CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-481

MEDICAL REVIEW(S)

NDA 21-481

Medical Officer's Review Of New NDA: Pediatric Use of Enfuvirtide

Date Submitted:	September 16, 2002
Date Completed:	February 28, 2003
Sponsor:	Hoffman-La Roche Inc 340 Kingsland Street Nutley, New Jersey 07110-1199
Generic Name:	Enfuvirtide
Trade Name:	Fuzeon
Dosage Forms/Dose:	Injectable 2mg/kg/dose (max 90 mg/dose) BID
Routes of Administration:	Subcutaneous
Indication Studied:	Treatment of HIV infection in children

1. Resume

The material reviewed from this submission includes the final study report for study T20-204A/B and results from ongoing study T20-310. A total of 40 subjects were studied in both trials.

T20-204 was a two part (A and B), phase 1/2 open label, dose finding/chronic dosing study of enfuvirtide (T-20) in HIV-1-infected, ARV treatment-experienced children age 3 to 12 years. T20-310 is an ongoing open-label, single arm, non-comparative study of enfuvirtide in combination with an optimized ARV regimen in HIV-1 infected children aged 3 through 16 years.

Results from T20-204 demonstrated slightly higher adjusted exposure to enfuvirtide in children receiving a dose of 2 mg/kg compared to adults administered a 90 mg dose. Safety appears to be similar to that observed in adults. Enfuvirtide in combination with a background ARV regimen was associated with reduction of HIV-1 RNA in children.

Based on the PK, safety, and efficacy results, the activity of enfuvirtide appears to be comparable to adults, although pediatric safety and efficacy information is very limited. The review supports the labeling of enfuvirtide for pediatric subjects ages 6 through 16 years.

2.0 Clinical Studies

TABLE 1. Studies of T-20 in Pediatric Subjects with HIV

Study	Design	Doses	n
T20-204A	Cohort 1:Open-label, single dose study Cohort 2;open-label, single dose study Cohort 2;open-label single dose study	SC T-20, 15 mg/m^2, followed by 12 h PK SC T-20, 30 mg/m^2, followed by 12 h PK SC T-20, 60 mg/m^2, followed by 12 h PK	4 4 4
T20-204B	Multi-center, open-label chronic bid SC injection 48 weeks	SC T-20, 30 (n=4) or 60 (n=10) mg/m^2	14 (11 from T20-204A)
T20-310	Open-label, single study, chronic bid SC injection 48 wks	SC T-20, 2mg/kg bid, max 90 mg bid	25
Total number of pediatric subjects exposed to T-20			40

2.1 Study T20-204A

Study T20-204A was an open label, phase 1, multi-center, dose escalation pharmacokinetic and safety study of three doses of enfuvirtide (15, 30, and 60 mg/m^2). The objective of the study was to identify a SC (subcutaneous) dose of enfuvirtide for chronic administration that was likely to result in a minimum12 hour enfuvirtide plasma trough concentration (C_{min}) of 1ug/ml. Based on preclinical data and early experience with enfuvirtide therapy in HIV-infected adults, this level was predicted to be effective for suppressing HIV-1 infection.

Eligible subjects included children 3 to 16 years of age with documented HIV-1 infection and a plasma HIV-1 RNA $\geq$ 10,000 copies/ml ($\log_{10}$ = 4.0). Subjects were required to be taking a stable combination of ARV drugs consisting of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) alone or in combination with either a nonucleoside reverse transcriptase inhibitor (NNRTIs) or a protease inhibitor (PI) for at least 16 weeks.

Children were excluded from enrollment if they had grade 3 or 4 clinical or laboratory toxicity, if they had an acute opportunistic or serious bacterial infection requiring therapy, or if they required chemotherapy for a malignancy.

Eligible subjects in part A continued their background ARV treatment. Three cohorts of four subjects each received T-20 at doses 15, 30 or 60 mg/m^2 of body surface area by a single sc injection followed by 12 hour pharmacokinetic (PK) sampling on Day 0. On Day 1 subjects received single IV infusion of enfuvirtide followed by 12 hour PK. All children in each dosage group were followed for at least 7 days post dosing for safety monitoring before enrollment at the next higher dosage was permitted.

2.2 Study T20-204B

T20-204B was a continuation of T20-204A with chronic dosing of enfuvirtide through 48 weeks. Study T20-204B evaluated the safety and ARV activity of chronic twice daily SC enfuvirtide administration at 30 or 60 mg/ m^2 in a total of 14 children. Doses were chosen based on the single-dose pharmacokinetic data obtained in Study T20-204A.

All subjects who completed T20-204A were eligible to be enrolled in study T20-204B. Additional subjects who did not participate in Part A were added in order to reach a target enrollment of 14 children. Enfuvirtide was administered twice daily by SC injection at 30 or 60 mg/m^2 of body surface area per dose in addition to the current background ARV therapy of all subjects. At Day 7, subjects' background treatment was changed to a regimen that was predicted to be virologically active while enfuvirtide was continued.

Evaluation of the short-term activity at Day 7 was followed by assessment of safety and ARV activity of chronic twice-daily sc enfuvirtide administration at 30 or 60 mg/m^2 through 48 weeks. Clinical and laboratory assessments for safety monitoring were obtained regularly during the study.

2.3 Study T20-310

T20-310 is an ongoing phase 1/2, open-label, single arm, multi-center, non-comparative study assessing the safety and efficacy of enfuvirtide 2 mg/kg dose SQ BID (max 90 mg BID) in combination with an optimized antiretroviral (ARV) regimen in HIV-1 infected children ages 3 through 16 years. Study duration is 48 weeks.

Eligible subjects include children with documented HIV-1 infection and a plasma HIV-1 RNA ≥ 5000 copies/mL. Subjects are required to be taking a stable combination of ARV drugs consisting of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) alone or in combination with either a non-nucleoside reverse transcriptase inhibitor or a PI for at least 3 months. Children are excluded from enrollment if they have a Grade 3 or 4 clinical or laboratory toxicity, if they have an acute opportunistic or serious bacterial infection requiring therapy, if they require chemotherapy for a malignancy or if they have a prior history of taking enfuvirtide. A total of 25 subjects have been enrolled and were stratified into two age groups: Group I, children ≥ 3 and <12 years of age (N=7), and group 2, adolescents ≥12 and <17 years of age (N=18). The study is a ongoing with the goal to enroll 25 subjects in each group.

3. Results and Demographics

This review evaluates the final data set from T20-204 and interim data available from T20-310 as of November 2002. Demographic data and baseline characteristics for both studies are shown in Table 2.

Table 2. Summary of Demographic Data

Characteristic	Study T 20-204A	Study T 20-204B	T-20 310
Total Number	12	14	25
Children <6 years	4	3	1
Gender: no. (%) female no. (%) male	8 4	8 (57%) 6 (43%)	11 (44%) 14 (56%)
Race/ethnicity: no. (%) White, Black, Other	 2 7 3	 4 (29%) 6 (43%) 4 (29%)	 11(44.0%) 12(48.0%) 2 (8%)
Age (years): Median (min, max)	7.4 3.7- 11.9	8.2 4.0, 12.1	13 5.0 - 16
Height (cm): Median (min, max)	116.5 87.5 – 154	118 96- 155	147 102-172
Weight (kg): Median (min, max)	21.90 12.7 – 69.6	24.1 14.3- 69.4	39.1 13.8- 68.9
Body surface area (m2): Median (min, max)	0.84 0.56- 1.71	0.89 0.62- 1.72	18.8 13.3-32.3
CD4+ count (cells/μl): Median (min, max)*	505 129 - 1497	523 53- 2343	143 7 - 959
CD4+ percentage (%): Median (min, max)*	23 8 – 28	24 11- 42	13.7 1.2 - 50.1
HIV-1 RNA (log): Median (min, max)	4.61 4.20-5.25	4.43 3.93-5.27	5.1 4.0 - 5.9 log
Baseline ARV: no. (%) 2 NRTIs + 2 PI 2 NRTIs + PI 2 NRTIs only 2NRTIs+ NNRTI	 2 (16.7%) 8 (66.7%) 2 (16.7%) 0(0%)	 2 (14%) 9 (64%) 3 (21%) 0(0%)	 12 (48%) 8 (32%) 0 (0%) 5 (20%)

3.1 Study T20-204A

Twelve subjects from six different sites were enrolled in Part A of the study (Table 3). Four subjects were below 6 years of age.

TABLE 3. Gender and Race/Ethnicity of the Subjects in Study T20-204A by Assigned Dose

	Total		Assigned Dose						P-value
			15 mg/m2		30 mg/m2		60 mg/m2		
	N	%	N	%	N	%	N	%	
Gender									
Male	4	33.3	2	50.0	1	25.0	1	25.0	1.00
Female	8	66.7	2	50.0	3	75.0	3	75.0	
Race/Ethnicity									
White Non-Hispanic	2	16.7	0	0	1	25.0	1	25.0	0.782
Black Non-Hispanic	7	58.3	2	50.0	3	75.0	2	50.0	
Hispanic (regardless of race)	3	25.0	2	50.0	0	0	1	25.0	

*p-values for comparing dose groupsSource: NDA 21-481, Volume 265, page 23.

Ten of the 12 subjects had treatment experience with both PIs and NRTIs, two subjects exposed to only NRTIs. No patient received an NNRTI. At the time of study enrollment, all 12 subjects were taking antiretroviral therapy including at least two NRTIs (Table 4).

TABLE 4. Subject Antiretroviral Therapy at Enrollment by Assigned Dose

	Total		**Assigned Dose**						**p-value**
			15 mg/m^2		30 mg/m^2		60 mg/m^2		
	N	%	N	%	N	%	N	%	
Antiretroviral Therapy									
2NRTIs only	2	16.7	0	0	1	25.0	1	25.0	1.00
2NRTIs + PI	8	66.7	3	75.0	2	50.0	3	75.0	
2NRTIs + 2PI	2	16.7	1	25.0	1	25.0	0	0	
TOTAL	12	100.0	4	100.0	4	100.0	4	100.0	

Source: NDA 21-481, Volume 265, page 25.

At the time of study enrollment eight subjects were taking one PI (amprenavir, nelfinavir, or ritonavir) + two NRTIs, two subjects were taking two PIs (nelfinavir and ritonavir) + two NRTIs, and two subjects were taking only NRTIs. Antiretroviral regimens at the time of study enrollment consisted predominantly of PIs + NRTIs (10 of the 12 subjects). Nelfinavir (NFV) was the most frequently used PI (8 of 12 subjects). The most common NRTIs received were lamivudine (8 subjects), stavudine (6 subjects), didanosine (5 subjects), and zidovudine (5 subjects).

The three cohorts of subjects (15, 30, 60 mg/m^2) were comparable in terms of their baseline characteristics with the exception of CD4+ count, which was substantially higher in the 60-mg/m^2 cohort.

3.2 Study T20-204B

T-20-204B evaluated the safety and ARV activity of chronic twice-daily sc enfuvirtide administration at 30 or 60 mg/m^2. Dosing was based on the results of T20-204A. Fourteen children from 8 different sites were enrolled into Part B; 11 of the 14 previously participated in Part A. One child did not enroll in Part B after completion of Part A. Three subjects were below 6 years of age.

3.3 Study T20-310

A total of 25 subjects have been enrolled in this ongoing study. Of these subjects, 7 were children (ages ≥ 3 to < 12 years) and 18 were adolescents (aged ≥ 12 to < 17 years). Median age was 7 for children (≥ 3y to <12y) and 14 for adolescents (≥ 12y to <17y). One child was below 6 years of age (Table 5).

Table 5. Summary of Demographic Data of Study T20-310 by Age Group

		Age >= 3y to <12y	Age >=12y to <17y	All Subjects
NUMBER OF SUBJECTS		7	18	25
SEX (n (%))	FEMALE	4 (57.1%)	7 (38.9%)	11 (44.0%)
	MALE	3 (42.9%)	11 (61.1%)	14 (56.0%)
RACE (n (%))	WHITE	1 (14.3%)	10 (55.6%)	11 (44.0%)
	BLACK	6 (85.7%)	6 (33.3%)	12 (48.0%)
	OTHER		2 (11.1%)	2 (8.0%)
ETHNICITY (n (%))	HISPANIC		6 (33.3%)	6 (24.0%)
	NON-HISPANIC	7 (100.0%)	12 (66.7%)	19 (76.0%)
TANNER STAGE	1	5 (71.4%)	1 (5.6%)	6 (24.0%)
	2		6 (33.3%)	6 (24.0%)
	3	1 (14.3%)	2 (11.1%)	3 (12.0%)
	4		2 (11.1%)	2 (8.0%)
	5		7 (38.9%)	7 (28.0%)
	Missing	1 (14.3%)		1 (4.0%)
AGE (YEARS)	MEAN	7.9	14.0	12.3
	STD DEV	2.3	1.5	3.3
	MEDIAN	7.0	14.0	13.0
	MIN : MAX	5.0 : 11.0	12.0 : 16.0	5.0 : 16.0
	N	7	18	25
WEIGHT (KG)	MEAN	23.2	46.8	40.2
	STD DEV	8.7	10.3	14.5
	MEDIAN	19.4	42.3	39.1
	MIN : MAX	13.8 : 38.3	33.8 : 68.9	13.8 : 68.9
	N	7	18	25

Source: NDA 21-481, Volume 122, page 56.

Baseline characteristics were similar between the two age groups with the exception that adolescents were more immunosuppressed based on baseline CD4+ values and clinical symptoms (Table 6).

TABLE 6. Summary of Baseline Characteristics of Subjects by Age Group

	Age >= 3y to <12y	Age >=12y to <17y	All Subjects
NUMBER OF SUBJECTS	7	18	25
BASELINE VIRAL LOAD (LOG10(COPIES/ML))			
MEAN	4.9	5.0	5.0
STD DEV	0.3	0.6	0.5
MEDIAN	5.1	5.0	5.1
MIN : MAX	4.6 : 5.3	4.0 : 5.9	4.0 : 5.9
N	7	18	25
BASELINE CD4 COUNT (CELLS/UL)			
MEAN	450.0	163.6	225.9
STD DEV	443.3	156.3	263.1
MEDIAN	443.0	131.5	143.0
MIN : MAX	7.0 : 959.0	7.0 : 478.0	7.0 : 959.0
N	5	18	23
BASELINE CD4 PERCENTAGE			
MEAN	19.2	13.1	14.4
STD DEV	20.7	10.9	13.3
MEDIAN	13.9	11.8	13.7
MIN : MAX	1.2 : 50.1	1.3 : 33.9	1.2 : 50.1
N	5	18	23
BASELINE CD8 COUNT (CELLS/UL)			
MEAN	942.8	608.6	681.2
STD DEV	808.6	498.2	574.9
MEDIAN	571.0	438.0	480.0
MIN : MAX	144.0 : 2141.0	145.0 : 1961.0	144.0 : 2141.0
N	5	18	23
BASELINE CD8 PERCENTAGE			
MEAN	43.8	48.4	47.4
STD DEV	14.6	16.0	15.5
MEDIAN	42.0	49.1	45.4
MIN : MAX	29.1 : 67.4	19.9 : 70.6	19.9 : 70.6
N	5	18	23
HIV CLASSIFICATION			
No signs/symptoms	1 (14.3%)	3 (16.7%)	4 (16.0%)
Mild signs/symptoms	3 (42.9%)	1 (5.6%)	4 (16.0%)
Moderate signs/symptoms	1 (14.3%)	5 (27.8%)	6 (24.0%)
Severe signs/symptoms	2 (28.6%)	9 (50.0%)	11 (44.0%)

Source: NDA 21-481, Volume 122, page 57.

Comment: The difference in immune status at baseline between adolescents and children may influence response to treatment in the final analysis when the study is complete and should be accounted for in the analysis.

4. Study Procedures and Monitoring:

Pediatric subjects in study T20-204 and T20-310 underwent clinical and laboratory evaluations at enrollment and throughout each study. Evaluations included history, physical examination and laboratory testing, the latter including periodic monitoring of complete blood count, blood chemistry, viral load and CD4 count.

5. Statistical Methods

Study T20-204A/B and ——— have enrolled a total of 39 subjects at the time of data cutoff ——————. In study T20-204A, data from the 12 subjects enrolled were used to determine pharmacokinetic parameters from IV and SC administration in the 15, 30, and 60 mg/m^2 dose groups.

Primary outcome measures for study T20-204B (n=14) and ——————— included adverse events related to enfuvirtide administration, PK of enfuvirtide during chronic sc dosing, and efficacy measures.

For the efficacy analyses, median changes from baseline for HIV-1 RNA levels and CD4+ cell count/percentage were analyzed. ——————————————

6 Summary of Efficacy

6.1 Study T20-204B

Ten of the 14 study subjects completed 48 weeks of chronic therapy. At week 48, 6/14 subjects had a ≥1 $\log_{10}$ decline in HIV-1 RNA and 4/14 subjects had an HIV-1 RNA level below 400 copies/mL. (ITT population, Table 7). Median reduction from baseline to week 48 in HIV-1 RNA was 0.66 $\log_{10}$ copies/mL for all children (ITT population, Table 8).

Table 7. HIV-1 RNA Suppression All Children (ITT Population)

Time from Start of Treatment	# Measured	ITT Number of Subjects			ITT Proportion (Exact 95% CI)		
		>1 $\log_{10}$ decrease	< 400	< 50	>1 $\log_{10}$ decrease	< 400	< 50
Day 7	13	8	0	0	0.57 (0.29, 0.82)	0.00 (0.00, 0.23)*	0.00 (0.00, 0.23)*
Day 10	14	11	2	0	0.79 (0.49, 0.95)	0.14 (0.02, 0.43)	0.00 (0.00, 0.23)*
Day 18	12	12	3	0	0.86 (0.57, 0.98)	0.21 (0.05, 0.51)	0.00 (0.00, 0.23)*
Week 4	12	12	6	0	0.86 (0.57, 0.98)	0.43 (0.18, 0.71)	0.00 (0.00, 0.23)*
Week 8	11	10	6	0	0.71 (0.42, 0.92)	0.43 (0.18, 0.71)	0.00 (0.00, 0.23)*
Week 12	12	9	6	3	0.64 (0.35, 0.87)	0.43 (0.18, 0.71)	0.21 (0.05, 0.51)
Week 16	11	9	6	4	0.64 (0.35, 0.87)	0.43 (0.18, 0.71)	0.29 (0.08, 0.58)
Week 20	13	8	6	4	0.57 (0.29, 0.82)	0.43 (0.18, 0.71)	0.29 (0.08, 0.58)
Week 24	12	10	6	3	0.71 (0.42, 0.92)	0.43 (0.18, 0.71)	0.21 (0.05, 0.51)
Week 32	12	8	5	4	0.57 (0.29, 0.82)	0.36 (0.13, 0.65)	0.29 (0.08, 0.58)
Week 40	11	5	4	2	0.36 (0.13, 0.65)	0.29 (0.08, 0.58)	0.14 (0.02, 0.43)
Week 48	10	6	4	2	0.43 (0.18, 0.71)	0.29 (0.08, 0.58)	0.14 (0.02, 0.43)

*One-sided, 97.5% confidence interval. Source: NDA 21-481, Volume 266, page 41.

Table 8. Changes in HIV-1 RNA from Baseline (log_{10} copies/mL) (ITT Population)

Measurement Time	All Children		Initial Dose 30 mg/m^2		Initial Dose 60 mg/m^2	
	Number	Median (95% CI)	#	Median**	#	Median (95% CI)
Day 7	14	-1.06 (-1.26, -0.69)	4	-1.00	10	-1.15 (-1.44, -0.69)
Day 10	14	-1.28 (-1.72, -0.98)	4	-1.38	10	-1.22 (-2.04, -0.98)
Day 18	14	-1.57 (-2.03, -1.37)	4	-1.68	10	-1.52 (-2.38, -1.37)
Week 4	14	-1.92 (-2.28, -1.34)	4	-1.73	10	-2.00 (-2.34, -1.34)
Week 8	14	-1.64 (-2.49, -0.22)	4	-1.77	10	-1.64 (-2.59, +0.18)
Week 12	14	-2.03 (-2.94, -0.74)	4	-1.88	10	-2.03 (-2.94, -0.74)
Week 16	14	-2.17 (-2.96, -0.60)	4	-1.73	10	-2.17 (-2.96, -0.65)
Week 20	14	-1.60 (-3.02, -0.13)	4	-1.85	10	-1.60 (-3.12, +0.07)
Week 24	14	-1.75 (-2.76, -0.23)	4	-1.99	10	-1.75 (-2.79, -0.23)
Week 32	14	-1.30 (-3.07, +0.40)	4	-1.34	10	-1.30 (-3.07, DT***)
Week 40	14	-0.75 (-2.85, +0.53)	4	-0.11	10	-0.96 (-2.85, DT***)
Week 48	14	-0.66 (-2.76, DT*)	4	-0.41	10	-0.90 (-2.76, DT***)

*** DT indicates that the upper confidence limit could not be obtained because it corresponds to a patient who discontinued study treatment.
Source: NDA 21-481, Volume 266, page 44.

At week 48 the median reduction from baseline in HIV-1 RNA among the 10 children with data at this time point (as-treated population) was 1.24 log_{10} copies/mL (Table 9).

Table 9 .Changes in HIV-1 RNA from Baseline (log_{10} copies/mL) (As Treated Population)

Measurement Time	All Children		Initial Dose 30 mg/m^2*		Initial Dose 60 mg/m^2	
	Number	Median (95% CI)	Number	Median*	Number	Median (95% CI)
Day 7	13	-1.01 (-1.18, -0.69)	4	-1.00	9	-1.13 (-1.26, -0.69)
Day 10	14	-1.28 (-1.72, -0.98)	4	-1.38	10	-1.22 (-2.04, -0.98)
Day 18	12	-1.57 (-1.91, -1.42)	4	-1.68	8	-1.52 (-2.38, -1.37)
Week 4	12	-2.00 (-2.28, -1.46)	3	-1.86	9	-2.03 (-2.34, -1.46)
Week 8	11	-2.27 (-2.59, -0.02)	4	-1.77	7	-2.27 (-2.87, +0.18)
Week 12	12	-2.36 (-2.94, -0.81)	4	-1.88	8	-2.36 (-3.10, -0.74)
Week 16	11	-2.37 (-2.96, -0.60)	4	-1.73	7	-2.37 (-3.47, -0.65)
Week 20	13	-1.81 (-3.02, -0.55)	4	-1.85	9	-1.81 (-3.12, -0.55)
Week 24	12	-1.75 (-2.69, -0.82)	3	-1.36	9	-2.02 (-2.79, -0.82)
Week 32	12	-1.64 (-3.07, -0.08)	4	-1.34	8	-1.64 (-3.28, +0.40)
Week 40	11	-0.85 (-3.01, +0.39)	4	-0.11	7	-1.07 (-3.15, -0.20)
Week 48	10	-1.24 (-3.05, +0.18)	3	-1.00	7	-1.48 (-3.17, +0.48)

Confidence intervals were not obtainable for the 30 mg/m^2 dose due to the small sample size. Source: NDA 21-481, Volume 266, page 45.

Table 10. HIV-1 RNA Suppression, Initial Dose = 30 mg/m^2 (ITT Population)

Time from Start of Treatment	# Measured	ITT Number of Subjects**			ITT Proportion (Exact 95% CI)		
		>1 log_{10} decrease	< 400	< 50	>1 log_{10} decrease	< 400	< 50
Day 7	4	3	0	0	0.75 (0.19, 0.99)	0.00 (0.00, 0.60)*	0.00 (0.00, 0.60)*
Day 10	4	3	0	0	0.75 (0.19, 0.99)	0.00 (0.00, 0.60)*	0.00 (0.00, 0.60)*
Day 18	4	3	1	0	0.75 (0.19, 0.99)	0.25 (0.01, 0.81)	0.00 (0.00, 0.60)*
Week 4	3	3	1	0	0.75 (0.19, 0.99)	0.25 (0.01, 0.81)	0.00 (0.00, 0.60)*

Week 8	4	3	2	0	0.75 (0.19, 0.99)	0.50 (0.07, 0.93)	0.00 (0.00, 0.60)*
Week 12	4	2	2	1	0.50 (0.07, 0.93)	0.50 (0.07, 0.93)	0.25 (0.01, 0.81)
Week 16	4	2	2	1	0.50 (0.07, 0.93)	0.50 (0.07, 0.93)	0.25 (0.01, 0.81)
Week 20	4	2	2	1	0.50 (0.07, 0.93)	0.50 (0.07, 0.93)	0.25 (0.01, 0.81)
Week 24	3	3	2	0	0.75 (0.19, 0.99)	0.50 (0.07, 0.93)	0.00 (0.00, 0.60)*
Week 32	4	2	2	1	0.50 (0.07, 0.93)	0.50 (0.07, 0.93)	0.25 (0.01, 0.81)
Week 40	4	1	1	0	0.25 (0.01, 0.81)	0.25 (0.01, 0.81)	0.00 (0.00, 0.60)*
Week 48	3	2	1	0	0.50 (0.07, 0.93)	0.25 (0.01, 0.81)	0.00 (0.00, 0.60)*

Source: NDA 21-481, Volume 266, page 43.

Table 11. HIV-1 RNA Suppression Initial Dose = 60 mg/m^2 (ITT Population)

Time from Start of Treatment	# Measured	ITT Number of Subjects			ITT Proportion (Exact 95% CI)		
		>1 $\log_{10}$ decrease	< 400	< 50	>1 $\log_{10}$ decrease	< 400	< 50
Day 7	9	5	0	0	0.50 (0.19, 0.81)	0.00 (0.00, 0.31)*	0.00 (0.00, 0.31)*
Day 10	10	8	2	0	0.80 (0.44, 0.97)	0.20 (0.03, 0.56)	0.00 (0.00, 0.31)*
Day 18	8	9	2	0	0.90 (0.55, 1.00)	0.20 (0.03, 0.56)	0.00 (0.00, 0.31)*
Week 4	9	9	5	0	0.90 (0.55, 1.00)	0.50 (0.19, 0.81)	0.00 (0.00, 0.31)*
Week 8	7	7	4	0	0.70 (0.35, 0.93)	0.40 (0.12, 0.74)	0.00 (0.00, 0.31)*
Week 12	8	7	4	2	0.70 (0.35, 0.93)	0.40 (0.12, 0.74)	0.20 (0.03, 0.56)
Week 16	7	7	4	3	0.70 (0.35, 0.93)	0.40 (0.12, 0.74)	0.30 (0.07, 0.65)
Week 20	9	6	4	3	0.60 (0.26, 0.88)	0.40 (0.12, 0.74)	0.30 (0.07, 0.65)
Week 24	9	7	4	3	0.70 (0.35, 0.93)	0.40 (0.12, 0.74)	0.30 (0.07, 0.65)
Week 32	8	6	3	3	0.60 (0.26, 0.88)	0.30 (0.07, 0.65)	0.30 (0.07, 0.65)
Week 40	7	4	3	2	0.40 (0.12, 0.74)	0.30 (0.07, 0.65)	0.20 (0.03, 0.56)
Week 48	7	4	3	2	0.40 (0.12, 0.74)	0.30 (0.07, 0.65)	0.20 (0.03, 0.56)

Source: Volume 266, page 43.

Changes in $CD4^+$ Cell Count and $CD4^+$ Percentage.

By week 48 the overall median increases in $CD4^+$ cell count and $CD4^+$ percent from baseline in all the children were 237 cells/μL and 3.5%, respectively (Table 12). The median changes from baseline CD_4 cell count for children who received 60 mg/m^2 was 122 cells/μL (Table 13). The median changes from baseline CD_4 cell count for children who received 30 mg/ was 476 cells/μL (Table 14).

Table 12. Changes in $CD4^+$ Count (Cells/μL/percentage) from Baseline All Children (As Treated Population)

Measurement Time	Number	Median Change in $CD4^+$ Count (95% CI)	Median Change in $CD4^+$ Percentage (95% CI)
Day 10	11	+28 (–244, +150)	+3.0 (-4.0, +4.0)
Week 8	12	+160 (-36, +407)	+3.0 (0, +9.0)
Week 16	12	+214 (–17, +486)	+2.0 (-1.0, +10.0)
Week 24	11	+146 (+13, +655)	+2.0 (0, +12.0)
Week 32	11	+134 (-65, +681)	+5.0 (+1.0, +9.0)
Week 40	10	+126 (-47, +736)	+6.0 (-1.0, +14.0)
Week 48	10	+237 (-75, +632)	+3.5 (+1.0, +8.0)

Source: NDA 21-481, Volume 266, page 47.

Table 13. Changes in $CD4^+$ Count (Cells/μL/percentage) Initial Dose = 60 mg/m^2

Measurement Time	Number	Median Change in $CD4^+$ Count (95% CI)	Median Change in $CD4^+$ Percentage (95% CI)
Day 10	7	+82 (–769, +150)	-3.0 (-7.0, +4.0)
Week 8	8	+143 (-571, +570)	+5.5 (-1.0, +12.0)
Week 16	8	+184 (–1621, +808)	+3.5 (-3.0, +21.0)
Week 24	8	+142 (-808, +827)	+3.0 (-1.0, +18.0)
Week 32	7	+134 (-65, +681)	+5.0 (-4.0, +22.0)
Week 40	7	+111 (-55, +1143)	+7.0 (-12.0, +22.0)
Week 48	7	+122 (-149, +751)	+5.0 (+1.0, +29.0)

Source: NDA 21-481, Volume 266, page 47.

TABLE 14. Changes in $CD4^+$ Count (Cells/μL) and Percentage Initial Dose = 30 mg/m^2

Measurement Time	Number	Median Change in $CD4^+$ Count	Median Change in $CD4^+$ Percentage
Day 10	4	+7	-1.5
Week 8	4	+220	+1.0
Week 16	4	+357	+0.5
Week 24	3	+189	+1.0
Week 32	4	+275	+4.0
Week 40	3	+147	+2.0
Week 48	3	+476	+1.0

Confidence intervals were not obtainable for the 30 mg/m^2 dose due to the small sample size.
Source: NDA 21-481, Volume 266, page 47.

6.2 T20-310

Study T20-310 is an ongoing, open-label, multi-center trial evaluating the pharmacokinetics, safety, and antiviral activity of enfuvirtide in treatment experienced children and adolescents. Fourteen subjects had decreases of ≥ 1 $\log_{10}$ copies/mL HIV-1 RNA at Week 2 of enfuvirtide administration. Improvements in $CD4^+$ and $CD8^+$ cells counts from baseline were noted in most subjects. Twenty-five subjects ages 3 through 16 years were enrolled (median age of 13 years). The evaluation of safety and antiviral activity is ongoing.

> **Comment:** Among the total of 39 subjects studied, most showed a reduction in HIV-1 RNA levels and a rise in CD4 lymphocyte count. Nevertheless, it is difficult to determine the relative contribution of enfuvirtide to the activity of the ARV drugs that have been used during the both studies.

7. Safety Analysis

7.1 Exposure

All 40 subjects from studies T204A/B (n=15) and T20-310 (n=25) were included in the safety analysis. The mean cumulative exposure in study T20-204B was 71 weeks and in study T20-310 was 23.4 weeks.

In study T20-204B, 14 children received at least one dose of enfuvirtide and 11 children completed 48 weeks of treatment. The first 4 children initially received the 30 mg/m^2 dose, and except for one subject, were dose escalated to 60 mg/m^2 by week 10; the remaining 10 children received the 60 mg/m^2 dose. Of the three children who did not complete 48 weeks of treatment with enfuvirtide, two were assigned to the 60 mg/m^2 dose. The third child was assigned to the 30 mg/m^2 dose but was dose escalated to 60 mg/m^2 at week 9. The duration of study treatment for the three children who were withdrawn prematurely was 22 days, 24 weeks, and 40 weeks. Study T20-310 is ongoing.

7.2 Adverse Events

7.2.1 Deaths

There were no deaths reported in either T20-204 A/B and T20-310.

7.2.2 Serious Adverse Events

Injection Site reactions (ISRs) are discussed separately in Section 8.

In study T20-204, five children required hospitalization because of adverse events (Table 15). One child was hospitalized due to *S. pneumoniae* bacteremia and concurrent asthma. A second child was hospitalized at week 24 for treatment of Herpes zoster. A third child was hospitalized at week 16 for a portacath replacement, while a fourth was hospitalized at week 33 for influenza B pneumonia. The fifth child was hospitalized at week 9 for repeated vomiting, upper gastrointestinal bleeding, and dehydration. None of these events were considered related to enfuvirtide.

Table 15. Grade 3 or 4 SAEs Reported at Any Time (Study T20-204)

Dose Initially Assigned (mg/m2)	Patient Number	Signs or Symptoms	Grade	Week(s) of Grade 3 / 4	Association with Study Treatment
30*	280771	Behavioral disturbance/Psychosis	3	20/56	Unable to Judge
60	280451	Pneumonia	4	16, 20	Not Related
60	361869	Allergic rash	4	3	Not Related
		Herpes Zoster	3	24	Not Related
60	500636	Pneumonia/fever	3	28	Possibly, Probably
60	440207	Dehydration/Vomiting	3	9	

*All the signs and symptoms listed occurred after the initial dose of 30 mg/m2 was increased to 60 mg/m2.
Source: NDA 21-481, Volume 266, page 33.

In study T20-310, three subjects (12%) were reported to have SAEs as November, 2002. All SAEs were considered unrelated to enfuvirtide. The SAEs were neutropenia in one child, and one event each of pneumonia and injection site infection in adolescents (Table 16).

Table 16. Serious Adverse Events (Study T20-310)

Diagnosis	Children ≥ 3 and <12 years of age N=7	Adolescents ≥12 and <17 years N=18	Total
Pneumonia	0	1	1
Blood Disorders Neutropenia	1	0	1
Injection Site infection	0	1	1
Total Number of SAEs	1	2	3

7.2.3 Withdrawals

No adverse events leading to withdrawal were reported for subjects in study T20-204. Three of the 14 children were prematurely discontinued from the study. One subject was discontinued from the study on day 22 at the request of their mother because of the child's aversion to injections. No follow-up of this child was obtained after discontinuation of study treatment. A second child voluntarily discontinued treatment with enfuvirtide immediately after completing 24 weeks of treatment. A third child stopped treatment with enfuvirtide on week 40 after virologic failure but continued follow-up to week 48.

In study T20-310 a total of 4 adolescent subjects withdrew from the trial. None of the premature withdrawals were reported to be due to safety reasons. The reasons for withdrawal included refusal of treatment, aversion to injections, non-compliance, and failure to return.

7.2.4 General Adverse Events

7.2.4. 1 T20-204

Twelve children completed Part A of the study. No Grade 3 or worse sign or symptom was reported from Part A of the study. Mild injection site reactions, Grade 2 vomiting and poor weight gain, cough, rhinorrhea, and scattered nasal congestion was observed in few of the subjects.

Eleven of 12 Part A participants and three additional subjects were enrolled in Part B. Thirteen subjects completed 48 weeks of treatment. One child discontinued enfuvirtide after 22 days of treatment because of aversion to injections. Among the 13 children that completed the study one stopped enfuvirtide treatment immediately after completing 48 weeks. Seven children reported fever. Four of the 7 children had a fever of Grade 2 (≥ 100.4 and < 103 degrees F) and one had a fever of Grade 3 (≥ 103 and ≤ 105 degrees F). The remaining 2 children had fevers less than Grade 2 intensity (< 100.4 degrees F). In all, only one of the Grade 2 fevers was considered related to enfuvirtide.

Bronchospasm was experienced by several subjects. Six episodes of wheezing or bronchospasm were seen in four subjects. Three of these subjects had a history of asthma. Enfuvirtide was continued in all four subjects who experienced wheezing or bronchospasm (Table 17).

Table 17. Grade 2 or Higher Treatment Emergent Signs or Symptoms

Dose Initially Assigned (mg/m2)	Patient Number	Description	Also Reported As	Week(s) Reported	Worst Grade
30	280413	Otalgia		12	2
	280771	Behavioral disturbance	SAE	20	3
	500520	Fever	ISR	26	2
60	280451	Wheezing	Diagnosis	16, 20	4
		Cough	Diagnosis	16, 20	3
		Fever	Diagnosis	16, 20	3
		Chest pain	Diagnosis	16, 20	2
		Lymphadenopathy		4, 8, 12, 16, 20, 26	2
	300482	Pain at injection site**	ISR	1	2
		Cough	Diagnosis	1	2
		Wheezing	Diagnosis	1	2
		Difficulty breathing	Diagnosis	1	2
	361869	Allergic rash	ISR	3	4
		Pain in left leg	ISR & Diagnosis	24	3
		Rash	Diagnosis	24	3
		Vesicles	Diagnosis	24	3
		Erythema, pain at injection site	ISR	2	2
	440207	Fecal discharge		9, 13	2
		Bronchospasm		13, 17	2
		Erythema, pain, induration at injection site	ISR	4	2
	470188	Swelling at injection site	ISR	4, 8	2
		Erythema, pain, induration at injection site	ISR	4	2
	500636	Erythema	ISR	1, 5, 8	3
		Plaque		1	2
		Scabies rash	Diagnosis	1	2

		Fever	ISR	2, 13	3
		Lymphadenopathy		2, 3	2
	505217	Behavior changes		3, 5, 8, 13, 16, 21	2
		Fever	ISR	21	2
	810007	Pain at injection site	ISR	2, 3	2
		Erythema and induration at injection site	ISR	1, 2, 3	2
		Fever	ISR & Diagnosis	4, 13, 21, 25	2
		Lymphadenopathy/ Induration		9	2
		SOB	Diagnosis	13	2
		Wheezing	Diagnosis	13	2
		Breath sounds abnormal (crackles)	Diagnosis	13	2
		Ear Pain	Diagnosis	25	2

Source: NDA 21-481, Volume 266, pages 34-35.

7.2.4.2 Study T20-310

The most common AEs reported (≥ 3 subjects) were ISRs, discussed in Section 8, followed by diarrhea, nausea, and upper respiratory tract infection. Most of the AEs reported were mild to moderate in intensity.

Fifteen of twenty-five (60%) subjects (4 children, and 11 adolescents) reported a total of 42 non-ISR AEs. The most frequently reported AEs (≥ 3 subjects) were nausea (0/7 children, 4/18 adolescents), upper respiratory tract infection, (1/7 children, 2/18 adolescents), and diarrhea (0/7 children and 3/18 adolescents) (Table 17).

There were 4 events in different subjects considered by the investigator to be remotely, possibly, or probably related to enfuvirtide. Of these, two events were considered remotely related: a mild decrease in appetite in a child, and mild diarrhea in one adolescent. The other two events considered possibly related were moderate diarrhea and mild tinnitus, each in one adolescent.

Table 18. Summary of All Adverse Events in Study T20-310 By Age Group

Adverse Event	Children (≥ 3 to < 12 y)(n = 7) No. [1] (%)	Adolescents (≥ 12 to < 17 y) (n = 18) No. [1] (%)	All Subjects (n = 25) No. (%) [2]
Nausea	-	4 (22.2%)	4 (16%)
Diarrhea nos	-	3 (16.7%)	3 (12%)
Upper Respiratory tract Infection nos	1 (14.3%)	2 (11.1%)	3 (12%)
Mouth ulceration	2 (28.6%)	-	2 (8%)
Vomiting nos	-	2 (11.1%)	2 (8%)
Dermatitis nos	-	2 (11.1%)	2 (8%)
Oral candidiasis	1 (14.3%)	1 (5.6%)	2 (8%)
Sinusitis nos	-	2 (11.1%)	2 (8%)
Appetite decreased nos	1 (14.3%)	1 (5.6%)	2 (8%)
Herpes Zoster	1 (14.3%)	-	1 (4%)
Otitis media nos	-	1 (5.6%)	1 (4%)
Pharyngitis streptococcal	-	1 (5.6%)	1 (4%)
Pneumonia nos	-	1 (5.6%)	1 (4%)

Vaginal candidiasis	1 (14.3%)	-	1 (4%)
Vaginal infection nos	-	1 (5.6%)	1 (4%)
Bronchospasm nos	-	1 (5.6%)	1 (4%)
Cough	1 (14.3%)	-	1 (4%)
Nasal Congestion	1 (14.3%)	-	1 (4%)
Rhinitis Allergic nos	-	1 (5.6%)	1 (4%)
Sore throat nos	-	1 (5.6%)	1 (4%)
Pruritus nos	-	1 (5.6%)	1 (4%)
Rash maculo-papular	-	1 (5.6%)	1 (4%)
Hypokalaemia	-	1 (5.6%)	1 (4%)
Injection site infection	-	1 (5.6%)	1 (4%)
Pyrexia	-	1 (5.6%)	1 (4%)
Neutropenia	1 (14.3%)	-	1 (4%)
Tinnitus	-	1 (5.6%)	1 (4%)
Hypersensitivity nos	1 (14.3%)	-	1 (4%)
Splinter	1 (14.3%)	-	1 (4%)

Multiple occurrences of the same adverse event in one individual counted only once.
Source: NDA 21-481, Volume 122, page 72.

7.2.5 Laboratory Adverse Events

7.2.5.1 T20-204

All but one subject experienced at least a one grade shift from baseline in one or more laboratory parameters. No subject reported Grade 4 abnormalities. Low grade shifts were usually transient and most commonly seen for sodium (n=7), glucose (n=5), cholesterol (n=4), potassium, alkaline phosphatase, SGOT, SGPT, and creatinine (3 subjects each). The maximum change in laboratory parameters did not exceed two grades from the baseline value. Two grade shifts were noted in glucose (n=2), potassium, calcium, lipase and creatinine phosphokinase (one subject each).

One child, assigned to the 60 mg/m^2 dose, entered the study with a Grade 1 CPK level and experienced an increase to a Grade 3 CPK level at week 25. This patient voluntarily discontinued study treatment at week 24. The last dose of enfuvirtide was given on the same day that the specimen was collected for the CPK evaluation. The CPK level was 637 U/L, compared to a level of 315 U/L prior to starting enfuvirtide treatment. Three days later, the CPK level was 237 U/L when the patient was tested for follow up.

A Grade 2 abnormal value for glucose at week 1 was also reported prior to enfuvirtide dosing and subsequently resolved to a lower grade during study treatment. However, this child and the other four children also had at least one Grade 2 abnormality that developed after starting study treatment. In all cases, these abnormal values resolved to lower grades at subsequent testing (Table 19).

Table 19. Grade 2 or 3 Laboratory Abnormalities Reported at any time: Study T20-204

Dose Initially Assigned (mg/m2)	Patient Number	Abnormality	Grade at Entry	Week(s) of Grade 2/3	Lowest Grade after Last Grade 2/3 Value	Association with Study Treatment
30*	280771	Glucose decrease	0	1	0	Not Related
30*	500520	Calcium decrease	0	1	0	Not Related
60	280451	SGPT increase	N/A	1	0	Unable to judge
		Glucose decrease	0	1	0	Not evaluated
60	440207	Potassium increase	0	5, 21	0	Not evaluated
		SGOT increase	1	2	1	Not evaluated
		CPK increase	1	1, 5, 21, 25**	N/A	Possibly/Probably
60	810007	Glucose decrease	2	0, 1	0	Baseline
		Lipase increase	0	1, 9	0	Possibly/Probably

N/A = No graded test result available

* Abnormalities occurred while the patient was receiving the 30 mg/m2 dose. ** Grade 3

Source: NDA 21-481, Volume 266, page 39.

7.2.5.2 T20-310

For each laboratory parameter, the majority of subjects had no change in grade during the study. A number of single grade shifts were seen which included: SGOT increased (n = 6) subjects, magnesium (Mg+) decreased (n = 6), hemoglobin decreased (n = 5), SGPT or GGT increased (n = 3), and potassium decreased (n = 3). One child with pre-existing neutropenia had a 4 grade shift in neutrophils (reported as a SAE as per the protocol) which resolved upon treatment with granulocyte colony stimulation factor. One adolescent had a 4 grade shift in amylase levels without a corresponding increase in lipase. Most changes in laboratory values were 1 to 2 grade shifts from baseline.

8. Adverse Events of Special Concern

The following events were evaluated because they are known to be of concern in adult subjects treated with enfuvirtide.

8.1 Injection Site Reactions (ISRs)

8.1.1 Study T20-204B

The most common adverse events associated with enfuvirtide use were ISRs. Eleven (79%) of the 14 children enrolled in T20-204B had local injection site reactions one or more times during the 48 week chronic dosing with enfuvirtide (Table 20). Local injection site reactions were

graded 1 (mild) to 4 (severe) for erythema, induration, pain and lymph node swelling. One child had Grade 3 erythema on 3 occasions; all other reactions were Grade 2 or less. Other local reactions include mild itching (n = 2), bruising (n = 2), edema (n = 2) and tenderness (n = 1). No child discontinued or interrupted enfuvirtide because of injection site reactions. Overall, the ISR was less frequent in children as compared to adults.

Table 20. Number of Children with Various Types of Local ISRs in Study T20-204

Worst Grade	Erythema	Induration	Pain	Lymph Node Swelling	All Reactions
Grade 1	1	6	4	2	5
Grade 2	4	3	4	0	5
Grade 3	1	0	0	0	1
All Grades	6	9	8	2	11

Source: NDA 21-481, Volume 266, page 31.

8.1.2 T20-310

The majority of subjects (72.0%) had at least 1 local ISR during the study. In 52% of these subjects, ISRs were associated with some degree of pain or discomfort at the injection site. Of these subjects, approximately 1/2 had mild tenderness at the injection site (Grade 1); one patient reported Grade 3 pain and discomfort. No Grade 4 events of pain and discomfort were reported.

The most frequent signs and symptoms from ISRs overall were erythema (10 subjects) and induration (11 subjects). Of the 10 subjects with erythema, 4 subjects had Grade 3 and one patient had Grade 4 erythema. Of the 11 subjects with induration, 3 subjects had Grade 3 induration and 2 subjects had Grade 4 induration. Ten subjects had 1 to 2 lesions evident at a study visit. For most subjects with lesions, the average duration was 72 hours.

Fewer children (3 to < 12 years) reported pain and discomfort associated with ISRs than adolescents (12 to < 17 years). Only two children reported mild pain and discomfort at the injection site; in contrast, 11 adolescents reported pain and discomfort. Five out of 18 adolescents reported mild tenderness (Grade 1) at the injection site and an additional 5 adolescents reported moderate pain without limitation of usual activities (Grade 2). One adolescent had an ISR that was associated with severe (Grade 3) pain.

The signs and symptoms of an ISR also differed in children vs. adolescents. Induration (2 subjects) and other ISR events (1 subject) were the only ISR signs and symptom reported in children. Of the two children with induration, one child had a slight induration (Grade 1) and the other had induration that was (Grade 2). The other ISR event reported was mild swelling in one subjects. One child had 1 to 2 lesions (Grade 1) evident at a study visit with an average duration of >24 hours to 72 hours (Grade 2).

The most frequent signs and symptoms of an ISR in adolescents were erythema (10 subjects), induration (9 subjects), and pruritus (5 subjects). Of the 10 adolescents with erythema, 4 had Grade 3 erythema and one subject Grade 4. Of the nine subjects with induration, 3 had Grade 3 induration and 2 Grade 4. Half of the adolescents had 1 to 2 lesions evident at a study visit. The average duration of lesions was 72 hours.

Most subjects had at least one ISR. The incidence of ISRs was similar for both age groups. The most frequently reported signs and symptoms of an ISR were erythema and induration in adolescents, and induration in children. Six adolescent subjects reported to have other symptoms with ISR: a lump (due to 1 mL of fluid, described as neither a cyst or nodule), abscess, itching, swelling, edema, cellulitis and mild tenderness.

8.2 Pneumonia

The increased rate of bacterial pneumonia that was observed in subjects treated with enfuvirtide in the Phase 3 clinical trials in adults compared to the control arm was not seen in pediatric subjects. Only one pediatric subject was reported to have bacterial pneumonia associated with enfuvirtide use. Another child required hospitalization for pneumonia due to influenza. In adult subjects associated risk factors for developing pneumonia were low CD_4 count, high viral load, intravenous drug use, smoking and past history of lung disease.

8.3 Hypersensitivity Reaction

Hypersensitivity reactions have been associated with enfuvirtide therapy in adults and may recur on re-challenge. Rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated serum liver transaminases changes were observed in adults who had hypersensitivity reaction. Only one pediatric subject was reported to have a generalized allergic reaction; this occurred on study day 286, and was attributed to a food allergy. Another child developed a grade 4 rash on study day 19, which was attributed to efavirenz. Immune mediated adverse events that may be associated with use of enfuvirtide such as primary immune complex reaction, respiratory distress glomerulonephritis, and Guillain-Barre syndrome were not seen in studies T20-204 and T20-310.

> Comment: The frequency and severity of overall pain and discomfort associated with enfuvirtide injections was lower in children than in adolescents. Because both trials had relatively few subjects, it is difficult to reach conclusions about adverse events of special concern such as ISRs, bacterial pneumonia and hypersensitivity reaction. The adverse events may be more commonly seen in clinical practice when more children are exposed to enfuvirtide. Because of this, unitl more data is available, pediatric patients should be as carefully monitored as adults for potential adverse events from enfuvirtide use. .

9. Pharmacokinetic Results

Please see Dr. Robert Kumi's Biopharmaceutics review for complete details.

Eighteen subjects, ages ranging 6 through 16 years (from studies T20-204 and T20-310) were included in the PK analysis report. Enfuvirtide pharmacokinetics were determined in the presence of concomitant medications including antiretroviral agents. A dose of 2 mg/kg bid (maximum 90 mg bid) provided enfuvirtide plasma concentrations similar to those obtained in adult subjects receiving 90 mg bid. The pharmacokinetics of enfuvirtide were not evaluated in pediatric subjects below 6 years of age.

10. Conclusions

A total of 39 subjects ages ranging 6-16 years, received enfuvirtide in combination with other antiretroviral agents in two clinical trials (T20-204 and T20-310). The mean cumulative exposure in study T20-204 was 71 weeks and in study T20-310 was 23 weeks. The safety information for all 39 pediatric subjects who received enfuvirtide at 15 mg/m^2, 30 mg/m^2, 60 mg/m^2, or 2mg/kg, for up to 48 weeks was reviewed.

Overall, the adverse event profile observed in pediatric subjects is similar to that observed in adults. Although an apparent increased incidence of pneumonia was not seen, nor were any hypersensitivity reactions observed, this may be a function of the small number of children studied. Enfuvirtide was generally well tolerated. The introduction of enfuvirtide as part of an ARV regimen was associated with decreases in HIV-RNA and increases in CD4 counts. There were no deaths related to study treatment in both studies. The most common reported AE were ISRs. Adverse events other than ISRs reported in over 3 subjects included diarrhea, nausea, and URI infection and fever.

Eleven of 14 (79%) children in T20-204 had an ISR. All ISRs were mild to moderate in degree except for one subject. The most commonly reported ISR was pain followed by induration and erythema. The incidence and severity of overall pain and discomfort with T-20 injections was less in younger children than in adolescents, although the number of children studied was small. Laboratory abnormalities that were associated with use of enfuvirtide included moderate decreases in serum glucose and calcium as well as mild elevations of SGPT, SGOT, creatinine lipase, potassium, cholesterol that were seen in some children. One subject who discontinued enfuvirtide voluntarily had a grade 3 elevation of CPK.

Enfuvirtide showed antiviral activity in both studies. By week 48, 6 of the 14 children enrolled in T20-204B achieved reductions from baseline HIV-1 RNA of > 1 $\log_{10}$ copies/mL. Median change in HIV-1 RNA was –0.66 $\log_{10}$ copies/mL with increases in $CD4^+$ cell count and $CD4^+$ percentage. At week 48, median increases in $CD4^+$ cell count and $CD4^+$ percentage from baseline were 237 cells/μL and 3.5%, respectively. A decrease in HIV-1 RNA $\geq$ 1 $\log_{10}$ copies/mL at Week 2 of enfuvirtide administration was observed in study T20-310 with improvements in $CD4^+$ and $CD8^+$ cells counts from baseline. (For T20-310 this was the only efficacy data available.)

The pharmacokinetic data reviewed by Dr. Kumi demonstrates similar exposure in pediatric subjects who received enfuvirtide at either 60 mg/m^2 or 2mg/kg sc bid to adults who received the currently recommended dose of 90 mg of enfuvirtide. Trough plasma concentrations were similar in all 3 regimens and support the use of a dose of 2 mg/kg/day in children. Due to the lack of PK information in younger children with enfuvirtide, pediatric use of enfuvirtide in lower age ranges (i.e.; children < 6 years of age) should not be cited in the package insert. The safety and pharmacokinetics of enfuvirtide needs further study in the subpopulation.

Overall, the pediatric studies reviewed indicate that enfuvirtide, in combination with other ARV therapy in HIV-1-infected children, is safe and effective for use in children 6 –1 6 years of age. .

11 Regulatory Recommendation

The package insert for enfuvirtide should include recommendations for dosing of children ages 6-16 years with enfuvirtide at 2 mg/kg dose BID for the treatment of HIV-1 infection in children.

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