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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

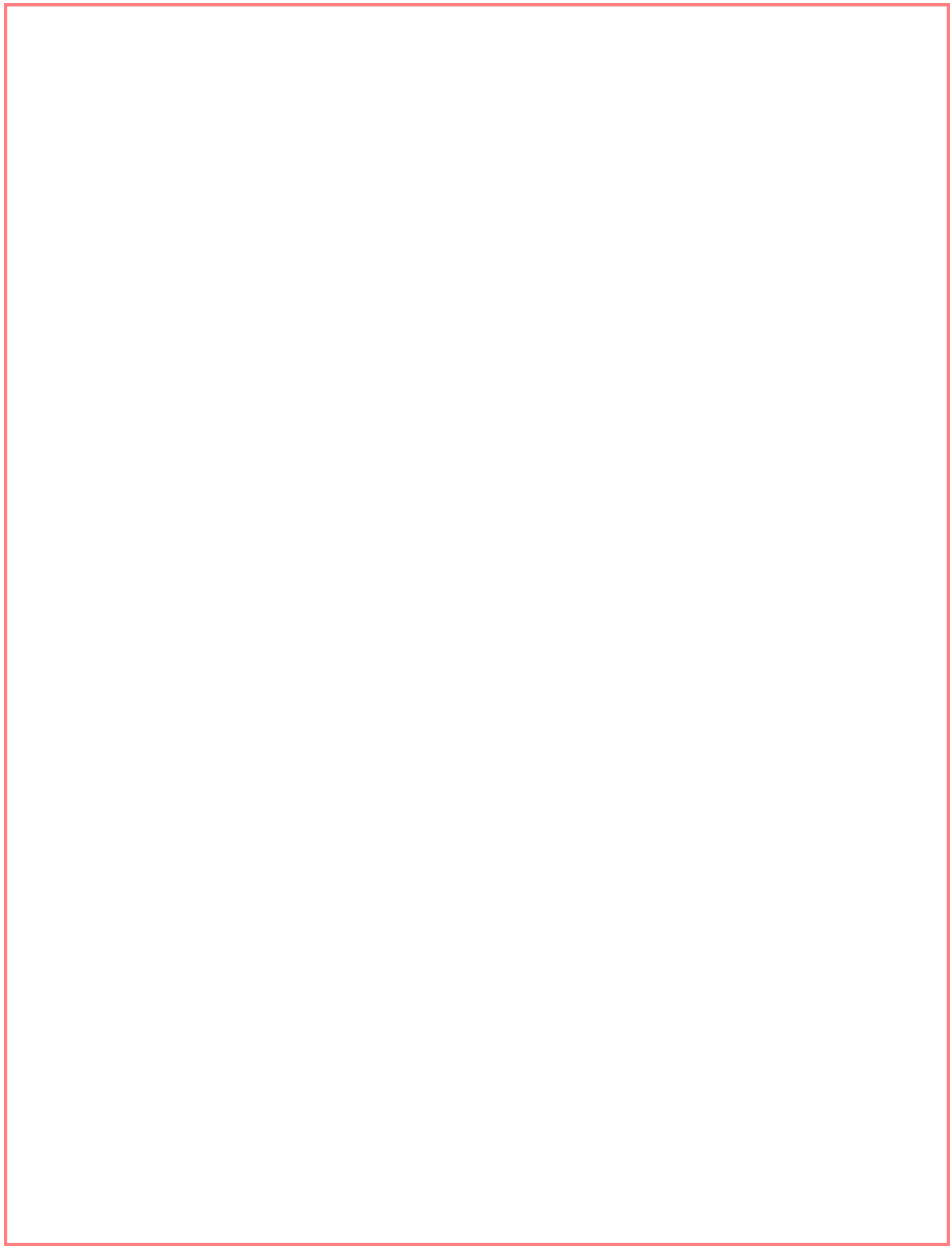
Commitment Number 5

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



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