed with the BSA dosing regimen, I recommend approval of nevirapine 150mg/m^2 BID and support replacement of the current BW dosing recommendation to that of a BSA dosing regimen in the label. With the exception of one patient, none of the neutropenia events were considered serious or led to discontinuation. Notably, AZT, known to cause bone marrow toxicity, was part of the background therapy. Therefore, the true contribution of nevirapine to neutropenia cannot be ascertained. While the proportion of patients with rash was higher in the BSA group, the proportion of patients who discontinued due to rash was similar between the two groups [2(3%) subjects in BSA vs. 2(4%) subjects in BW]. For these 4 subjects, the rash occurred early in the course of therapy (< 4 weeks) and resolved upon nevirapine discontinuation. Furthermore, the proportion of subjects with severe and serious AEs was higher in the BW group and hepatotoxicity was observed more frequently in the BW group.

In totality, an increased risk for adverse events does not appear to be associated with the BSA dosing regimen. Given the marginal safety differences observed between the two dosing regimens, the potentially increased antiviral activity observed with BSA dosing should be taken into consideration and the label should be changed to recommend BSA dosing calculation. The cause for the apparent increase in activity with the use of BSA dosing regimen is not clear. The source for the disparity may be related to underperformance of the BW dosing regimen during the lead in period due to lower dose received by subjects <8 year old when compared to the same age group from the BSA dosing group. Unfortunately, no PK data from the lead-in dosing period is available for confirmation. In addition, the dose reduction in the BW dosing regimen when subjects graduate to their 8^{th} birthday may have contributed to the lower efficacy seen in that age group. Revising the dose recommendation to BSA dosing regimen may improve nevirapine activity without increasing safety risks.

Currently only 2 non-nucleoside reverse transcriptase inhibitors (NNRTI), including nevirapine, are available for use in pediatric patients. By recommending the BSA dosing regimen, the benefit

of nevirapine can be maximized. Furthermore, HIV-1 infection is a life threatening disease when left untreated due to limited options or suboptimal therapy.

HIV-1 virus has the potential for developing class resistance with single amino acid mutations. For example, mutations at codon 103 confer high level resistance to all the available NNRTIs. Cross-resistance among three of the four currently available NNRTIs is almost complete and the NNRTI currently available for adults who have NNRTI resistance mutations is not available for pediatric patients. This risk for development of cross-resistance argues for a dosing regimen that will minimize any potential under-exposure which will likely lead to development of resistance.

1.3 Recommendations for Postmarketing Risk Management Activities

No additional postmarketing risk management activities are planned.

1.4 Recommendations for other Post Marketing Study Commitments

No additional post marketing study commitments will be sought.

2 Introduction and Regulatory Background

2.1 Product Information

Established name:	Nevirapine
Trade name:	VIRAMUNE
Chemical:	$C_{15}H_{14}N_4O$
Class:	non-nucleoside reverse transcriptase inhibitor
Proposed indication:	Treatment of HIV-1 infection in pediatric population 15 days to <16 years old

Dose and regimen (Pediatric):

- By Body Surface Area (BSA) for pediatric patients 15 days to <16 years old
  - First 14 days: 150mg/m^2 orally once daily, not to exceed adult maximum of 200mg once daily.
  - Maintenance: 150mg/m^2 orally twice daily, not to exceed adult maximum of 200mg BID.

Dosage form:	200 mg tablet 50mg/5ml suspension

Nevirapine is a non-nucleoside reverse transcriptase inhibitor and structurally is a member of the dipyridodiazepinone chemical class of compound. Nevirapine was first approved in 1996 for treatment of HIV-1 adults and in 1998 for treatment of HIV-1 infection for children 2 months of to 16 years of age.

2.2 Tables of Currently Available Treatments for Proposed Indications

Non-nucleoside reverse transcriptase inhibitors have become the mainstay of highly active antiretroviral therapy (HAART) when given in combination with nucleoside reverse transcriptase inhibitors (NRTIs). Nevirapine in combination with 2 NRTIs is highly recommended as initial NNRTI based HAART for patients less than 3 years of age. 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®

- The following ARVs are approved for use in children < 2 months of age: 3TC (all pediatric patients), D4T (all pediatric patients), AZT (all pediatric patients), ddI (2 weeks of age and older) ritonavir (1 month of age and older)

2.3 Availability of Proposed Active Ingredient in the United States

Nevirapine is currently marketed in the United States under the trade name Viramune. It is approved for use in children ≥ 2 months of age and is available both in suspension and tablet formulation.

2.4 Important Safety Issues with Consideration to Related Drugs

General safety issues associated with NNRTI is skin rash. In addition, nevirapine is associated with hepatitis and/or elevated hepatic transaminases. Section 7 further discusses the adverse events associated with nevirapine when administered to a pediatric population.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Nevirapine was first approved for treatment of adults infected with HIV-1 in 1996, under accelerated approval. The submission for traditional approval (1997) was not granted due to inadequate information on clinical endpoints presented in the trials; approval was granted at a later date. Supplements to NDAs 20-636 and 20-933 were submitted in 1998 for indication of treatment of HIV-1 infection in children. The applicant submitted results from 3 pediatric trials of nevirapine [namely 1100.882 and 892 (ACTG 180) and 1100.882 (ACTG 245)]. Safety and pharmacokinetic analyses were the primary focus of the review, with minimal analyses on the activity of nevirapine in pediatric patients.

At the time of the pediatric NDA approval, among the postmarketing commitments (PMC) were to provide executive summary of study 245 (1100.245):

- "The efficacy of the double- and triple-drug regimen of nevirapine as measured by changes of surrogate markers over 48 weeks"

This requirement has already been met.

An additional PMC (under Pediatric Research Equity Act, PREA) issued at a later date, required

- "Information to determine the appropriate dosage of VIRAMUNE for chronic treatment of neonates and infants younger than 2 months of age"

The current submission fulfills the PMC requirements as stated above.

A request was also issued by the Division in July of 1998 to provide further efficacy data on use of nevirapine in pediatric patients 2 months and older. This request was not tied to a PMC or PREA. The current submission provides the additional efficacy data which was requested by the Division.

Multiple Pediatric Written Requests (PWRs) had been issued to BI. However, the terms of the Written Requests were not met on their respective due dates and thus exclusivity was not granted.

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Sponsor states that studies were carried out in accordance with the provisions presented in the Declaration of Helsinki. All data submitted were accessible and with good quality.

3.2 Compliance with Good Clinical Practices

The Sponsor states that studies were carried out in accordance with the provisions presented in the Declaration of Helsinki and its amendments and in accordance with International Harmonized Tripartite (ICH) guidelines for GCP.

3.3 Financial Disclosures

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new information was submitted with this sNDA.

4.2 Clinical Microbiology

No new information was submitted with this sNDA for study 1100.1368.

4.3 Preclinical Pharmacology/Toxicology

No new information was submitted with this sNDA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Nevirapine is a potent non-nucleoside reverse transcriptase inhibitor of HIV-1. The NNRTIs interfere with the function of the viral reverse transcriptase enzyme by binding to regions outside the active site and causing conformational changes that render the enzyme inactive.

4.4.2 Pharmacodynamics

It is not ethical to administer nevirapine as a monotherapy in adults or pediatric patients. High level resistance develops rapidly when non-nucleoside reverse transcriptase inhibitors are administered alone. Nevirapine in combination with other antiretroviral drugs was used during the submitted trial. It is therefore, difficult to determine the absolute contribution of nevirapine to changes in HIV RNA. However, it is known from numerous past trials comparing triple therapy with dual nucleoside therapy that very few if any patients achieve and maintain undetectable HIV-1 RNA on dual nucleoside therapy alone. In the pediatric study from this application, a substantial proportion of patients on nevirapine and dual nucleoside are able to maintain an undetectable HIV-RNA which can be attributed to the addition of nevirapine.

No formal analysis of nevirapine exposure and virologic response was done in this submission.

4.4.3 Pharmacokinetics

Please refer to Dr. Derek Zhang's Clinical Pharmacology review of this sNDA. Briefly, Study U06-3417 was submitted as part of this sNDA. U06-3417 is a study report on pharmacokinetic data analysis among pediatric patients. Data was derived from the following sources: 1) five Pediatric AIDS Clinical Trials Group (PACTG) protocols (245, 356, 366, 377, and 403) comprising 495 subjects aged < 1 month to 19 years, and 2) study BI 1100.1368, the 48-week pediatric safety and efficacy trial conducted in South Africa, which contributed pharmacokinetic data on 104 HIV-infected treatment naïve subjects aged 3 months to 16 years.

Pharmacokinetic exposure in HIV-infected children was assessed by modeling plasma nevirapine concentrations obtained following dosing using either body surface area and body weight methods.

The calculated dose of 150mg/m^2 was expected to produce an average steady state concentration of 5.3 mcg/ml in children of all ages, similar to the 4-6 mcg/ml seen in adults dosed at 200 mg BID. This pharmacokinetic study found that either dosing method for nevirapine suspension produced the desired result of predictable plasma nevirapine concentrations at steady state.

5 Sources of Clinical Data

This submission contains data from a new uncontrolled, randomized pediatric study, Study 1100.1368. The study was conducted by the Sponsor and utilized 4 participating sites in South Africa. In addition, Study U06-3417 contains a robust pharmacokinetic review of data obtained from multiple PACTG trials and Study 1100.1368. Finally, a study summary report was submitted for subset of subjects from study U06-3417, containing safety data on pediatric subjects < 3 months of age who received nevirapine as part of their HAART regimen. Specifically, this was PACTG Study 356 (BI 1100.1222)

This submission contains electronic materials documenting the study results and BI's conclusions regarding Study 1100.1368, 48-Week Report. 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 were also submitted.

5.1 Tables of Clinical Studies

Table 2 summarizes the studies included in this review.

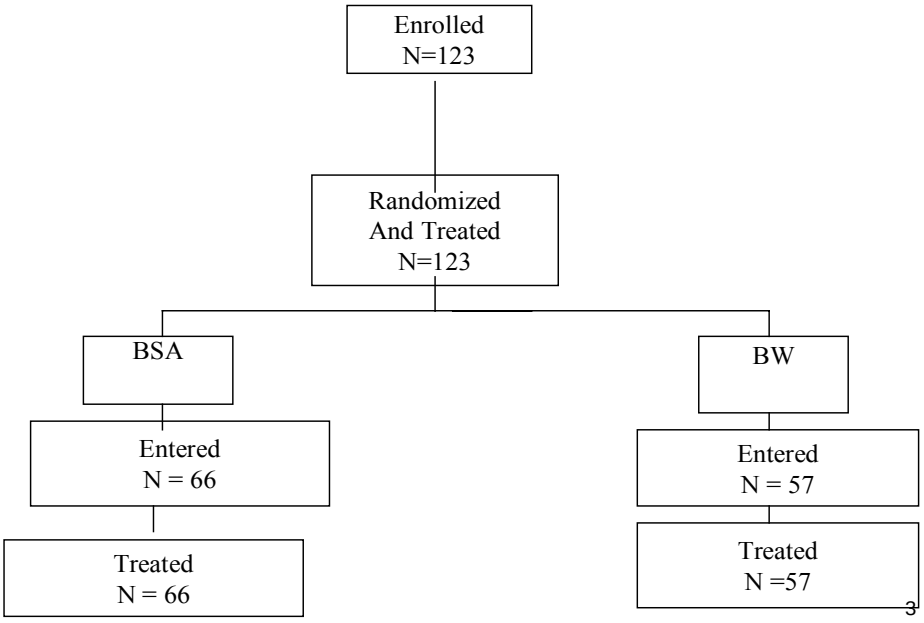
Table 2: Studies conducted in support of this submission

Study Name	Type of Study	Number of Subjects Enrolled	Number of subjects with ≥ 24 week data
1100.1368	A Phase 2 randomized open-label pediatric study*	123	105
1100.1222	Executive summary of safety on pediatric subjects <3 months of age	36	N/A
U06-3417	Pharmacokinetic study**	604	N/A

* See Figure 1

** Study U06-3417 contains a robust pharmacokinetic review of data obtained from multiple PACTG trials

Figure 1: Patients Disposition



5.2 Review Strategy

Study 1100.1368 was reviewed for safety, tolerability, pharmacokinetics and efficacy. The Sponsor's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. As part of this review, I evaluated study design, patient demographics, adverse events and laboratory safety monitoring data and reviewed the efficacy and safety results using JMP Statistical software.

In addition to Study 1100.1368, a review of the safety summary from 1100.1222 on subjects <3 months of age is 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 1100.1368 is the pivotal study conducted in pediatric subjects ≥ 3 months of age. This study supports the recommendation of the new BSA dosing regimen for nevirapine in pediatric patients infected with HIV-1. Pharmacokinetic data from Study U06-3417 supports the dosing recommendation. In addition, a safety summary provided for subjects <3 months of age, along with the pharmacokinetic data from study 1100.1222, supports extension of use of nevirapine in pediatric patients younger than 2 months of age.

Study 1100.1368: A Phase 2 study of safety, tolerability, and pharmacokinetics of nevirapine in HIV-1 infected treatment-naive children. This is a single country, multi-center, open-label, randomized study. The primary objective was to determine the pharmacokinetics, safety and tolerability profile of nevirapine oral suspension. Evaluation of PK data from previous pediatric study (ACTG 245) suggested that a dose based on body surface area (BSA) rather than body weight might be a better regimen in that it will mimic more closely the adult concentration. Previous BSA dosing studied includes a 120mg/m^2 BID, which was anticipated to result in an average exposure of 4.3 mcg/ml, a level marginally close to the targeted adult level (4-6 mcg/ml). A dose of 150 mg/m^2 was therefore selected for further investigation.

Two dosing regimens were used during the study. One group (n=57) received study drug based on the currently approved dosing calculation regimen: 4 or 7 mg/kg BID after 4 mg/kg/day has been administered for 14 days. The second group was dosed based on body surface area calculation: 150mg/m^2 BID after 150mg/m^2 QD has been administered for 14 days. Children were stratified according to their age into four cohorts (3 months to <2, 2 to <7 years, 7 to <12 years, and 12 to 16 years), and randomized to one of two group.

M.O. Comment: The age group stratification was slightly modified by this reviewer during analysis of the data: 3 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to 16 years.

The study design incorporated pharmacokinetic (PK) endpoints. An intensive pharmacokinetic (PK) sampling was performed on a subset of subjects (n=33) at Day 28. Additional non-intensive PK data was gathered on 24 subjects from BSA group and 47 subjects from BW group.

Additional Studies: Extensive PK data was submitted. Data was contributed from Study 1100.1368 as well as from 5 PACTG pediatric trials (under Study U06-3417). Safety summary was also submitted for subset of subjects (<3 months old) from the PACTG trial (PACTG 356, BI 1100.1222).

6 Review of Efficacy

Efficacy Summary

Study 1100.1368 was an open-label, randomized study. Treatment-naïve subjects (with exception of 4 treatment experienced) were stratified according to age (3 months to <2 years, 2 to <6 years, 6 to <12 years and 12 to 16 years) and randomized to one of two doses of nevirapine with AZT and 3TC as background ARV therapy.

Analysis of the PK data on 33 subjects on Day 28 showed that the trough concentration were similar between the two groups.

Nevirapine oral suspension exhibited good antiretroviral activity when used in combination with AZT and 3TC over the 48 weeks of the study period. Overall, 48% of study subjects achieved and sustained an HIV RNA level < 400 copies/mL. The overall treatment response was higher in the BSA dose group when compared to the BW dose group (56% vs. 42%). The difference is even greater when comparing proportion of subjects with viral load < 400 copies/mL at 48 weeks in the youngest age group (56% in BSA group vs. 29% in the BW group). This may be explained by the following reasons: 1) this age group had highest baseline viral load and, 2) subjects in the BW group received a lower dose during the first 14 days when compared to the BSA group and those who received a higher dose likely responded better . In addition, when comparing the lead in dose to the maintenance dose, subjects in the BW group received 25% of their maintenance dose while subjects in the BSA group received 50% of their maintenance dose. This dosing difference may have decreased the effectiveness of BW dosing among some patients.

Similar to the <2 years old group, the proportion of subjects in the 6 to <12 years group who responded to treatment was higher in the BSA group. The lower treatment response in the BW group may be due to abrupt dose reduction from 7mg/kg to 4mg/kg when subjects turn 8 years old. The 2 to <6 age group had similar proportion of subjects in each dosing group who responded to treatment. No subjects aged 12- 16 were enrolled in the BW dosing group. Table 3 summarizer treatment responses by dose group and age.

Importantly, this study was not designed for formal statistical analysis nor was it powered for subgroup analysis. Due to the small number of subjects in each age group, any small difference between groups may lead to a large percentage difference. Therefore, results should be interpreted with caution.

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 3: Proportion of subjects with HIV RNA < 400 copies/mL (week 48)

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
Proportion of subjects with virologic Response	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
	9(56)	5(29)	12(63)	10(63)	13(52)	9(38)	3(50)		37(56)	24(42)

6.1 Indication

This supplement broadens the VIRAMUNE indication for combination antiretroviral treatment to include HIV-1 infected pediatric patients 15 days old to <16 years old. This indication (which was already approved for patients >2 months of age) is based on analyses of PK data and review of safety summary from PACTG 356 study, also known as BI 1100.1222.

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6.1.1 Methods

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)
- Proportion of subjects who are treatment failures. Treatment failure is defined as:
  - Never achieved VL <400
  - Discontinued prior to Visit 12 (Week 48) for any reason
  - After achieving VL<400, have 2 consecutive VL>400
  - Last recorded visit is the only visit with VL <400 (i.e. not confirmed)
  - Visit 12 with VL > 400 despite previously considered a responder

Efficacy data were evaluated at 48 week time point. The analysis compared treatment response between the two dose groups as well as among the 4 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 missing efficacy parameter value (i.e. viral load < 400c/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, 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 nevirapine dose groups. There were 49% male, 81% black, and 19 % white. Table 4 summarizes the demographics.

Table 4: Demographics

	BSA	BW	Total
Age			123
<2	16	17	33
2-<6	19	16	35
6<12	25	24	49
12-16	6	0	9
Gender			
male	27	33	60
female	39	24	63

Baseline HIV Characteristics

Overall, the median baseline HIV RNA count was 5.45 (range 3.33 to 7.55) log10 copies/mL, while CD4 counts and percentage were 527 (range 37 to 2279) cells/mm^3 and 24%, respectively. Overall, 96% of subjects had no prior history of ART. These values were comparable between the two treatment groups.

Table 5a: Baseline HIV characteristics

	BSA	BW	Total
Previous ART experience	1	4	5
Baseline HIV RNA log10 c/mL			
median	5.38	5.69	5.45
mean	5.37	5.53	
range	3.33-7.55	3.96-7.23	3.33-7.55
Baseline CD4+			
Median	537	525	527
Mean	639	602	619
Range	37-2279	70-2162	37-2279

Table 5b: Baseline viral load by dose

	BSA	BW	Total
N	66	56	122
Mean	1,211,497	1,593,100	1,391,920
Median	193,000	439,000	313,000
Min	898	1,500	898
Max	34,400,000	33,000,000	34,400,000

Baseline viral load was the highest in the youngest age group and lowest in two middle age groups (2-<6 and 6 to <12 years). Vertical transmission was the most common cause for acquisition of HIV infection. Table 5c summarizes the findings.

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)	
	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=15)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0
mean	3,541,343	4,127,352	232,963	539,913	471,284	456,246	1,181,486	
median	750,000	688,000	133,000	507,000	155,000	456,246	49,150	
min	45,500	135,000	898	27,700	13,500	224,100	9,140	
max	34,400,000	33,000,000	750,000	1,320,000	2,860,000	2,290,000	6,790,000	

Table 5c: Baseline viral load by age group and dose

Previous Antiretroviral Treatment History

There were only 5 subjects (4%) with previous ARV treatment history. The protocol allowed for subjects to enroll if previous ARV treatment was for prevention of maternal-to-child-transmission.

Baseline HIV Resistance

No resistance testing data was submitted with this application.

6.1.3 Patient Disposition

One hundred and four (85%) subjects completed the 48 week period while 15% discontinued prematurely. Of the subjects who discontinued prematurely, 3 (2%) discontinued due to virologic failure, and 10 (8%) discontinued due to adverse reactions. Table 6 summarizes patients' enrollment and disposition.

Table 6: Patient Disposition

Disposition	BSA	BW	Total
Total screened			223
Randomized	66	57	123
Treated	66	57	123
Completed 48 weeks	60(91)	44 (75)	104(85)
Prematurely D/C	6(9)	12 (21)	18(15)
AEs	5(8)	5(9)	10(8)
Worsening of disease	0	0	0
AE	3(5)	4 (7)	7(6)
Death	2(3)	1(2)	3(2)
Virologic failure (resistance)	1(2)	2(4)	3(2)
Other*	0	5(9)	5(4)

*Other included: moved away or lost to follow-up (n=4), non-compliance (n=1)

6.1.4 Analysis of Primary Endpoint(s)

The primary objective of the study was the assessment of pharmacokinetic profile at steady state, over the age range studied for nevirapine administered as 150mg/m^2 BID. Exposure (AUC), Cmax, Cmin, and oral clearance were the parameters used for analysis of primary endpoints.

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

6.1.5 Analysis of Secondary Endpoint(s)

Secondary objectives of the study included assessment of safety and tolerability of nevirapine as well as assessment of efficacy. 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). The primary efficacy endpoint used is measurement of viral load at end of 48 weeks.

Treatment Response
Overall, the proportion of patients with protocol defined treatment response was higher in the BSA group [37 (56%) subjects in the BSA group vs. 24 (42%) subjects in the BW group]. The Sponsor's findings slightly differed from this reviewer's findings.

Table 7: Treatment Response (48 weeks)

	N=123	
	BSA (N=66)	BW (N=57)
Virologic Responders		
My Analysis	37(56)	24(42)
Sponsor's analysis	37(56)	21(37)

Reasons for Treatment Failure
The most common reason for treatment failure in the BSA group was discontinuation due to adverse events (8%); only one patient had virologic failure. In the BW group, the most common reasons for treatment failure were "other" (9%) and adverse events (9%). Two subjects in the BW group had virologic failure. The overall efficacious advantage of the BSA dose is apparent here, as the proportion of subjects in the BW group considered treatment failures was more than double that of the BSA group. Table 8 summarizes these results.

Table 8: Reasons for Treatment Failure (48 weeks)

	BSA	BW	Total
Prematurely Discontinued	6(9)	12 (21)	18(15)
AEs	5(8)	5(9)	10(8)
Worsening of disease	0	0	0
AE	3(5)	4 (7)	7(6)
Death	2(3)	1(2)	3(2)
Virologic failure (resistance)	1(2)	2(4)	3(2)
other	0	5(9)	5(4)

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subanalysis

Analysis by Age

Efficacy of nevirapine was analyzed based on the 4 stratified age group (3 months to 2 years, 2- <6 years, 6- <12 years, and 12-18 years). When analyzed by age group, it appears that BSA dosing regimen maintains its additional efficacy benefit over the BW dosing regimen (with the exception of the 2 to <6 years group). Table 9 and Figure 2 summarize treatment responses based on age and doses given. The difference in response was largest in the youngest age group, where 56% of the subjects in the BSA dose group had virologic response compared to 29% of subjects in the BW group. This difference is most likely due to dosing difference during the first 14 days of therapy. Subjects in the BSA group received a higher lead in dose compared to subjects in the BW group. The currently approved nevirapine dosing regimen for pediatric is based on age:

- Children younger than 8 years: 4 mg/kg once daily for the first 14 days followed by 7mg/kg twice daily
- Children 8 years and older: 4mg/kg once daily for the first 14 days followed by 4mg/kg twice daily

An alternative angle of analysis of this difference in the lead-in period is by comparing the lead in doses with the maintenance doses. The dose administered during the first 14 days is 25% of the maintenance dose in the BW dosing group and 50% of the maintenance dose in the BSA dosing group.

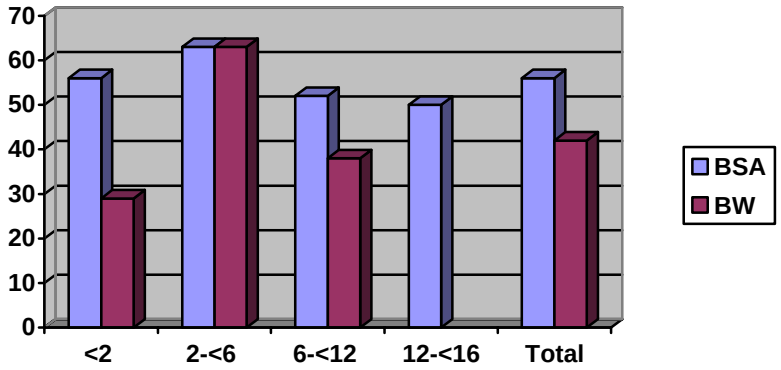
This lower lead-in dose for subjects in the BW group who are less than 8 years of age may have contributed to the blunted response of the BW dosing regimen when compared to the BSA dosing regimen. Unfortunately, no confirmatory PK data is available from the lead in period. The effect appears strongest in the youngest age group (<2 years) which is the group likely with the highest apparent clearance. In addition, this age group has the highest viral load, likely requiring higher exposure for response.

Similar to the <2 years old group, the proportion of subjects in the 6 to <12 years group who responded to treatment was higher in the BSA group. The lower treatment response in the BW group may be due to abrupt dose reduction from 7mg/kg to 4mg/kg when subjects turn 8 years old (although the overall troughs for the two dosing groups were similar).

Table 9: Proportion of subjects with HIV RNA < 400 copies/mL by age and dose

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
Virologic Responders										
My Analysis	9(56)	5(29)	12(63)	10(63)	13(52)	9(38)	3(50)		37(56)	24(42)
Sponsor's analysis									37(56)	21(37)

Figure 2: Proportion of subjects* with HIV RNA < 400 copies/mL by age and dose



**NOTE: No subjects were enrolled in the 12 - <16 years BW dosing group.*

Analysis by Exposure

A total of 103 nevirapine trough samples were available for analysis. Of these, 32 were from the intensive PK group and 71 samples were from non-PK intensive group. The Sponsor states that in both BSA and BW groups, subjects had nevirapine trough concentration levels similar to the adult range of 4-6 mcg/mL. This analysis is reflective of the steady state concentration at 4 weeks (not the lead-in dosing concentration). No PK data are available from the lead-in period.

Analysis by Prescribed and Calculated Doses

With the exception of the 7 to <12 years group, the BSA dosing methodology does not appear to have resulted in higher exposures. For the 7 to <12 age group, the BSA dosing appears to have resulted in a higher daily dose than the dose subjects would have received under a BW calculated dose.

If similar analysis were performed on the prescribed and calculated doses during the first 14 days of treatment, it is highly likely that a clear disparity between the calculated and prescribed doses

would have been observed for subjects younger than 8 years of age. As discussed previously, this subgroup of subjects received 25% of the BID dose as their lead-in dose when dosing was calculated based on body weight. Table 10 is Sponsor's analysis of prescribed and calculated doses.

Table 10: Comparison of prescribed and calculated dose (Sponsor's analysis)

	BW-Based Dosing - NVP 4 / 7 mg/kg				BSA-Based Dosing - NVP 150 mg/m2			
Age group [mo/years]	Median Prescribed Dose (BW) ml/day*	Median Calculated Dose (BSA) ml/day +	% BLQ at Week 48 (NCF)	Geo. Mean Cmin Day 28	Median Prescribed Dose (BSA) ml/day*	Median Calculated Dose (BW) ml/day +	% BLQ at Week 48 (NCF)	Geo. Mean Cmin Day 28
3 mo to < 2	16.0	15.17	(29.4)	5.2	15.50	16.73	(62.5)	5.7
≥ 2 to < 7	24.0	21.08	(68.4)	4.9	20.0	23.66	(65.2)	4.2
≥ 7 to < 12	20.0	29.22	(33.3)	5.1	26.0	19.28	(57.1)	4.9
≥ 12 to ≤ 16	----	----	----	---	39.0	32.80	(50.0)	5.0

+ Calculated dose derived using the patient's weight and height information and converted to millilitres per day.
* Prescribed dose was calculated at the clinic and recorded on the case report forms in millilitres per day.
Source: Study 1100.1368

Analysis by HIV Treatment History

Overall, there were 5 (4%) subjects with previous history of treatment with antiretroviral. The treatment experience was in the setting of prevention of maternal-to-child-transmission (MTCT). Four of the subjects were in the BW group and 1 subject was in the BSA group.

Eighty percent (4/5) of these subjects were treatment failures. All 4 (100%) were in the BW group and all were in the 3 months to < 2 years.

When efficacy is analyzed without these treatment experienced subjects, the treatment differences between the two dosing regimens is reduced (see table 11).

Table 11: Proportion of treatment naïve subjects with HIV RNA < 400 copies/mL by age and dose (week 48)

	< 2 (N=28)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=118)	
	BSA (n=15)	BW (n=13)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=65)	BW (N=53)
Virologic Responders	8(53)	5(39)	12(63)	10(63)	13(52)	9(38)	3(50)		35(54)	24(45)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Overall, an improved efficacy outcome has been observed when BSA dosing was used to calculate dose. The trough level obtained from intensive PK subjects at Day 28 suggests no difference in the trough level, regardless of dosing regimen or age. Analysis of prescribed and calculated dose during the BID dosing period for both BSA and BW groups did not show significant difference (with the exception of the 7 to <12 years old group). A potential reason

explaining the difference in treatment response may be the dosing difference between BSA and BW regimens during the lead-in period, particularly for the <8 year olds. In addition, although the maintenance trough levels were shown to be similar between the 2 dosing groups, it is plausible that the abrupt dose reduction in the BW dosing regimen around the 8th birthday may have contributed to the lower exposure and thus lower treatment response as seen in the 6 to <12 years old group.

Of importance, more subjects contributed to PK (n=103) and efficacy (n=123) data with the current study (1100.1368) when compared to study 1100.882 (ACTG 180) (n=37). Study 1100.882 contributed the primary PK data for the original approval of nevirapine in pediatric patients. Therefore, more emphasis should be placed on results from study 1100.1368

Dosing recommendation for the label will be based on the current study, where the BSA dosing regimen results in an improved efficacy. Dosing recommendations should be solely on BSA calculations.

The currently approved dosing recommendations should be removed for the following reasons: Retaining the BW dosing regimen in the label will lead to inconsistent dosing recommendations. For example for children < 8 years of age, depending on the regimen selected by a physician, very different lead-in dosing will be prescribed. Furthermore, as patients approach their 8th birthday, some will require dose reduction while others do not (depending on which dosing regimen is selected).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The durability of the treatment effect was not studied beyond the 48 week period. Given that nevirapine has been approved and used in pediatric population since 1998, there is already a rich database on the safety and tolerability of nevirapine when used in the pediatric population. Therefore, continuation of this trial for efficacy and tolerability assessment is not necessary.

6.1.10 Additional Efficacy Issues/Analyses

In summary, nevirapine was shown to be effective as treatment for HIV-1 infection in treatment naïve pediatric subjects 3 months of age through 16 years of age. BSA dosing (150 mg/ m^2 BID) resulted in numerically higher virologic successes at 48 weeks of treatment. This was demonstrated by analysis of the overall proportion of subjects with viral load <400c/mL. The advantage was generally maintained when treatment response was evaluated by age group and doses administered. One reasonable explanation for this advantage would be that subjects were given a higher dose (thus exposure) of nevirapine when dose was calculated by body surface area, compared to what they would have received by body weight (4/7 mg/kg BID). However, analysis of trough for the two groups did not show any significant difference between the two groups. Furthermore, when the prescribed dose is compared to the calculated dose using the alternative methodology, significant differences in daily dose were not seen. Therefore, it is not very clear as to why the BSA group had greater proportion of its subjects responding to treatment. The dose disparity during the lead-in period for subjects younger than 8 years of age

may offer a plausible explanation. In addition, there is likely an abrupt reduction in exposure when subjects reach their 8th birthday and their dose is reduced from 7mg/kg BID to 4mg/kg BID.

The efficacy of nevirapine demonstrated in this pediatric trial is comparable to the adult trial (BI 1046). At week 48, the proportion of adult subjects with HIV RNA <400 copies/mL was 45%.

The extrapolation of efficacy for antiretroviral drugs like nevirapine is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric patients (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)[4]. DAVP agrees that HIV disease in pediatric patients 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 patients 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 patients. 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 patients, 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), non-nucleoside 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 patients. 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, nevirapine in combination with 3TC and AZT was safe and tolerable when administered to pediatric subjects 3 months and older. The types of adverse events reported were similar to those reported in previous pediatric studies and adults. Rash and neutropenia were observed more frequently in the pediatric population when compared to adults. When the BSA and BW dosing are compared, the overall adverse events profile was similar for the two groups. However, the number of subjects with hepatic adverse events (i.e. hepatotoxicity) was slightly higher in the BW dose group. In addition, serious and drug related adverse events were reported more frequently in the BW group. In contrast, rash and neutropenia were reported in greater proportion of subjects in the BSA group. No exposure-safety relationship analysis was conducted to correlate specific adverse events (rash, hepatic adverse events and neutropenia) with nevirapine exposure.

Please note the statistical design of study 1100.1368- this study was not powered or designed to have safety analysis. Descriptive statistics were applied to describe the observed findings. Caution should be exercised when interpreting these results.

Safety summary provided for pediatric subjects less than 3 months of age did not indicate any difference in the type of AE reported, although neutropenia was reported more frequently in this age group.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The safety profile of nevirapine has already been established in adults and pediatrics with adequate number of patients.

Study 1100.1368 was conducted in response to FDA's request to update the Pediatric Use section of the P.I., specifically to update the section of the efficacy of nevirapine for the treatment of HIV-infected pediatric patients. Safety data was also collected. The population of Study 1100.1368 includes HIV-1 infected pediatric subjects who were 3 months to 16 years of age at the time of randomization. With the exception of 5 patients, all were treatment naive. The primary objective of this study was to assess the pharmacokinetic profile of nevirapine in combination with other ARV drugs (AZT and 3TC). Study was completed and 48 week study report was submitted in December 2007.

Study 1100.1222
This submission also contains safety summary report on pediatric subjects (<3 months of age). Safety data has been provided for 36 subjects who were less than 3 months of age (Table 12). Out of the 36 patients, 25 were less than 3 months of age with safety and PK data. Furthermore, 17 out of the 25 subjects were less than 2 months of age. This safety analysis specifically on subjects <2 months of age was conducted in response to a PMC, requiring study of nevirapine in neonatal population. Based on result from Study 1100.1222, the Sponsor proposed to update the Dosage and Administration section of the label and extend the indication to include ---------- old pediatric patients.

Title: A Phase 1/2 Open-Labe Trial to Assess the Antiretroviral Activity of Triple Drug Regimen (AZT/3TC/NVP), Quadruple Drug Regimens (AZT/3TC/NVP/ABC and d4T/3TC/NVP/NFV) and the Tolerance and PK Profile of NFV (cohort 7) in HIV-1 Infected Infants and Children Between the Ages of 15 Days and 2 years with Limited Prior Antiretroviral Therapy. The study had three parts:

Part A (AZT/3TC/ NVP), cohort 1 = age 15 days to 3 months;
Part B (AZT/3TC/NVP/ABC), cohort 3 = ages 30 days to 3 months;
Part C d4T/3TC/NVP/NFV), cohorts 5 and 7 = ages 15 days to 3 months.

The dosing regimen for study 356 (one of the PACTG trials) was nevirapine suspension 5mg/kg QD for 14 days followed by 120mg/m^2 QD for 14 days followed by 200 mg/m^2 BID for subjects <30 days old. Subjects >30 days old received nevirapine 120mg/m^2 QD for 14 days followed by 200 mg/m^2 BID.

Table 12: Enrollment

Cohorts	Age group 15 days </= 3 months	Age group 30 days-3 months	Total
A	8	0	8
B	0	8	8
C	20	0	20
Total	28	8	36

In summary, adequate numbers of pediatric subjects were exposed to nevirapine. No minimum numbers have been requested by the Division for safety analysis as nevirapine is already approved for used in children.

7.1.2 Adequacy of Data

The data submitted to support the currently existing indications in pediatric patients 2 months to <16 years of age is adequate. The safety summary and PK dataset submitted on the use of nevirapine in pediatric patients <2 months of age supports extension of the pediatric age group to include children < 2 months of age. Data from study 1100.1368 was 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.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Study 1100.1368 is a descriptive study. No formal statistical analysis was performed. In addition, safety information from Study 1100.1222 is contained only as a summary report (i.e. without dataset). Therefore incidence of AEs can only be generally compared between the 2 studies.

7.2 Adequacy of Safety Assessments

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

The Sponsor has submitted safety data on 123 pediatric subjects (3 months to 16 years) with 48 week safety data. In addition, safety report on 36 subjects (<3 months of age) from study 1100.1222 has been submitted. Table13 summarizes the number of subjects from each study.

Table 13: Pediatric Trials with Safety Data

All Pediatric Patients, Regardless of age		Pediatric Subjects Receiving nevirapine Treatment for ≥48 Weeks
Trial Number	Total Number of Subjects	Total Number of Subjects
1100.38	123	109
1182.33	36	26
Total Number of Patients	159	185

7.2.2 Explorations for Dose Response

No formal exploration for dose response was performed.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the original and the traditional review of nevirapine 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, 8, 12, 18, 24, 36, 42, and 48). Pre-specified adequate monitoring plans were also in place for rash and hepatic adverse events.

7.2.5 Metabolic, Clearance, and Interaction Workup

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

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

No evaluation for potential adverse events for similar drugs in drug class was submitted. During the study period, nevirapine specific adverse events assessments such as rash and hepatic adverse events (including laboratory assessment) were conducted.

7.3 Major Safety Results

7.3.1 Deaths

Study 1100.1368
During the 48 week study period, 3 subjects died - 2 in BSA group and 1 in the BW group. None were related to drug.

- BSA:
    - A 14 year old female, after 1 month into study, was diagnosed with oral candidiasis. She was started on antimicrobial therapy. No abdominal pain, emesis or rash accompanied her symptom (pharyngitis). One day after starting antimicrobial medications the subject died (Sudden Death). No autopsy was done.
    - A 3 year old female presented with shortness of breath and cough 2 weeks into study. She was diagnosed with pneumonia and E. coli sepsis. She was admitted to a hospital for management of pneumonia and sepsis. Few days after admission, patient died of septic shock.
- BW:
    - An 8 year old girl withdrew from study 2 months post enrollment and treatment with study drug. She complained of abdominal pain and emesis 5 days post discontinuation of treatment drug. Patient had also been taking herbal medicines. The patient was not taken for medical care. She died of abdominal pain. The cause of death was unknown and no autopsy was performed.

Table 14: Causes of Death

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)	
Medically Preferred Terms	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0
E. Coli sepsis			1					
Pneumonia			1					
Abdominal pain						1		
Vomiting						1		
Sudden Death							1	
Oropharyngeal candidasis							1	

Study 1100.1222
No deaths were reported from this study summary report.

7.3.2 Nonfatal and Fatal Serious Adverse Events (SAEs)

Study 1100.1368
Serious adverse events (SAEs) were reported by 37 (30%) subjects during the 48 week study period. The proportion of subjects with SAE was higher in the BW group compared to the BSA group (37% vs. 24%). The higher proportion was reported across the age groups.

Table 15: Serious Adverse Events (48 week)

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
Number of subjects with SAEs	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
	5(31)	6(35)	5(26)	7(44)	3(12)	8(33)	3(50)		16 (24)	21(37)

Table 16: Serious AE (during BID dosing period)

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
Number of subjects SAEs	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
	5(31)	6(35)	4(21)	7(44)	1(4)	7(29)	2(33)		12(18)	20(35)

The most serious adverse reactions associated with adult clinical trials with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions.

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 17 lists the type of SAEs

Table 17: Description of the SAEs

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
Serious AEs	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
Viral meningitis				1		1			0	2(4)
Bacterial Meningitis	1								1(2)	0
Sepsis			1						1(2)	0
Hemiplegia	1								1(2)	0
Lower RTI	1	2			1		1		3(5)	2(4)
Upper RTI			1	1		1			1(3)	2(4)
PCP	1								1(3)	0
Broncho-pneumonia	4	1	1	1		1	1		6(10)	3(5)
Lobar Pneumonia		1		1					0	2(4)
Anemia	1								1(2)	0
Cellulitis/abscess			1	1					1(2)	1(2)
Otitis Media			1						1(2)	0
Candidasis oral		1				1			0	2(4)
Hepatitis A			1						1(2)	0
Abdominal. Pain						1			0	1(2)
Vomiting						2			0	2(4)
Ileus				1					0	1(2)
Gastroenteritis		4		2					0	6(10)
Dehydration		1							0	1(2)
Metabolic acidosis		1							0	1(2)
Hypokalemia		1							0	1(2)
Ranula						1			0	1(2)
Injury/poison							1		1(2)	0
Fever						1			0	1(2)
Bone TB				2					0	2(4)
Arthritis bacterial				1					0	1(2)
synovitits						1			0	1(2)
HSV						1			0	1(2)
headache						1			0	1(2)

* One subject may have more than 1 SAE

7.3.3 Dropouts and/or Discontinuations

Study 1100.1368

During the 48 week treatment period, 10 (8%) patients discontinued trial due to AE (9% in the BW group and 8% in the BSA group). There were no discontinuations due to AE in the youngest age group who received BW dosing regimen. The most common reason for discontinuation was rash (3%). One of the patients in the BSA group who discontinued due to rash also experienced vomiting, nausea and fever. All the rash adverse events occurred during the once daily lead-in period. No subjects discontinued due to hepatic adverse events. All the rash AEs leading to discontinuation were considered related to study drug,

Table 18: Adverse events leading to interruption or discontinuation of study drug (48 Week)

	AGE									
	< 2 (N=32)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
Interruption due to AE	4	1	2	2	1	2	2		9(14)	5(9)
Discontinuation to AE , including death	1	0	2	1	1	4	1		5(8)	5(9)

Description of AE leading to discontinuation:

BSA Group
1 patient with rash (QD)
1 patient with rash, vomiting, nausea, fever (QD)
1 patient with Neutropenia (BID)
2 subjects died

BW Group
1 patient with rash (QD)
1 patient with rash (QD)
1 patient with Pulmonary TB (BID)
1 patient with Bone TB (BID)
1 subject died

Description of AE leading to treatment interruption

BSA Group
3 months to <2 years: vomiting, neutropenia, pneumonia, broncho-pneumonia, bacterial meningitis, hemiplegia
2-< 6 years old: fecaloma, hepatitis A, LFT abnormality
7 < 12 years group: varicella
>12 years old: broncho-pneumonia, neutropenia

BW Group
3months to <2 years old: neutropenia, anemia
2 -<6 years old: lobar pneumonia, gastroenteritis, ileus, hypophosphatemia, hepatotoxicity
6 -<12 years old: hepatotoxicity, abdominal pain, distention, emesis

Study 1100.1222
No patient discontinued treatment due to adverse events. Twelve subjects discontinued after meeting the protocol defined virologic endpoint (failure). Additional 5 subjects discontinued study due to withdrawal.

Table 19: Treatment Discontinuation

Cohorts	Age group 15 days </= 3 months	Age group 30 days-3 months
A	3 with virologic failure 1 patient withdrew	
B		2 with virologic failure 1 patient withdrew
C	7 with virologic failure 3 subjects withdrew	

At the 48 week analysis of the adult trial (BI 1090) 7% of subjects in the nevirapine arm discontinued due to adverse events.

7.3.4 Significant Adverse Events

The protocol did not have any predefined significant adverse events. Rash and hepatic adverse events are reviewed under Submission Specific Primary Adverse Events (see section 7.3.5). In this section, severe adverse events are discussed.

Study 1100.1368
No increased severe adverse events were noted with administration of BSA dosing regimen. The mild and moderate AEs were seen in similar proportion of subjects between the two dosing groups. Severe AEs were slightly higher in the BW group.

Table 20: Severity of AEs

Number of subjects with AEs	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
Mild	16 (100)	16 (94)	19 (100)	16 (100)	25 (100)	22 (92)	6 (100)		66 (100)	54 (95)
Moderate	6(38)	6(35)	12(63)	10(62)	12(48)	12(55)	4(67)		34(52)	28(49)
Severe	5(31)	5(29)	3(16)	6(38)	1(4)	4(17)	1(17)		10(15)	15(26)

Appears This Way On Original

Table 21: Description of Severe AE

Number of subjects with severe AEs	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=58)
Bacterial pneumonia	4		1	1					5 (8)	1(2)
Bacterial meningitis	2								2(3)	0
Viral meningo-encephalitis				1					0	1(2)
Lower RTI	1								1(2)	0
Anemia	1			1					1(2)	1(2)
PCP	1								1(2)	0
Molluscum cont.			1						1(2)	0
Sepsis		1	1						1(2)	1(2)
OM			1						1(2)	0
Fever					1	1			1(2)	1(2)
Neutropenia		1					1		1(2)	1(2)
Abdominal pain						1			0	1(2)
Vomiting						1			0	1(2)
Mobility decreased				1					0	1(2)
TB				1					0	1(2)
Gastroenteritis		3							0	3(5)
HIV infection		1							0	1(2)
HSV						1			0	1(2)
Hepatic enzyme. ↑				1					0	1(2)
Rash papular		1							0	1(2)

Study 1100.1222

Severe AEs were described as Grade 3 and/or 4 AEs. The table below summarizes the AEs listed as Grade 3 and/or 4. The number of subjects with severe neutropenia was higher in this younger age group compared to older pediatric subjects and adults. The AEs listed here are not restricted to drug related AEs. The number of subjects with neutropenia decreases to 5 when only drug related AEs are evaluated. Of note, AZT was part of HAART for cohorts A and B. AZT is known to cause neutropenia.

Table 22: Grade 3 and 4 AEs

	A	B	C	Total
Skin	0	0	0	0
GI	1	0	0	1(3)
diarrhea	1			1(3)
Liver	0	0	1	1(3)
AST			1	1(3)
Hematology	3	5	6	14 (39)
anemia	1	1	1	3 (8)
neutropenia	2	4	5	11(30)

General Body	0	0	5	5(14)
fever			2	2(6)
chills			1	1(3)
weakness			1	1(3)
SOB			1	1(3)
Neurologic	0	0	3	3(8)
stiffness			1	1(3)
spasm			1	1(3)
Reflexes abnormal			1	1(3)
Cardiovascular	0	0	1	1(3)
cyanosis			1	1(3)
Misc.	0	0	4	4 (11)
BUN			1	1(3)
glucose			2	2(6)
CPK			1	1(3)

7.3.5 Submission Specific Primary Safety Concerns

Rash and hepatic adverse events are known to be associated with use of nevirapine. Both fatal and nonfatal rash and hepatic adverse events are known to occur. The current nevirapine label includes both rash and hepatic adverse events in boxed warning. Both events have also been reported in previous pediatric studies.

Hepatic Adverse Events

Study 1100.1368
Within the MedDRA System Organ Classes, group of adverse events were selected for analysis. These included: Nausea, vomiting, abdominal pain, hepato-, investigation, LFT, ALT, AST, GGT, alkaline phosphatase and bilirubin. Table 23 summarizes the AEs across the age groups and by dose of nevirapine given.

For all the selected AEs, the proportions of subjects with these adverse events were similar between the two dosing groups. Hepatotoxicity was reported slightly more in the BW group (5%) compared to no cases in the BSA group.

Table 23: GI and Hepatic AEs

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
Number of subjects with AEs	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
GI and Hepatic										
Abdominal pain		2	6	2	2	7	2		10(15)	11(19)
vomiting	7	8	7	11	10	10			24(36)	29(51)
nausea			1	1	3	2			4(6)	3(5)
Hepatomegaly			2	1	2	2			4(6)	3(5)
Hepatotoxicity				1		2			0	3(5)
Investigation										
Abnormal LFT			1	1					1(2)	1(2)
Alk phos			1						1(2)	0

Study 1100.1222
Only one patient (Cohort C) was reported to have increased ALT. However, the AEs were reported only if severity was ≥ 3 or if AEs were believed to be related to drug.

Rash (selected)
Study 1100.1368
Selected skin and soft tissue 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 proportion of subjects with rash was higher in the BSA group. Rash was also more frequent in the pediatric trial when compared to the adult studies where 15% reported rash.

Table 24: Rash

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
Number of patients with rash	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
Rash (selected terms)										
Urticaria					1				1(2)	0
Rash	5	2	5	3	9	4	1		20(30)	9(16)
Rash papular	1	2	4	1	6				11(17)	3(5)
Rash pruritic			1			1			1(2)	1(2)
Pruritis	1	1	1	1	5	1			7(11)	3(5)
Erythema	1				1				2(3)	0
Skin inflammation	1								1(2)	0
Facial swelling						2			0	2(4)

Hepatic adverse events and rash were also compared between the two dosing regimens and the frequency of nevirapine administration.

Table 25: Selected AEs QD vs. BID

Number of subjects with AE	QD		BID	
	BSA (n= 66)	BW (n=57)	BSA (66)	BW (57)
GI and Hepatic				
Abd pain	4 (6)	3(5)	8 (12)	8(14)
Diarrhea	6 (9)	3(5)	17 (26)	20(35)
vomiting	10 (15)	51(89)	18 (27)	29(50)
nausea	3 (5)	1(2)	2 (3)	2(3)
Hepatomegaly	1 (1)	0	3 (5)	1(2)
Hepatotoxicity	0	0	0	3(5)
Investigation				
Abnormal LFT	0	0	1 (1)	1(2)
Alk phos	0	0	1(1)	0
Rash (selected terms)	8 (12)	4(7)	23(35)	12(21)

The number of subjects with rash in study 1100.1222 was 2 (6%).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the number of subjects with AEs was similar between the two dose groups and between the comparative age group. The most frequently system Organ Class (SOC) adverse events were similar to adults, with GI and Infection being most common.

Table 26: Most frequently reported AE (>10%)

	< 2 (N=33)		2-<6 (N=35)		6-<12 (N=49)		12-<16 (N=6)		Total (N=123)	
Number of subjects with AEs	BSA (n=16)	BW (n=17)	BSA (n=19)	BW (n=16)	BSA (n=25)	BW (n=24)	BSA (n=6)	BW 0	BSA (N=66)	BW (N=57)
Anemia	2 (12)	2(12)	2(11)	2(12)	2(8)	0	0		6(9)	4(7)
Neutropenia	3(19)	2(12)	1(5)	0	1(4)	1(4)	1(17)		6(9)	3(5)
Conjunctivitis	3(19)	4(24)	5(26)	2(12)	0	4(17)	0		8(12)	6(11)
Diarrhea	7(43)	7(41)	2(11)	5(31)	7(28)	8(33)	1		17(26)	20(35)
Vomiting	4(25)	8(47)	6(32)	11(69)	8(32)	10(42)	0		18(27)	29(50)
Abdominal pain	0	2(12)	6(32)	2(12)	2(8)	4(17)	0		8(12)	8(14)
Fever	3(19)	3(18)	5(26)	5(31)	6(24)	4(17)	0		14(21)	12(21)
Acrodermatitis	4(25)	2(12)	7(37)	4 (25)	4(16)	1(4)	0		15(23)	7(12)
Gastroenteritis	0	5(29)	3(16)	3(19)	2(8)	3(13)	0		5(8)	11(20)
HSV										
Infection	0	2(12)	0	1(6)	2(8)	3(13)	0		2(3)	5(9)
Simplex	0	2(12)	1(5)	1(6)	3(12)	2(8)	0		4(6)	5(9)
Zoster	0	0	0	0	3(12)	1(4)	0		3(5)	1(2)
stomatitis	0	2(12)	1(5)	1(6)	2(8)	2(8)	0		3(5)	5(9)
Impetigo	2(12)	3(18)	4(21)	2(12)	2(8)	2(8)	0		8(12)	7(12)
Lower RTI	4(25)	3(18)	4(21)	8(50)	7(28)	6(25)	1(17)		16(24)	17(30)
Oral Candidasis	4(25)	2(12)	1(5)	2(12)	6(24)	3(13)	1(17)		12(18)	7(12)
O.M	10(62)	3(18)	7(37)	9(56)	12(48)	3(13)	0		29(44)	15(26)
Pharyngitis	3(19)	3(18)	1(5)	1(6)	1(4)	4(17)	0		5(8)	8(14)
Rhinitis	3(19)	1(6)	2(11)	6(38)	1(4)	2(8)	0		6(9)	9(16)
Tinea capitis	2(12)	1(6)	5(26)	3(19)	2(8)	6(24)	0		9(14)	10(18)
Tonsillitis	3(19)	3(18)	2(11)	3(19)	0	2(8)	0		5(8)	8(14)
URI	11(69)	7(41)	8(42)	15(94)	7(28)	8(34)	3(50)		29(44)	30(53)
Arthropod bite	4(25)	3(18)	3(16)	2(12)	0	2(8)	0		9(14)	7(12)
Headache	0	0	1(5)	0	3(12)	3(13)	3(50)		7(11)	3(5)
Bronchospasm	0	1(6)	0	2(12)	0	3(13)	0		0	6(11)
Cough	5(31)	5(29)	7(37)	6(38)	6(24)	6(24)	0		18(27)	17(30)
Eczema	4(25)	3(18)	2(11)	4(25)	3(12)	4(17)	0		9(14)	11(19)
Rash	5(31)	2(12)	4(21)	3(19)	4(16)	2(8)	2(33)		15(23)	7(13)
Rash papular	0	2(12)	4(21)	1(6)	5(31)	1(4)	0		9(14)	4(7)

7.4.2 Laboratory Findings

Chemistry

DAIDS Grade 3 and 4 laboratory adverse events are summarized in table 27. Increase in ALT and/or (Grade 3 and/or 4) was reported more frequently in the BW dose group (7% vs. 3.5%). No other liver associated abnormal laboratory value of Grade 3/4 was reported for either group.
In the adult clinical trials, abnormal ALT/AST were reported in 5 to 14% of the subjects.

Table 27: Chemistry Laboratory

Number of subjects with Grade 3/4 laboratory toxicities		
	BSA (n= 66)	BW (n=57)
ALT	1(2)	3(5)
AST	1(2)	1(2)
Bilirubin	0	0
Alkaline phosphatase	0	0

Hematology
Overall, the proportion of subjects with neutropenia was slightly more in the BSA group compared to BW group. However, AZT was part of the HAART regimen for all patients. It is therefore difficult to decipher the true cause of neutropenia.

Table 28: Hematology

Number of subjects with Grade 3/4 laboratory toxicities		
	BSA (n= 66)	BW (n=57)
Hemoglobin	1(2)	1(2)
Platelets	4(6)	2(4)
Absolute neutrophils	5(8)	2(4)

7.4.3 Vital Signs

Baseline vital signs were collected for all randomized patients. 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)

Not applicable

7.4.5 Special Safety Studies

Not applicable

7.4.6 Immunogenicity

Please refer to the original NDA for detail. Nevirapine is an NNRTI and is not expected to have an immunogenic effect.

7.5 Other Safety Explorations

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

This study has already been conducted and included in the label.

7.6.2 Human Reproduction and Pregnancy Data

Nevirapine is classified as category B. Please refer to the current label for more information. There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1 infection. To monitor fetal outcomes of pregnant women exposed to nevirapine, healthcare providers are encouraged to register subjects with the Antiretroviral Pregnancy Registry.

7.6.3 Pediatrics and Effect on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no withdrawal or abuse potential with nevirapine. There is no information on overdoses in pediatric patients.

7.7 Additional Submissions

Not Applicable

8 Postmarketing Experience

9 Appendices

9.1 Literature Review/References

1. NDA (accelerated)
NDA 20-636 (S-000)
Approved: June 21, 1996

2. NDA (traditional)
sNDA 20-636 (S-017)
sNDA 20-933 (S-007)

Reviewer: Harry Haverkos, M.D.
Approved: March 27, 2002

3. sNDA (pediatrics)
sNDA 20-636 (S-009)
sNDA 20-933 (S-000)
Reviewer: Teresa C. Wu, M.D., Ph.D.
Approved: September 11, 1998

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 patients, 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 patients, 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 Attachment (Section 9.4)

6. Pediatric Research Equity Act (PREA)/PMC

Commitment Number 5

Commitment Required Under	Pediatric Research Equity Act
Original Projected Completion Date	02/15/2007
Commitment Description	Deferred pediatric study under PREA for the chronic treatment of HIV in pediatric patients ages 0 to 2 months of age.
Current Status	Pending

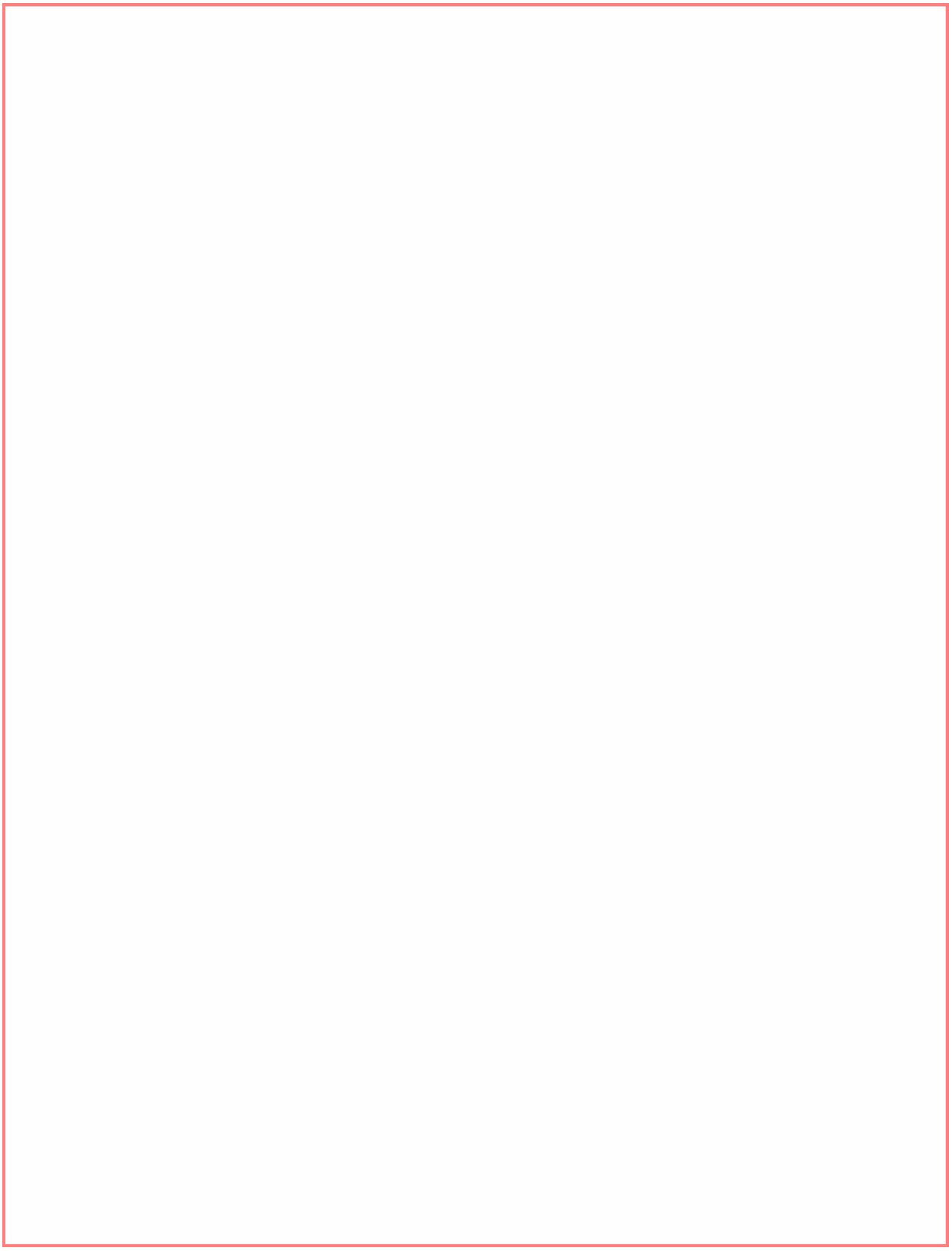
9.2 Labeling Recommendations

9.3 Advisory Committee Meeting

Not Applicable

9.4 Attachments

1. Pediatric Written Request (issued December, 23, 1999)



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