Title:	A Phase 2 rollover protocol for HIV-infected adults with prior T-20 treatment
Investigators/Sites:	Multi-investigators/Multicenter (United States)
Period:	01/99 – 04/01
Study:	T20-205

Pharmacokinetic Objective
To determine plasma pharmacokinetics (PK) of T-20 given by SC injection for 96 weeks

Study Design
The pharmacokinetic (PK) substudy was conducted as part of a larger safety and efficacy study. The study enrolled HIV-infected adults who had previously participated in short-term Phase I studies of T-20. Patients received T-20 50 mg twice daily by SC injection for up to 96 weeks. The main PK methodology involved blood sample collection. In addition to T-20, all patients were on an optimized antiretroviral background regimen.

Assay
The applicant indicates that T-20 concentrations were determined by [redacted] immunoassay. This assay has been used in other T-20 studies and has performed acceptably. Because results from this study will not be included in the label and the study was not conducted at the proposed clinical dose this reviewer did not further explore the performance of the assay. Consequently the results presented in this review can be viewed in a qualitative manner.

Formulations
T-20 batch numbers used during the study were 711013, 800288, 800320, 800426, 800463, 800517, 800569, TTA001, TTA002, TTA003, ADP0407, ADP0319, ADP0405, and ADP0415.

Blood Samples
- Intensive blood samples were obtained at 0, 0.5, 1, 2, 4, 6, 8, and 12 hours post dose from most patients on Day 28
- Trough blood samples were obtained from all patients on Day 14 and at weeks 8, 12, 16, 20, 24, 32, 40, 48, 56, 64, 72, 80, and 88.

PK Analyses
Noncompartmental methods were used to estimate the following PK measures for T-20 (Day 28): C_{max}, C_{ss}, T_{max}, C_{min}, $AUC_{0\text{-}12\ hr}$, and CL/F.

Patient Compliance
The applicant indicates that patient compliance to T-20 administration was assessed though determination of number of vials used by patient. Additionally, the patients were required to complete diary cards. Ideally, T-20 administration should have been conducted or closely monitored by the study staff because patient compliance will affect the PK results.

Results
PK data were available from the majority of subjects (65 out of 70) who took part in the trial. The PK data obtained in this study are summarized in Table I.

Table I: Mean ± SD (range) Day 28 T-20 PK Measures following twice daily administration of 50 mg (n = 65).

C_{ss} (µg/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC_{0-12hr} (µg·hr/mL)	T_{max}* (hr)
1.88 ± 0.73	2.57 ± 0.81	1.13 ± 0.56	22.61 ± 8.22	4.0 ± 1.45

Interindividual variability in exposure ranged from [redacted] (CV), with the greatest variability occurring with C_{min} values. It is difficult to determine the source of the variability; potential sources of variability include patient compliance and the role of concomitant medications. In essence, data from this trial are more observational (uncontrolled or limited control) than experimental (controlled clinical setting). Nevertheless, the information from this trial suggests that the proposed dose of 90 mg is likely to yield adequate T-20 exposure, particularly in terms of the trough data (target IC_{50} = 1.0 µg/mL). Overall the PK data from this study are comparable to the PK data obtained in other studies at the 50 mg dose, particularly Study 206. In study 206, the C_{minss} was approximately 1 µg/mL. Other exposure measures were comparable for study 205 and 206.

Selected trough concentrations collected during the course of the trial are summarized below (Table II)

Table II: Mean ± SD Trough T-20 plasma concentrations at the 50 mg BID dose.

Study Week	N	C_{trough} (µg/mL)
Week 16	50	1.10 ± 0.71
Week 24	41	1.09 ± 0.58
Week 48	30	1.04 ± 0.66
Week 72	28	1.22 ± 0.69
Week 96	20	1.05 ± 0.85

(N) number of subjects

Trough data were highly variable (CV generally [redacted]). Although the number of subjects varied at the various trough collection weeks, the mean trough concentrations were fairly consistent (≈ 1 µg/mL) throughout the study period.

Conclusion

The 50 mg BID T-20 regimen achieves a mean C_{min} of approximately 1 µg/mL (applicant's proposed target plasma concentration) and this trough concentration is sustained over a 96-week period.

Study Information: [redacted] Study P1005 (IND [redacted]
Study: T20-204
Investigators/Sites: Multiple investigators/Multiple sites within USA
Study Period: 11/99 – 05/2000 (Part A)

Introduction

Clinical study T20-204 was conducted as a two-part study comprising Part A and Part B. This review will address the two study Parts in turn; Part A (pages 1 –9) and Part B (Pages 10 - 13)

Objectives (Part A)

- To obtain preliminary information on the safety, tolerability, and pharmacokinetics of T-20 given as a single SC injection and a single IV bolus.
- To determine the dose range to use for chronic twice daily (BID) SC injections in Part B.

Study Design

This was a Phase I/II, dose-escalating, open-label, single and chronic dosing study to evaluate the safety, tolerability, and pharmacokinetics of T-20 given as a single SC injection, a single IV infusion, and as chronic bid SC injections in HIV-1 infected children ages 3 to 12 years old. The study was conducted in two parts, Part A (dose-escalating single dose study) and Part B (dose-escalating chronic dosing study). The design of Part A of the study is summarized as follows:

Part A – Single Dose Study

		Day 0		Day 1
Cohort 1 N = 4 (Age 3 - 12 years)	→	Cohort 1 SC T-20, 15 mg/m^2, followed by 12 h PK	→	Cohort 1 IV T-20, 15 mg/m^2, followed by 12 h PK
Cohort 2 N = 4 (Age 4 - 12 years)	→	Cohort 2 SC T-20, 30 mg/m^2, followed by 12 h PK	→	Cohort 2 IV T-20, 30 mg/m^2, followed by 12 h PK
Cohort 3 N = 4 (Age 4 - 8 years)	→	Cohort 3 SC T-20, 60 mg/m^2, followed by 12 h PK	→	Cohort 3 IV T-20, 60 mg/m^2, followed by 12 h PK

The study nurse administered the SC injection into the abdomen, deltoid area, or anterior aspect of the thigh of the subjects. The IV infusion was administered over a 10-minute period either via IV push or rapid drip. Dose adjustments to antiretroviral (ARV) therapy were allowed to adjust for changes in body surface area. Additionally, substitutions to a patient's add-on ARV therapy regimen, other than T-20, were made for cases of intolerance or toxicity.

Previous and Current Antiretroviral Therapies

Most subjects had treatment experience with both protease inhibitors and NRTIs and continued treatment during Part A. No patient received an NNRTI during Part A of the study.

Reviewer Comment

Ideally, these subjects should not have received other medications during this phase due to drug-drug interaction potential that may influence T-20 exposure. T-20 has a low potential to interact

with ARV via common metabolic pathways (e.g. CYP); however, ritonavir increases T-20 exposure. Thus, subjects receiving T-20 and RTV may have higher exposure, particularly C_{min}, than subjects not receiving RTV; consequently, the PK results in this study may be confounded.

Dosage Selection Rationale

According to the applicant, *in vitro* and *in vivo* data suggest that steady state trough concentrations of 1 μg/mL are effective for viral suppression. Therefore, doses for Part A of this study were chosen so that the expected plasma trough concentrations bracketed the target 1 μg/mL plasma trough concentration. In adult subjects who received 100 mg T-20 IV every 12 hours, trough concentrations were maintained above 1 μg/mL throughout the 12-hour dosing interval. Similarly, subjects receiving T-20 by continuous SC infusion and SC injection maintained steady state plasma trough concentrations in a dose-dependent manner. The projected concentrations, based on adult data were as follows:

Dose Group	Projected Steady State T-20 Plasma Trough Concentration	Adult bid Dose by SC Route	Pediatric bid Equivalent Dose*
1	0.5 μg/mL	25 mg	15 mg/m^2
2	1.0 μg/mL	50 mg	30 mg/m^2
3	2.0 μg/mL	100 mg	60 mg/m^2

*Target adult daily doses were converted to mg/m^2 units, assuming an adult to have a surface area of 1.73 m^2 (dose rounded off to nearest 0.5 mg)

Based on these projected steady state plasma trough concentrations, the 15, 30, and 60 mg/m^2 T-20 doses were evaluated in Part A of this study.

Formulation

T-20 was supplied as a lyophilized powder in 25 mg and 50 mg vial sizes. T-20 lot numbers: 25 mg (800123), 50 mg (800426 and ADP0415), and 100 mg (ADP0425).

Blood Sampling

For pharmacokinetic analysis, blood (0.5 mL) was collected prior to dosing (SC Day 0 and IV Day 1) and at 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, and 12 hours post-dosing. On Day 1, the pre-dose blood draw also served as the 24-hour blood draw for SC dosing. The total volume of blood drawn for Part A of this study was approximately 37 mL (volume includes all kinetic and safety samples).

Assay

No information was provided on the assay other than that plasma samples were analyzed by [redacted]

Reviewer Comment

This reviewer could not locate information on the assay in the study report. Because Study 204 was a pilot study and results from this study will not be included in the label, the omission of assay information can be pardoned. It is noted that [redacted] conducted previous T-20 analyses using a validated assay [redacted]

PK Parameters

Estimated T-20 parameters include C_{max}, C_{12} (C_{min}), T_{max}, AUC, $t_{1/2}$, CL (after IV), CL/F (apparent clearance), V_d (for IV) and V_d/F. The bioavailability of T-20 following SC administration was estimated as AUC_{inf} (SC)/AUC_{inf} (IV). Plasma PK parameters were estimated with WinNonlin Professional (Version 3.0,) based on model-independent techniques. The report indicates that nominal sample times were used for all analyses. It is unclear why nominal sampling times were used. This approach of using nominal times could influence the PK analyses and lead to inaccurate determinations. Because this is a pilot study and the results will not be included in the label, the applicant will not be asked to provide justification for using nominal sampling times.

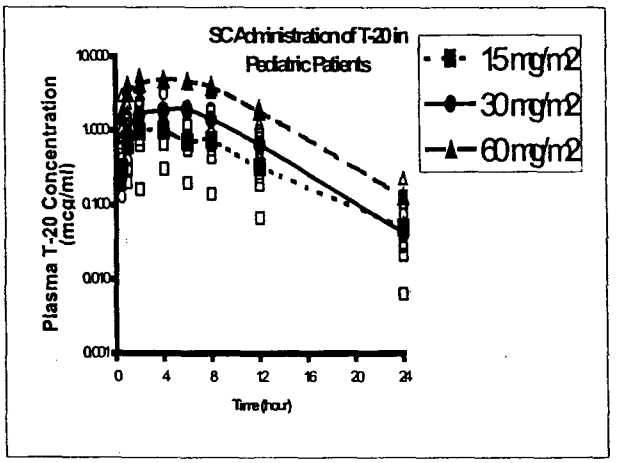
Results

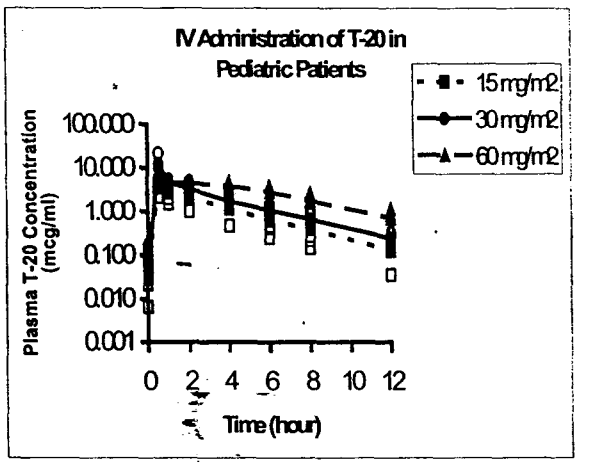
Subjects

The pharmacokinetic and safety analyses included all 12 subjects enrolled in Part A of the study. No subjects prematurely withdrew from Part A of the study. Most subjects in this Part of the study were Black. The three cohorts of subjects 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 ($p < 0.05$). Additional details on the demographic and baseline characteristics of the subjects in the trial are tabulated in the appendix.

Pharmacokinetic Results

Mean plasma T-20 concentration-time profiles for the 15, 30, and 60 mg/m^2 dose groups are presented in the figures below:





Mean PK parameters for the IV and SC routes of administration are summarized in table I. As indicated previously, subjects received T-20 IV 24 hours after administration of the SC dose. The applicant indicates that all subjects had measurable T-20 concentrations prior to IV dosing on Day 1. According to the applicant, IV PK parameters were comparable with and without baseline correction. Thus, all reported IV PK values are for non-adjusted data. Because T-20 will be given SC, accurate determination of IV PK parameters is not critical thus, the applicant's approach is acceptable. These data were not reanalyzed in this review. Ideally, an adequate washout period should be present before administering a drug by another route. The remainder of this review will focus on the SC results. Generally, T-20 plasma PK (particularly, exposure measures) exhibited high inter-patient variability (up to 86%).

Table I: Mean (%CV) Pharmacokinetic Parameters in Pediatric Subjects Following IV or SC Administration of T-20

Dose Group	n	Dose^ (mg)	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	C_{12} (μg/mL)	AUC_{inf} (μg.h/mL)	CL* (L/h)	V_d (L)
					IV				
15 mg/m^2	4	14.6	3.53	0.5	2.48	0.126	12.6	1.39	5.03
30 mg/m^2	4	33.0	10.2	0.5	2.73	0.243	22.5	1.60	5.34
60 mg/m^2	4	48.9	4.89	0.75	3.06	0.708	36.2 (27)	1.33	5.69
All	12	-	-	-	2.75	-	-	1.44	5.31
					SC				
15 mg/m^2	4	14.6	1.13	4.0	3.99	0.323	10.9	2.32	12.9
30 mg/m^2	4	33.0	2.16	6.0	3.13	0.641	21.5	1.51	5.91
60 mg/m^2	4	48.9	5.16	4.0	3.22	1.81	56.4	0.842	3.82

* For SC administration, CL refers to apparent clearance

^ Dose is average for four patients; CV associated with each mean dose < 20 %

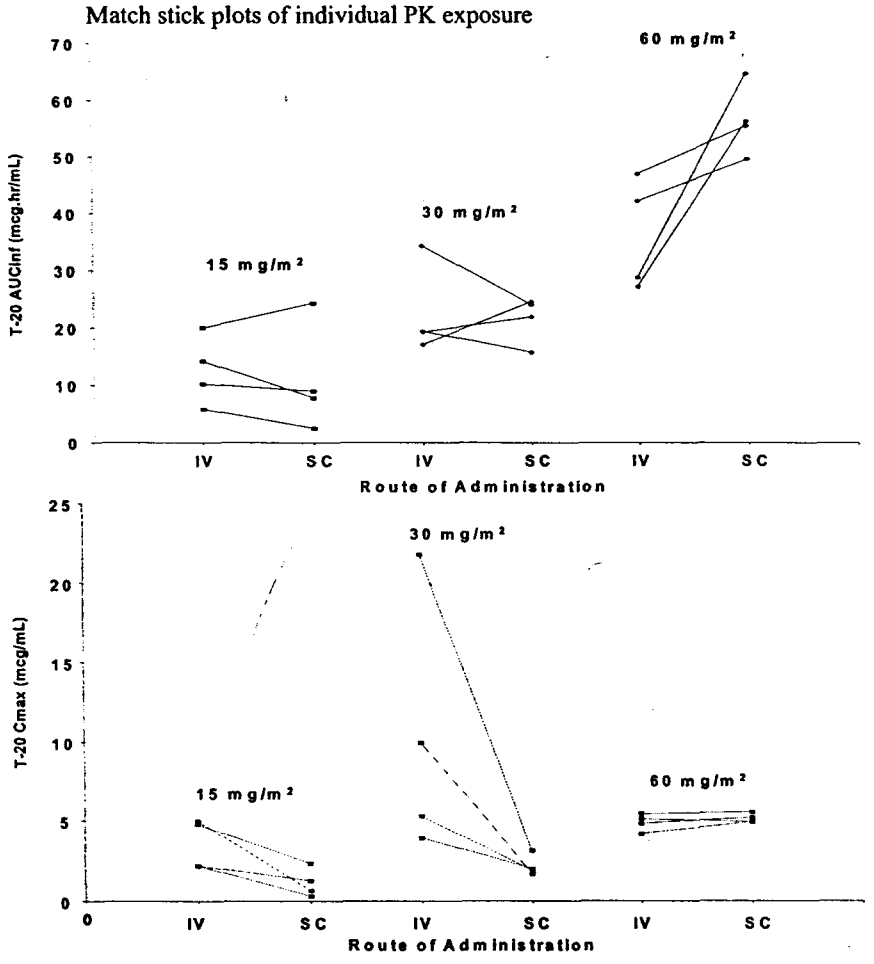
IV Administration

Following IV administration, plasma T-20 concentrations rapidly attained C_{max} (T_{max} < 1 hr), subsequently declining in a monoexponential (n= 5) or biexponential (n = 4) fashion. Overall, the IV PK of T-20 were dose independent over the 15 – 60 mg/m^2 range as shown by the constant clearance (1.5 L/hr) and volume of distribution values. C_{max} values increased in a dose proportional fashion for the 15 and 30 mg/m^2 IV dose groups, but were less than proportional for the 60 mg/m^2 IV dose group. The reason for this observation is unclear. The C_{12}, which served as a surrogate for C_{min}, was less than the target 1 μg/mL concentration at all doses tested. It is unclear why the IV doses, particularly the 60 mg/m^2 dose did not attain target concentrations. Based on PK principles (complete absorption) and data obtained in adults, the 60 mg/m^2 dose should have readily achieved the target concentration.

SC Administration

As expected, plasma T-20 concentration-time profiles following SC administration were characterized by delayed T_{max} and lower C_{max} values relative to the IV route of administration. Unexpectedly, the 60 mg/m^2 dose group exhibited similar C_{max} values for both the IV and SC routes of administration. The delayed and prolonged absorption following SC administration appears to result in a flip-flop in the kinetics ($t_{1/2}$ for SC generally > $t_{1/2}$ for IV) of T-20. One critical finding with the SC route is that the T-20 C_{12} values were below 1 μg/mL for all subjects in the 15 and 30 mg/m^2 dose groups whereas, C_{12} values for the subjects in the 60 mg/m^2 SC dose group were all greater than 1 μg/mL (range: [redacted] μg/mL). Following SC administration of T-20, T-20 exposure increased in approximately dose-proportional manner from 15 to 30 mg/m^2, but a greater than dose-proportional increase occurred at the 60 mg/m^2 dose. This lack of dose-proportionality (apparent non-linearity) across the evaluated dose range makes it difficult to interpolate data, if interpolation were necessary. In the 60 mg/m^2 dose group, all subjects had a higher AUC_{inf} following SC dosing compared to the IV route of administration. If subjects received accurate doses, the results are not expected and can not be readily explained, because exposure following IV administration should be higher than that following SC administration. It is noted that in two subjects (patient numbers 503254 and 505217), AUC_{inf} following SC administration was 2-fold higher than the AUC_{inf} after IV dosing. A similar but less profound trend was also seen for C_{max} following SC administration. Due to the limited

number of subjects, the values for these two subjects may have unduly influenced the mean data for the 60 mg/m^2 SC dose.



In summary, the data obtained following single SC administration suggest that a dose above 30 mg/m^2 is required to attain the applicant's proposed target concentration.

Exploratory Bioavailability

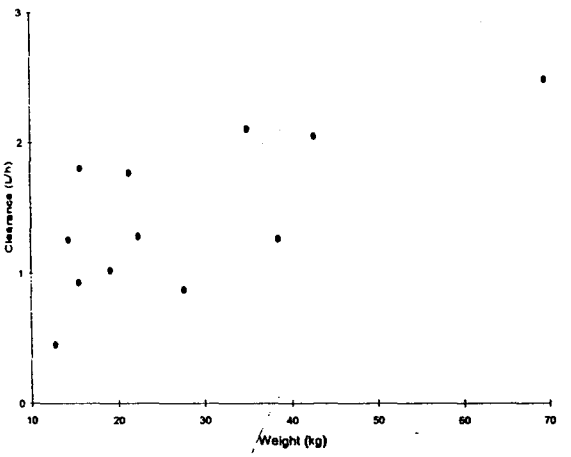
The applicant determined absolute BA of the SC route. T-20 bioavailability following SC administration was 115% and ranged from 42% to 225%. All subjects in the 60 mg/m^2 dose group had a bioavailability estimate of greater than 100%, while only three of the eight remaining subjects in the 15 and 30 mg/m^2 dose groups had a bioavailability estimate greater than 100%. The accuracy of these BA estimates is questionable because one does not expect an absolute BA estimate above 100 %. As stated previously, these findings suggest that dosing or procedural errors may have occurred during the study.

Selection of Pediatric Dose for Further Evaluation

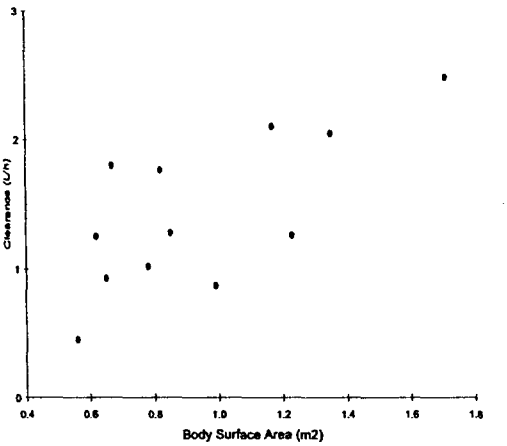
1. Influence of Covariates on T-20 exposure

Examination of plots of body weight and body surface area suggests a correlation exists between body size and clearance, however, the high variability and small sample size make interpretation of these data difficult. The sponsor did not assess age as a covariate on T-20 exposure; this may have been due to the small number of subjects and relatively narrow age distribution.

Plot of Clearance vs. Body Weight



Plot of Clearance vs. Body Surface Area



2. *Post hoc* Analysis

The applicant conducted a *post hoc* analysis of the pharmacokinetic data collected in Part A to estimate a pediatric dose for future studies. This pediatric dose was supposed to provide a T-20 AUC comparable to that seen in adults following SC administration of the 90 mg dose. The target adult exposure was approximately 44 μg·hr/mL. Projected pediatric doses were calculated on a mg, mg/kg and mg/m^2 basis. The applicant does not explicitly state how the projected doses were derived, but it is likely that dose-proportionality was assumed. This assumption of dose-proportionality might not be valid in light of the dose-exposure data obtained in this study. Projected doses obtained in the *post hoc* analyses were as follows:

- Mean Dose in mg = 58.44 ± 3.049
- Mean Dose in mg/kg = 2.08 ± 0.58
- Mean Dose in mg/m^2 = 57.90 ± 17.61

The applicant indicates that consistent and targeted exposure can be achieved in the pediatric population when T-20 is dosed on a mg/kg or mg/m^2 basis. Based on the *post hoc* analysis, a dose of 2 mg/kg, up to a maximum deliverable dose of 90 mg, was selected for future pediatric studies. The mg/kg (weight-adjusted) dosing is expected to be more convenient than mg/m^2 (body surface area-adjusted) dosing, and will reduce the potential for dose calculation errors. The applicant's analysis and dosing approach appears reasonable in the context of the available data. The 2 mg/kg dose is being evaluated in an ongoing study (Protocol NV16056/ T20-310).

3. Comparison of Single Dose PK Data: Pediatric Subjects (this study) vs. Adults

Key pediatric pharmacokinetic parameters were similar to those seen previously in adult subjects. Mean CL, V_d, and $t_{1/2}$ values for the IV dose group in this study were 1.4 L/h, 5.3 L, and 2.7 h, respectively, which are comparable to the results seen with IV dosing in adult subjects

in Study [redacted]-001 (CL 1.7 L/h, V_d 6.6 L, and $t_{1/2}$ 2.7 h). T-20 exhibited a small volume of distribution, which is consistent with plasma volume (high plasma protein binding), a small clearance, and a relatively short elimination half-life.

Safety Results (applicant's summary)
The applicant's report indicates that T-20 was generally well tolerated in Part A. Only two injection site reactions were reported in Part A of this study. Other mild and moderate adverse events occurred, but no serious adverse events were reported.

Conclusions
The PK data in Part suggest that a 2.0 mg/kg twice daily T-20 dose in pediatric patients will achieve the applicant's proposed target minimum concentration of 1 μg/mL.

Part A Appendix

Concomitant Medications

The following medications were NOT allowed:

therapeutic HIV vaccines, astemizole (Hismanal), terfenadine (Seldane), triazolam (Halcion), midazolam (Versed), immunomodulators (interleukins and interferons), routine childhood immunizations during the first 10 days of study therapy, any other experimental therapy, all contraindicated medications pertinent to the patient's antiretroviral therapy regimen as stated in package inserts. However, subjects could continue to take the following medications during the study: prophylactic medications for *P. carinii* pneumonia and *M. avium*, including azithromycin (in accordance with current CDC recommendations), antibiotics for bacterial infections, medications for symptomatic treatment (such as antipyretics, analgesics, and antiemetics), expanded access antiretroviral agents, intravenous immunoglobulin

Table 1 Selected Baseline Characteristics of the Subjects by Assigned Dose (Part A)

MEASURE	GROUP	NUMBER	MEDIAN	MIN	MAX	P*
AGE (years)	total	12	7.43	3.72	11.93	
	dose=15	4	7.36	3.72	11.28	
	dose=30	4	9.62	4.11	11.93	0.480
	dose=60	4	6.74	3.75	7.64	
HEIGHT (cm)	total	12	116.55	87.50	154.00	
	dose=15	4	123.15	87.50	154.00	
	dose=30	4	134.25	98.20	152.00	0.592
	dose=60	4	114.70	95.30	117.10	
WEIGHT (kg)	total	12	21.90	12.70	69.60	
	dose=15	4	27.10	12.70	42.70	
	dose=30	4	31.30	15.40	69.60	0.557
	dose=60	4	20.25	14.30	22.40	
BSA (mg/m2)	total	12	0.84	0.56	1.71	
	dose=15	4	0.95	0.56	1.35	
	dose=30	4	1.08	0.65	1.71	0.557
	dose=60	4	0.80	0.62	0.85	
CD4 (cells/μL)	total	11	505.00	129.00	1497.00	
	dose=15	3	360.00	171.00	389.00	
	dose=30	4	524.00	129.00	632.00	0.042
	dose=60	4	1094.50	505.00	1497.00	
CD4 (%)	total	11	23.00	8.00	28.00	
	dose=15	3	8.00	8.00	24.00	
	dose=30	4	22.00	17.00	27.00	0.132
	dose=60	4	25.00	23.00	28.00	
HIV-1 RNA (copies/mL)	total	12	40809.50	16011.00	180152.00	
	dose=15	4	36017.00	16011.00	57447.00	
	dose=30	4	40809.50	28536.00	120474.00	0.630
	dose=60	4	49404.00	26278.00	180152.00	

*p-value for Kruskal-Wallis Test comparing dose groups

Table 3 Gender and Race/Ethnicity of the Subjects by Assigned Dose for Part A

	Total		Assigned Dose						p-value* of Fisher's Exact Test
			15 mg/m^2		30 mg/m^2		60 mg/m^2		
	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	
Black Non-Hispanic	7	58.3	2	50.0	3	75.0	2	50.0	0.782
Hispanic (regardless of race)	3	25.0	2	50.0	0	0	1	25.0	

*p-values for comparing dose groups

Table 3 Demographics and Dose Group Assignment by Patient

Patient Number	Weight (kg)	Height (cm)	BSA[a] (m^2)	Dose Group (mg/m^2)	Dose (mg)
440207	12.7	87.5	0.56	15	9
470188	38.5	142.3	1.23	15	18
500520	42.7	154	1.35	15	21
810001	15.7	104	0.67	15	10.5
280413	69.6	152	1.71	30	48
280451	15.4	98.2	0.65	30	18
280750	27.6	127	0.99	30	30
500636	35.0	142	1.17	30	36
280771	22.4	117	0.85	60	54
503254	14.3	95.3	0.62	60	36
505217	21.4	113	0.82	60	48
690214	19.1	116	0.78	60	48

[a] Calculated as $\sqrt{\frac{WT(kg) \cdot HT(cm)}{3600}}$

Table 4: Bioavailability of T-20 in Pediatric Subjects Following SC Administration

Patient Number	AUC_{inf} (µg.h/mL)		F (%)
	IV	SC	
440207	20	24.2	121.0
470188	14.3	7.78	54.4
500520	10.2	8.99	88.1
810001	5.82	2.46	42.3
280413	19.2	21.9	114.1
280451	19.4	15.7	80.9
280750	34.3	24	70.0
500636	17.1	24.5	143.3
280771	42.1	49.5	117.6
503254	28.7	64.5	224.7
505217	27.1	56.2	207.4
690214	46.9	55.4	118.1
Mean			115.2
Min			42.3
Max			224.7
%CV			48.5

APPEARS THIS WAY
ON ORIGINAL

Part B Pharmacokinetic-related Objectives

- To obtain information on the safety, tolerability and pharmacokinetics of multiple doses of T-20 given as chronic twice daily SC injections.
- To provide preliminary information on the antiviral activity of T-20 given as chronic BID SC injections in children with viral replication >10,000 copies per/mL, stable on their initial combination ARV therapy consisting of two NRTIs alone, or in combination with an NNRTI and/or a PI.
- To determine the dose (30 or 60 mg/m^2) to use for chronic BID SC injections.

Study Design

New subjects and subjects who completed Part A of the study (Study 204) were eligible for enrollment into Part B, provided they met study eligibility criteria. However, subjects who completed Part A but did not want to enroll in Part B were replaced. The duration of the study was 24 weeks. On day 7 of T-20 dosing, children began a new optimized ARV therapy regimen. Subjects were sequentially assigned to the 30 mg/m^2 and 60 mg/m^2 cohorts. The third cohort was enrolled at 60 mg/m^2 based on safety and virology results of cohorts 1 and 2 on day 7. Overall, four subjects received the 30 mg/m^2 dose and eight subjects received the 60 mg/m^2 dose. Injections were administered into the abdomen, deltoid area, or anterior aspect of the thigh, twice daily. The SC injection site was rotated each time an injection was given to minimize local reactions. Some subjects applied [redacted] cream 30-60 minutes prior to each injection to minimize discomfort. It is noted that the parent (or patient) was taught how to give the injection at the baseline visit and the remaining injections were self-administered at home. Patient adherence was not assessed in this trial even though adherence was likely to impact the PK outcome. Formulations and assays were the same as in Part A of the trial.

Pharmacokinetic Assessments

- Single point blood samples (0.5 mL) were drawn on day 1, 3, 7, and 10, week 4, week 16, and week 24 for population pharmacokinetic analyses (details of the collection times were not provided in this report)
- Trough drug levels were collected before the next dose on Day 7

The applicant indicates that population PK analysis will be carried out using NONMEM at [redacted] to estimate population values for standard PK exposure measures. The population PK analysis was not provided in this submission. Only the PK results for C_{min} (trough levels) values on day 7 were presented in the study report.

Reviewer Comment

The results from the NONMEM analyses will provide additional supportive information for pediatric subjects. The findings from this analysis should be more accurate than that in Part A, as actual blood sampling times will be used.

Key efficacy assessments and procedures

- Subjects in the 30 mg/m^2 treatment group who did not achieve 0.7 $\log_{10}$ copies/mL reduction in their plasma HIV-1 RNA levels or T-20 plasma trough concentrations $\geq$ 1 µg/mL by day 7 had their T-20 dose increased to 60 mg/m^2 for the duration of the study.
- Subjects who did not achieve and maintain a viral load of greater than 1 $\log_{10}$ less than baseline (as measured in the Virology Core Lab) at the week 12 evaluation were considered

to have met a virologic endpoint. These subjects could discontinue T-20 treatment and start the best new therapy as determined by their care provider.

Results

Disposition of Subjects

Fourteen children from eight different sites were enrolled into Part B of the study. Eleven of the 14 children had previously participated in Part A of the study. Thirteen children completed 24 weeks of treatment with T-20. The majority of subjects were female and race was fairly evenly balanced for all study participants. The age range of subjects was 6 to 12 and 4 to 11 in the 30 and 60 mg/m^2 dose groups, respectively. For additional patient characteristics, please refer to appendix.

The following two subjects withdrew from the study:

- Patient number 503254, assigned to the 60 mg/m^2 treatment group, discontinued treatment 22 days after starting treatment with T-20 due to the child's resistance to receiving injections.
- Patient number 440207 voluntarily discontinued treatment with T-20 immediately after completing 24 weeks of treatment.

All subjects were treatment experienced. The first 4 children initially received the 30 mg/m^2 dose and all (see appendix) except one of these children was dose-escalated to the 60 mg/m^2, per the protocol procedure. In all ten children received the 60 mg/m^2 dose.

- **Pharmacokinetics**

The steady state (Day 7) T-20 trough concentration data were available from 12 subjects who received 30 or 60 mg/m^2 T-20. These were the only PK data provided in Part B. The individual and mean PK and viral load data are presented in Table I.

Table I: Day 7 individual and Mean (%CV) T-20 Trough Concentrations and Individual Viral Load Response

Dose Group	Patient No	Study Day 7 (µg/mL)	Viral Load Response (log drop in HIV RNA copies/mL)
30 mg/m^2	[redacted]	0.905	[redacted]
		0.783	
		0.470	
		1.32	
	N	**4**	**4**
		0.870 (Mean)	**-1.0 (Median)**
60 mg/m^2	[redacted]	---	[redacted]
		0.27	
		4.88	
		1.31	

		4.1	
		1.85	
		2.78	
		2.93	
		0.823	
	N	**8**	**9**
		2.53 (Mean)	**-1.15 (Median)**

PK data were not provided for patient number 280451 in the 60 mg/m^2 group because the child was inadvertently dispensed the 30 mg/m^2 dose for the first three days of study treatment. This exclusion was acceptable, although data from adults indicate that dosing for four days should achieve steady-state T-20 levels.

T-20 plasma trough concentrations for subjects receiving 30 mg/m^2 were below the 1 μg/mL target for all but one patient. This subject (subject number 690214) received the 30 mg/m^2 dose of T-20 through week 24. Trough concentrations for subjects receiving 60 mg/m^2 were well above the target concentration for all but two children. The trough concentrations for subjects who initially received the 60 mg/m^2 were generally above the target concentration, and similar to trough concentrations seen when 90 mg SC BID is administered to adults. However, the C_{min} data were highly variable in this study ranging from ≈ 0.3 – 5.0 μg/mL; the source of variability is unclear.

Exploratory Exposure-Response Relationship
There was no clear relationship between C_{min} and reduction in viral load on Day 7. Additional analyses may be possible once the Population PK report is available. According to the applicant's efficacy analysis, by week 24, 10 of the 14 children enrolled achieved reductions from baseline HIV-1 RNA of > 1.0 $\log_{10}$ copies/mL. The median change in HIV-1 RNA was – 1.75 $\log_{10}$ copies/mL, and there were median increases in CD4 cell count and CD4 percentage.

Reviewer Comment
The PK results suggest that the 60 mg/m^2 dose will achieve the applicant's proposed target C_{min} in the majority of children, whereas the 30 mg/m^2 dose will not. Because patient adherence was not measured in this trial it is unclear if the results reflect accurate steady state C_{min}. It should be noted that the impact of concomitant medications on T-20 concentrations is unknown. The absence of an exposure-relationship suggests that C_{min} may not be a major determinant of efficacy or the time (Day 7) at which data were collected was not long enough to demonstrate any such relationship. The applicant indicates that the efficacy is reflective of T-20 monotherapy as most subjects were using recycled (previously used) antiretroviral drugs that were unlikely to improve efficacy.

Safety Results (applicant's summary)
T-20 containing therapy was generally well tolerated by the children enrolled and had a favorable safety profile over the 24 weeks described in this study report. One child discontinued T-20 treatment due to injection aversion. Mild to moderate injection site reactions were the most common adverse events and were reported in 11 out of the 14 children.

Conclusions
- The 60 mg/m^2 achieves sponsor's proposed target C_{min} of 1 μg/ml in the majority of subjects
- T-20 delivered SC twice daily was well tolerated in HIV infected children and had antiviral activity

Appendix

Characteristic	30 mg/m^2 dose (n=4)	60 mg/m^2 dose (n=10)	All Subjects (n=14)
Gender: no. (%) female	3 (75%)	5 (50%)	8 (57%)
no. (%) male	1 (25%)	5 (50%)	6 (43%)
Race/ethnicity: no. (%)			
White, non-Hispanic	0 (0%)	4 (40%)	4 (29%)
Black, non-Hispanic	2 (50%)	4 (40%)	6 (43%)
Hispanic	2 (50%)	2 (20%)	4 (29%)
Age (years):			
median (min, max)	9.4 (6.4, 12.1)	8.2 (4.0, 11.0)	8.2 (4.0, 12.1)
Height (cm):			
median (min, max)	135 (116, 155)	117 (96, 147)	118 (96, 155)
Weight (kg):			
median (min, max)	35.6 (19.1, 69.4)	22.5 (14.3, 40.5)	24.1 (14.3, 69.4)
Body surface area (m^2):			
median (min, max)	1.16 (0.78, 1.72)	0.86 (0.62, 1.29)	0.89 (0.62, 1.72)
CD4 count (cells/μl):			
median (min, max)*	536 (53, 897)	523 (248, 2343)	523 (53, 2343)
CD4 percentage (%):			
median (min, max)*	20.0 (11.0, 42.0)	29.0 (12.0, 41.0)	24.0 (11.0, 42.0)
HIV-1 RNA (copies/mL):			
median (min, max)	26528 (23521,72430)	30648 (8555,187288)	26886 (8555,187288)
Baseline ARV therapy: no. (%)			
2 NRTIs + 2 PI	0	2 (20%)	2 (14%)
2 NRTIs + PI	3 (75%)	6 (60%)	9 (64%)
2 NRTIs only	1 (25%)	2 (20%)	3 (21%)

*One child (assigned to receive the 60 mg/m^2 dose) did not have a CD4 evaluation within 30 days prior to starting study treatment.

Title: A Phase I/II Evaluation of the Safety, Plasma Pharmacokinetics, and Antiviral Activity of T-20 Administered to HIV-1 Positive Adults ([redacted]001)

Investigators/centers: [redacted]

Study Period: 11/1996 (first subject visit) to 08/1997 (last subject visit)

Objectives

- Evaluate safety of T-20 (single and multiple dose) given by intravenous injection
- Determine plasma pharmacokinetics of T-20 following IV administration of single and multiple escalating doses of T-20
- To assess T-20 antiviral activity vs. placebo over a 14 day period

Study design

This was an active dose concurrent control study. Four dose levels of T-20 were evaluated. Subjects were sequentially assigned to one of four dosing groups. Subjects received T-20 at a dose of 3, 10, 30 or 100 mg by intravenous infusion. All subjects received their assigned T-20 dose as an intravenous infusion given over 15 to 20 minutes. The duration of patient exposure was 15 days, consisting of a single dose intravenous infusion (followed by a two-day washout period) and two weeks (14 consecutive days) of twice-daily intravenous infusions.
Day 1: subjects received a single dose.
Days 4 - 18: subjects received two doses per day, approximately 12 hours apart.
All doses were administered by the clinic staff as direct observational therapy. No food or beverages were allowed after 10:00 p.m. on the evening prior to blood specimen collection for pharmacokinetic analysis. No food or fluid was permitted for two hours after dosing. Controlled meals were provided throughout the study.

Blood Sampling

Blood samples were obtained prior to dosing and at the following times: 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, and 24 hours post dose on Day 1 (after first dose). On Day 4, blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, and 12 hours post dose.

Assay

Concentrations of T-20 in plasma were determined by [redacted] in a [redacted] format with a [redacted]

Reviewer Comment

Because this assay was not the final assay used for determination of T-20 concentrations, this reviewer did not critically assess the performance of this assay. Results from this study are not included in the proposed package labeling; therefore, the study was not reviewed in detail. However, information obtained in this study is supportive of the information obtained in another studies where T-20 was administered intravenously.

Pharmacokinetic Assessments:

The following pharmacokinetic parameters were calculated from the plasma T-20 concentration data: $AUC0_{-12}$, C_{max}, C_{min}, T_{max} and C_{ss}.

Safety Assessments:
T-20 safety was assessed by monitoring treatment-emergent AEs, the change from baseline for vital signs and selected laboratory parameters (hematology and chemistry), laboratory parameter shifts, and changes in EKG and physical examination results.

T-20 Formulations
Two dose strengths were supplied: 2.5 mg/mL and 25 mg/mL. Batch numbers used during the study were 609008 and 609009.

Subjects
Seventeen male and female HIV+ subjects enrolled in the study and fourteen completed the study. All subjects, except one subject in the 10 mg dose group, completed the study. The reason for the withdrawal was not provided. Fourteen of the enrolled subjects received all scheduled doses. Two subjects missed one or more doses. There was one protocol violation during the study. One subject (#2866) left the clinic on Day 11 on a day pass and during her absence self-administered crack cocaine. The subject returned to the clinic on Day 12 and completed the treatment period. None of these deviations from the protocol are expected to affect the PK outcome (results).

Demographic Data and Baseline Characteristics
The baseline demographic parameters of the patients are summarized in Table I.

Table I: Demographic Characteristics

Characteristic		3 mg N=4	10 mg N=5	30 mg N=4	100 mg N=4
Sex	Male	4 (100.0)	4 (80.0)	4 (100.0)	4 (100.0)
	Female	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Race	Caucasian	3 (75.0)	3 (60.0)	1 (25.0)	2 (50.0)
	Black	1 (25.0)	2 (40.0)	3 (75.0)	2 (50.0)
Age (years)	N	4	5	4	4
	Mean ± SE	36.3 ± 5.02	36.6 ± 1.75	36.3 ± 4.85	33.0 ± 1.29
	Range	25-47	30-40	25-48	30-36
Baseline Plasma HIV RNA (log_{10} copies/mL)	N	4	4	4	4
	Mean ± SE	5.1 ± 0.09	4.9 ± 0.33	4.7 ± 0.15	4.2 ± 0.10
	Range	4.9-5.3	4.2-5.8	4.3-5.0	4.0-4.5
Baseline Absolute CD4 Cell Count (cells/μL)	N	4	5	4	4
	Mean ± SE	248.8 ± 69.77	324.6 ± 76.85	486.0 ± 216.74	345.3 ± 127.90
	Range	111-415	114-463	51-931	125-673

Baseline is the Day 1 pre-dose measure.

The majority of subjects were male (94.1%). Race was fairly balanced in the study (Caucasian = 53 % and Black = 47 %). The ages and baseline viral load and CD4 counts of subjects were comparable in all groups; although, subjects in the 10 mg and 30 mg dose group tended to have higher viral loads and lower CD4 counts at baseline than subjects in the 20 and 100 mg dose groups. This difference in baseline values may have influenced the outcome of the antiviral activity analyses.

Pharmacokinetic Results

T-20 pharmacokinetic results following administration of four T-20 doses are summarized in Table II.

Table II: Mean ± SD Pharmacokinetic Measures Obtained after First and Seventh Dose of T-20

	3 mg	10 mg	30 mg	100 mg
Measure[a]	N=4	N=5	N=4	N=4
C_{max} (μg/mL)				
First Dose	0.472 ± 0.299	1.76 ± 0.780	5.57 ± 2.97	20.1 ± 3.97
Seventh Dose	0.455 ± 0.188	1.71 ± 0.768	6.57 ± 2.43	21.3 ± 2.47
AUC[c] (μg/hr/mL)				
First Dose	2.92 ± 3.51	5.23 ± 2.43	18.8 ± 9.34	61.6 ± 14.1
Seventh Dose	1.99 ±1.83	5.68 ± 3.27	21.2 ± 11.7	75.8 ± 16.9
Trough Concentration (μg/mL)				
Seventh Dose	0.043 ± 0.071	0.080 ± 0.075	0.454 ± 0.367	1.67 ± 0.521
$t_{½}$ (hr)				
First Dose	3.36 ± 2.99	2.27 ± 0.438	2.43 ± 0.551	2.73 ± 0.309
Seventh Dose	2.80 ± 1.71	2.29 ± 0.292	2.53 ± 0.532	2.65 ± 0.128
CL (L/hr)				
First Dose	2.34 ± 1.46	2.15 ± 0.668	1.86 ± 0.757	1.68 ± 0.325
Seventh Dose	2.27 ± 1.13	2.22 ± 1.190	1.70 ± 0.711	1.36 ± 0.267
V_d (L)				
First Dose	6.99 ± 2.39	7.16 ± 2.58	6.12 ± 1.49	6.61 ± 1.49
Seventh Dose	7.13 ± 1.61	7.04 ± 3.14	5.79 ± 1.56	5.23 ± 1.21

The exposure measures increased in a dose-proportional manner. The PK of T-20 were dose-independent over the dose range studied. Only the 100 mg twice daily dosing regimen resulted in plasma concentrations of T-20 that were in excess of 1.0 μg/mL (IC_{50}, target concentration) throughout the 24-hr dosing period. Accumulation was not evident at any dose levels, apart from the 100 mg level, where accumulation was negligible (accumulation index ≈ 1.2). The applicant concludes that the half-life indicates that either intermittent or continuous parenteral administration is a feasible method of delivery to achieve the target plasma level.

Reviewer Comment on Administration Route

Although intravenous administration produced target drug concentrations ($\geq IC_{50}$), it is not a feasible or practical mode of drug administration in the outpatient setting that is typically required for patients undergoing antiretroviral therapy.

Efficacy Results: ***Exploratory Exposure Response Analyses based on applicant's analysis***

The applicant investigated the effects of T-20 administration on antiretroviral activity as measured by:

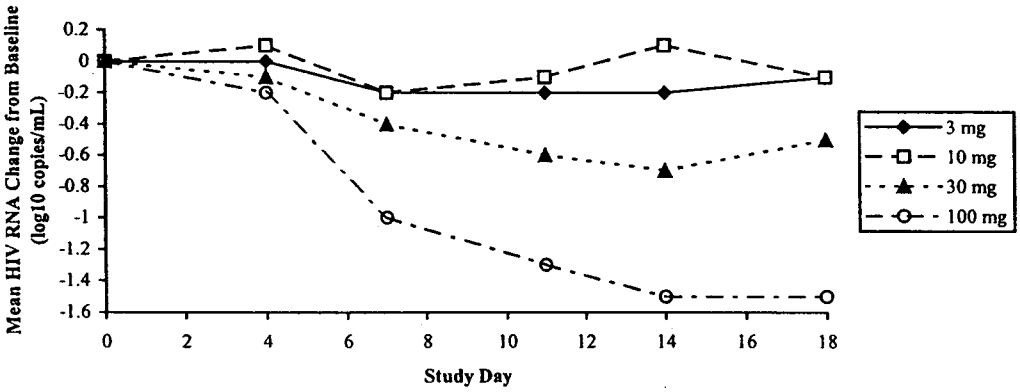
1. Plasma HIV RNA change from Baseline
2. CD4 cell number change

- **HIV Viral Load**

The mean plasma HIV RNA level ranged from 4.2 to 5.1 log10 copies/mL at baseline. The order of activity, expressed as decline in mean plasma baseline HIV RNA, of the four dose groups was as follows: 100 mg T-20 (-1.5 log) > 30 mg (-0.5 log10 copies/mL) > 3 and 10 mg (-0.1 log10

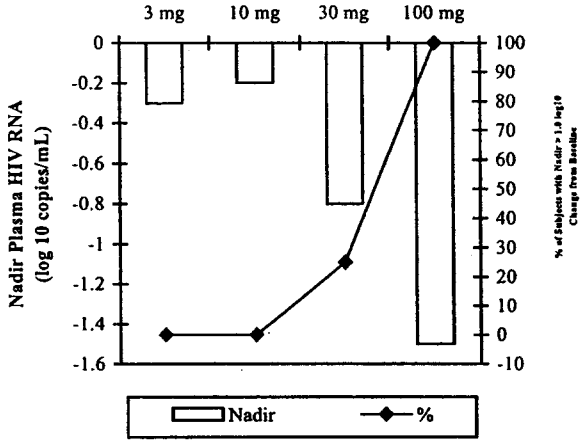
copies/mL) by Day 18. A paired t-test comparing the Day 18 change from baseline plasma HIV RNA results of all dose groups combined against zero revealed a significant (p=0.005) T-20 treatment effect. A plot of the change in plasma RNA levels as a function of time is depicted in figure 1.

Figure 1 **Plasma HIV RNA Change from Baseline**



A dose-response relationship existed between the T-20 dose and the nadir plasma HIV RNA levels achieved and the percent of subjects achieving a nadir greater than 1.0 log10 reduction from baseline (figure 2).

Figure 2: Dose Response of Nadir Plasma HIV RNA



The applicant identified three potential factors that may have influenced the outcome of the efficacy analyses: (1) Baseline viral load and CD4 cell counts (2) the mean number of antiretroviral medications previously administered and (3) subjects' total prior antiretroviral exposure by class (see Appendix, Table). Most subjects (98.5%) had prior antiretroviral treatment, with a median exposure to ten antiretroviral agents.

Reviewer's Comment
The applicant's conclusions regarding the dose-response relationship are acceptable with the following caveats and limitations:

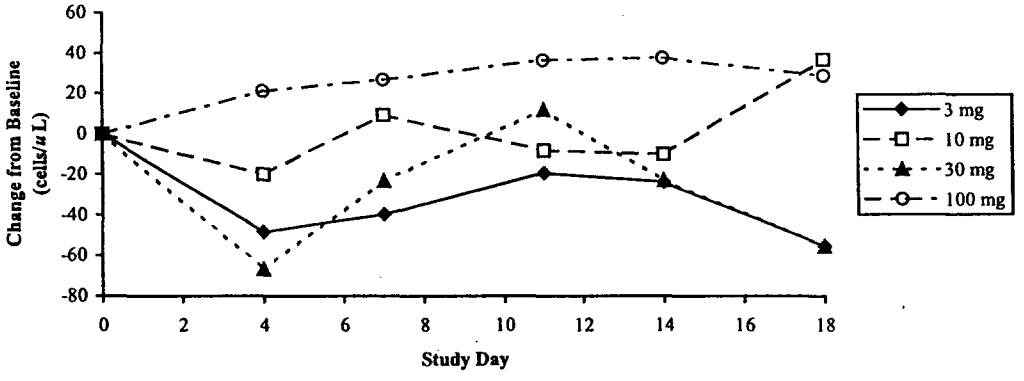
- *unknown effect of baseline viral load and lymphocyte values*
- *unknown role of previous antiretroviral medications*

The first factor has been shown to affect treatment outcome in some studies; however, the impact of the second factor is unclear for a drug that acts by a different mechanism. Hypothetically, previous therapy with agents acting via a different mechanism may influence (sensitize or desensitize) a subject to a new agent working via a different mechanism.

CD4 and CD8 Cell counts

The dose response-relationship, if any, between T-20 and change in CD4 or CD8 counts was unclear. Patients in the 3 and 30 mg dose groups both experienced a mean loss of 55 cells/μL by Day 18. On the other hand, subjects in both the 10 and the 100 mg dose groups realized mean CD4 cell count gains of 36.8 and 29.0 cells/μL, respectively. Unlike viral load changes, a paired t-test comparing the Day 18 change from baseline CD4 cell count results of all dose groups combined against zero did not indicate a significant difference following T-20 treatment and placebo. This observation of "no difference" appears to be driven primarily by the high degree of variability (inter-visit). The patterns of change in percent CD4 cell counts were comparable to those for the change in absolute CD4 cell. No significant changes in CD4 or CD8 cell counts were observed. The changes in lymphocyte counts are illustrated in Figure 3.

Figure 3: Absolute CD4 Cell Count Change from Baseline



Reviewer Comment on Exploratory Exposure-Response Analyses
In general, viral load tends to exhibit clearer dose-response relationships for antiretroviral therapy than CD4 or CD8 cell counts. Consequently, changes in viral load (surrogate marker) are used as the basis of regulatory assessments and actions for antiretroviral agents

Safety Results: (applicant's analysis)

A total of 47 treatment-emergent adverse events (AEs) was reported by 13 (76.5%) of the subjects. The order of adverse events in terms of frequency of occurrence was: headache (41.2%) > fever (23.5%) and pain (11.8). None of the following events occurred during the study: death, discontinuation due to AEs, changes in clinical chemistry, changes in vital signs or,

changes in EKG. No dose-response relationship was apparent for any single adverse event, nor for the pattern of reporting across treatment groups.

Conclusion

- T-20 exhibits dose independent kinetics, and dose proportional increases in exposure over the 3 to 100 mg dose range
- a dose response relationship exists for T-20 monotherapy and nadir viral load,

Appendix

Table 1: Plasma HIV RNA Change from Baseline

		3 mg	10 mg	30 mg	100 mg
Study Visit	**Statistic**	**N=4**	**N=5**	**N=4**	**N=4**
Day 4	N	4	4	4	4
	Mean ± SE	0.0 ± 0.07	0.1 ± 0.07	-0.1 ± 0.07	-0.2 ± 0.18
Day 7	N	4	4	4	4
	Mean ± SE	-0.2 ± 0.10	-0.2 ± 0.12	-0.4 ± 0.10	-1.0 ± 0.16
Day 11	N	4	4	4	3
	Mean ± SE	-0.2 ± 0.10	-0.1 ± 0.15	-0.6 ± 0.14	-1.3 ± 0.27
Day 14	N	4	4	4	3
	Mean ± SE	-0.2 ± 0.08	-0.1 ± 0.14	-0.7 ± 0.26	-1.5 ± 0.14
Day 18	N	4	3	4	4
	Mean ± SE	-0.1 ± 0.05	-0.1 ± 0.10	-0.5 ± 0.25	-1.5 ± 0.10

Table 2: CD4 Cell Count Response

		3 mg	10 mg	30 mg	100 mg
Study Visit	**Statistic**	**N=4**	**N=5**	**N=4**	**N=4**
Day 4	N	4	4	4	4
	Mean ± SE	-48.3 ± 21.81	-19.8 ± 20.98	-66.8 ± 35.17	21.3 ± 23.80
Day 7	N	4	4	4	4
	Mean ± SE	-39.8 ± 27.08	9.5 ± 23.69	-23.3 ± 45.70	26.8 ± 15.91
Day 11	N	4	4	4	3
	Mean ± SE	-19.3 ± 10.31	-8.0 ± 43.15	12.0 ± 55.72	36.7 ± 15.30
Day 14	N	3	4	4	3
	Mean ± SE	-23.7 ± 13.74	-9.8 ± 46.92	-22.8 ± 74.48	37.7 ± 4.37
Day 18	N	4	4	4	4
	Mean ± SE	-55.3 ± 10.18	36.8 ± 62.39	-55.3 ± 62.40	29.0 ± 17.72

Table 3: Mean Number of Antiretroviral (ARV) Medications Previously Administered

		3 mg	10 mg	30 mg	100 mg
ARV Class	**Statistic**	**N=4**	**N=5**	**N=4**	**N=4**
NRTIs	N	3	3	1	0
	Mean ± SE	1.7 ± 0.33	2.3 ± 0.33	1.0	
	Min-Max				
Protease Inhibitors	N	2	2	1	0
	Mean ± SE	1.5 ± 0.50	1.0 ± 0.00	2.0	
	Min-Max				

APPEARS THIS WAY
ON ORIGINAL

Study Title:	A phase II evaluation of the safety, plasma pharmacokinetics, and antiviral activity of T-20 administered to HIV-1 positive adults by continuous subcutaneous infusion or subcutaneous injection
Study #:	003
Investigators/Centers:	multi-investigator and multicenter in the US
Period of trial:	08/18/98 - 01/07/99

Introduction

This study was one of the original T-20 studies; the first in which T-20 was administered subcutaneously. In this trial, patients received T-20 SC via continuous infusion or rapid injection. This review will focus on the results from SC injection because it is the route of drug administration that was pursued by the applicant.

Objectives

- To evaluate safety of six dose levels of T-20 given by continuous subcutaneous infusion (CSI) or subcutaneous injection (SC) to HIV-1 positive adults
- To determine plasma pharmacokinetics following the administration of six dose levels of T-20 given by CSI or SC to HIV-1 positive adults.
- To determine antiviral activity of six dose levels of T-20 given by CSI or SC injection for 28 days to HIV-1 positive adults.

Study Design

This was a randomized, phase II, active dose controlled trial. Treatment experienced patients were randomly assigned to receive T-20 at one of four dose levels (12.5, 25, 50 or 100 mg per day) given by CSI, or at one of two dose levels (50 or 100 mg BID) given by SC injection over a 28-day period. During the treatment period patients returned to the clinical research unit at defined intervals. Medications that were being taken at 12-hour intervals were administered close to the same time as T-20 by injection (SC group). On PK collection days, patients had a regular diet for breakfast and continued their regular diet for the remainder of the day. No food or beverages were allowed after midnight on the evenings prior to specimen collection for safety laboratory assessments and for the determination of antiviral activity.

Concomitant Medication/ Treatment

The use of systemic concomitant medications of any type was avoided or reduced to those drugs that were medically necessary. Among the concomitant medications allowed were antiretroviral agents that were FDA-approved or available in expanded access programs. Concomitant medications prohibited during this study included therapeutic HIV vaccines and any other experimental therapy.

Formulation

T-20 drug product was provided as a white lyophilized powder in glass vials. The vials delivered either 25 mg or 50 mg T-20 drug product. T-20 batch numbers used during the study were 711013, 800123, and 800426.

Blood Sampling for the SC Infection group

T-20 concentration was determined on Days 0 and 14 at hours 0, 0.5, 1, 2, 4, 6, 8, and 12 hours post dose.

Assay
Pharmacokinetic samples were analyzed by [redacted] Plasma T-20 concentrations were determined by [redacted]. The assay performed acceptably.

Pharmacokinetics
The following pharmacokinetic parameters were calculated from the plasma T-20 concentration data for Day 14 (SC only): $AUC_{(0-12)}$, C_{max}, C_{min}, C_{ss} and T_{max}.

Statistical Methods
Selected PK parameters of SC patients between Day 0 and Day 14 were compared using a paired t-test. Exploratory analyses in dose response were conducted using a regression approach.

Efficacy
Efficacy was assessed by measuring changes from baseline in plasma HIV-1 RNA levels, analyzing maximum change from baseline of plasma HIV RNA, immunophenotyping (CD4 cell count), and development of resistance to T-20 as determined by plasma genotyping and analysis of peripheral blood mononuclear cells (PBMCs).

Results
Disposition of Patients
Seventy-eight patients were randomized to one of six dose groups (13 patients per dose group). A total of 70 patients (89.7%) completed the study. Two subjects receiving SC injection discontinued the study due to an adverse event (100 mg BID) and due to a protocol violation (50 mg BID), respectively. Key demographic data and baseline characteristics were as follows:

- Most subjects were male (91.0%)
- Most subjects were Caucasian (76.9%),
- Mean age of 42.4 years (range 27-68)
- Mean baseline plasma HIV RNA across groups was 4.9 $\log_{10}$ copies/mL and the mean CD4 cell count was 130.3 cells/μL.

All treatment groups had similar baseline demographics. For additional information on demographics see Appendix.

Protocol Violations/Deviations
One patient (patient # 0075) randomized to the 50 mg BID SC dose group had a violation of inclusion/exclusion criteria (absolute neutrophil count below the entry criteria). The patient was discontinued from the study. The most common protocol deviations were PK sampling and vital sign measurements performed out of the protocol-specified timeframes.

Pharmacokinetics Results
The key PK findings from the CSI groups were that exposure increases were not dose-proportional and none of the doses tested achieved the target C_{min} of 1 μg/mL. PK data for the CSI groups will not be discussed further in this review for previously stated reasons; however, PK data for the CSI group is in the appendix.

T-20 pharmacokinetic parameter data for the SC injection are summarized in Table I.

Table I: T-20 Plasma Pharmacokinetic Parameters

	SC			
	50 mg BID		100 mg BID	
Parameter	Day 0	Day 14	Day 0	Day 14
$AUC_{(0-12)}$ (ng.hr/mL)				
N	12	10	12	10
Mean	14447.2	21374	29626.0	36501.7
(SE)	(2246.5)	(2540.5)	(4714.0)	(4930.4)
p*		0.005		0.213
C_{max} (ng/mL)				
N	12	10	12	11
Mean	1838.3	2626.0	3933.3	4725.5
(SE)	(246.3)	(274.6)	(673.5)	(490.3)
p*		0.005		0.333
C_{min} (ng/mL)				
N	12	10	12	11
Mean	301.9	931.7	405.4	1413.1
(SE)	(58.7)	(119.1)	(117.0)	(276.3)
C_{ss} (ng/mL)				
N		10		10
Mean		1781.2		3041.8
(SE)		(211.7)		(410.9)
T_{max} (hr)				
N	12	10	12	11
Mean	5.7	4.2	5.7	4.2
(SE)	(0.7)	(0.6)	(0.4)	(0.63)

*Comparison of T-20 pharmacokinetic parameters on Day 0 and Day 14 for SQI patients.

The exposure measures, AUC, C_{max}, C_{min}, and C_{ss}, increased in a dose-proportional manner. T_{max} was the same for both doses. The T-20 half-life could not be calculated, as the elimination rate could not be estimated from the limited number of samples obtained after the last dose of study drug was administered.

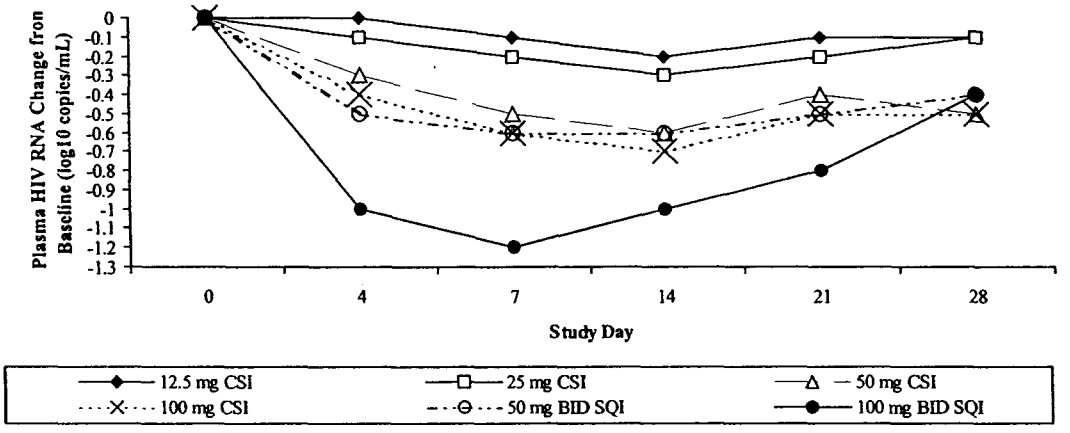
On Day 14, the mean $AUC_{(0-12)}$ values had increased from those measured on Day 0, suggesting that drug accumulation had occurred. However, a comparison of the mean $AUC_{(0-12)}$ on Day 0 versus Day 14 revealed a significant increase in mean $AUC_{(0-12)}$ on Day 14 for the 50 mg BID dose group, but there was no statistically significant increase in mean $AUC_{(0-12)}$ for the 100 mg BID dose group.

Exploratory Dose-Response Relationships (Efficacy Results)

- HIV Viral Load

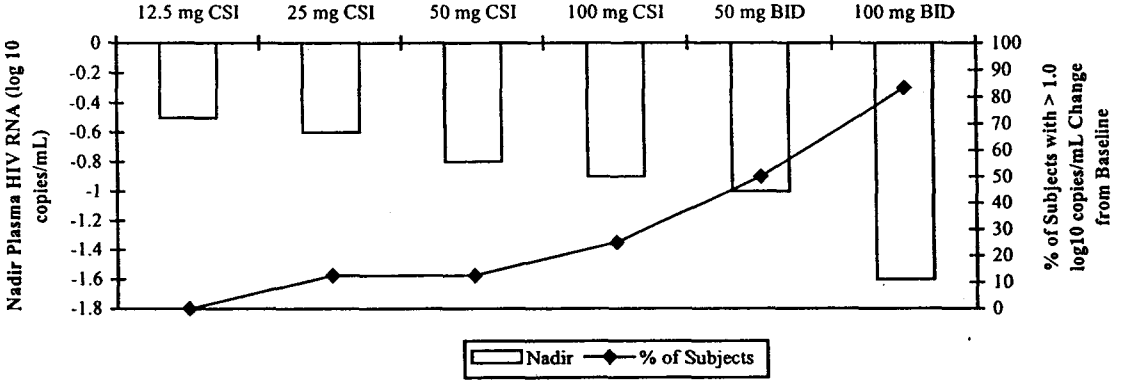
A dose-response relationship was observed for the SC injections, as shown in the following two figures.

Figure 1: Dose Response of Maximum Change from Baseline Plasma HIV RNA



In figures 1 and 2, CSI refers to continuous subcutaneous infusion and SQI refers to SC injection

Figure 2: Mean Change from Baseline of Plasma HIV RNA over Time



The 100 mg group had greater viral suppression than the 50 mg dose group. The maximum suppression was observed at the 100 mg BID SC (the highest dose group) on Day 7 (-1.2 $\log_{10}$ copies/mL, $p<0.001$). After reaching their maximal suppression, the viral load started to rebound. At the 50 mg and 100 mg BID SC doses, plasma HIV RNA was significantly suppressed at all visits from Day 4 through Day 21, with the exception of Day 21 in the 50 mg BID SC dose group.

There appeared to be a dose-response relationship following CSI administration.

- CD4 Cell Counts

The dose-response relationship between T-20 dose and CD4 counts was unclear. After 28 days of treatment, the mean change from baseline in absolute CD4 cell count ranged from 1.0 to 28.3 cells/μL

across dose groups. Only the change observed in the 100 mg BID SC treatment group (a mean gain of 26.0 cells) was statistically significantly different at Day 28 from the baseline value (data not shown).

Overall, the dose-response findings suggest that T-20 had antiviral activity in a patient population that was heavily pre-treated with all commercially available classes of antiretroviral agents and with the advanced stage of infection.

Safety Results (applicant's analysis)

The most common treatment-emergent adverse event (AE) was injection site reaction (72 patients, 96.0%). The percent of patients experiencing injection site reaction was comparable across the different dose groups (83% to 100%). With the exception of the injection site reactions, T-20 was well tolerated at all doses throughout the 28-day treatment period. No deaths occurred during this study. During the study, two patients discontinued due to AEs. Adverse events leading to discontinuation included injection site induration, rash and pain, and injection site reaction with rash and pruritus. No other clinically relevant changes occurred in the study.

Conclusions

- Plasma concentrations of 1 μg/ml were achieved with the 100 mg BID SC group.
- Subcutaneous injection of T-20 100 mg BID provided antiviral activity over a 28-day period
- Apart from injection site reactions, T-20 was generally well tolerated

CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA number:	21-481
Submission date:	November 2, 2001
Product:	Lyophilized powder for injection, 90 mg
Brand name:	Fuzeon
Generic name:	enfuvirtide, T-20, Ro 29-9800
Sponsor:	Hoffmann-La Roche Inc.
Type of submission:	PM consult (Population Pharmacokinetic Analysis)
Primary Reviewer:	Robert O Kumi, Ph. D.
PM reviewer:	Jenny J Zheng, Ph.D.

The sponsor conducted a population pharmacokinetic (PPK) analysis using the data from two pivotal safety and efficacy phase 3 trials, NV16054/T20-301 and BV16052/T20-302. The pharmacokinetic of enfuvirtide in special population such as female, renal, and hepatic impaired subjects was solely based on this analysis. This review will focus on the PPK analysis. Please refer to Dr. Robert Kumi's review for the detailed background information about this drug.

SUMMARY:

A total of 628 patients with 2920 enfuvirtide concentrations obtained from two pivotal phase 3 trials were included in this analysis. The patients were randomly divided into two groups for inclusion in the "model building database" and the "validation database". The inclusion of patients in the validation database was made by random selection of patients from each study separately such that 15% and 85% of available patients for each study were included in the validation database and the model building database, respectively. The final database that was used for model building and covariate identification included 2417 observations from 534 patients. A total of 446 observations from 94 patients (98.5% of the initial observations and 100% of the total patients intended for inclusion) were retained in the database for model validation.

Log likelihood profiles and maximum a [redacted] methods are used for validation of the model.

The findings of the PPK analysis are as the follows:

- The pharmacokinetics of enfuvirtide in HIV-infected patients was well described by a one-compartment open model with first order absorption and first order elimination from the central compartment.
- The population mean estimates for clearance and volume of distribution for a 70 kg male reference patient were 1.82 L/h and 4.43 L, respectively, and were in agreement with previously reported values.
- Total body weight and sex were the only covariates found to significantly contribute to inter-individual variability in clearance. Using a 70 kg male as the reference, the clearance of a 40 kg female was about 36% lower and clearance of a 110 kg male was about 26% higher.

- The clearance of enfuvirtide was similar in the patients with creatinine clearance ≥ 35 ml/min. The pharmacokinetic of enfuvirtide across patients with creatinine clearance < 35 mL/min is unknown.
- The hepatic function markers, albumin, SGOT, SGPT, total bilirubin and prothrombin time, were individually tested. No tested markers contributed to inter-individual variability in enfuvirtide pharmacokinetics.

COMMENTS:

1. Using a 70 kg male as the reference, the PPK analysis predicted that female with low body would have higher exposure and the male with high body weight would have lower exposure. It is recommended that the safety and the efficacy to be compared between female with low body weight (e.g. bodyweight <50kg) and male with high body weight (e.g. >100 kg) in attempting to explore if the exposure is associated with the adverse event or efficacy.

2. The influence of hepatic function on the pharmacokinetic of enfuvirtide was assessed using markers such as albumin, SGOT, SGPT, total bilirubin and prothrombin time separately. It is suggested that the sponsor re-evaluate the effect of hepatic function using Child Pugh Score as suggested in Hepatic Impairment Guidance.

3. The impact of hepatic function on the pharmacokinetic of enfuvirtide is not conclusive because the severity of impaired hepatic function was not classified. It is not clear if sufficient number of severe hepatic impaired subjects were included the study to conclude the lack of hepatic effect on the pharmacokinetics of enfuvirtide.

RECOMMENDATION:

The population pharmacokinetic analysis (PPK) was found to be acceptable to support the label with regard to the renal impaired population, but not the hepatic impaired population.

Jenny J Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

- *Traditional Phase I study designs would require short-term monotherapy with enfuvirtide. Because the clinical implications of such short term monotherapy are unknown, patients that participate in such studies are offered continued access to enfuvirtide after completing such studies. This becomes logistically complex, and is further complicated when one considers that the supply of enfuvirtide was limited during clinical development.*

sample was to have been obtained at Week 48 at any time during the clinic visit. The sampling scheme was summarized in Table 1. The exact sample dates and times, and the dates and times of the proceeding 4 doses were recorded in the Case Report Form.

Data Exclusion:
The same criterions were used to exclude the samples for both model building and validation data sets. The number of samples and the reasons for excluding the data from the model building data are shown in the following table:

Reason for Removal	Number of Points Removed
Plasma concentrations rising more than 24 hours after the last dose	4
Error in the sample date	1
No supporting dose information	3
Sample date or sample time not adequate	18

During the initial model development process, there were 10 pharmacokinetic observations that were removed as a consequence of having high weighted residuals (absolute value of the weighted residuals greater than 4). These observations were returned to the database after the modeling work was complete to assess their effect on the final model parameters.

Data for Model Building and Validation:
The patients were randomly divided into two groups for inclusion in the "model building database" and the "validation database". The inclusion of patients in the validation database was made by random selection of patients from each study separately such that 15% and 85% of available patients for each study were included in the validation database and the model building database, respectively.

The final database that was used for model building and covariate identification included 2417 observations from 534 patients. A total of 446 observations from 94 patients (98.5% of the initial observations and 100% of the total patients intended for inclusion) were retained in the database for model validation

Tested Covariate:
The covariates assessed in the PPK are shown in Table 2 and definitions of several covariates are described in the following:
Creatinine Clearance was estimated using the method described by Cockroft and Gault:

$$CLCR\,(mL/min) = \frac{(140 - Age(y)) \cdot Body\ Weight\,(kg)}{72 \cdot Serum\ Creatinine\,(mg/dL)} \cdot 0.85 \text{ for Females}$$

Body Surface Area was estimated using the method described by DuBois and DuBois:

$$BSA\,(m^2) = 0.007184 \cdot Body\ Weight\,(kg)^{0.425} \cdot Height\,(cm)^{0.725}$$

AIDS Wasting Syndrome (AWS) was defined as profound involuntary weight loss of > 10 % of baseline body weight plus either chronic diarrhea (at least two loose stools per day for ≥ 30 days), or chronic weakness and documented fever (for ≥ 30 days, intermittent or

constant) in the absence of a concurrent illness or condition other than HIV infection that could explain the findings. For purposes of this population pharmacokinetic analysis, AIDS wasting syndrome was treated as a categorical covariate, with patients assigned a value of either "yes" (AWS=1) or "no" (AWS=0).

Anti-Enfuvirtide Reactive Antibodies: The effect of anti-enfuvirtide reactive antibody status on enfuvirtide pharmacokinetics was assessed using either group (GPGR) or percent change from baseline (PCTG) variables. A noncompetitive, indirect ELISA was used for the [redacted] A [redacted] format was used with antigen passively bound to solid-phase. T-20 and T-786 (a negative control peptide) were coated in parallel to assess the specific binding of IgG in each serum sample. IgG was detected using an [redacted] which caused a colorimetric change in the presence of substrate.

For the assessment using GPGR, patients with measurable antibody titers at any assessment point were considered "positive" (GPGR=1). Patients with antibody titers below the limit of quantification at all assessment points were considered "negative" (GPGR=2). Non-quantifiable titers, (signal to noise ratio of <3:1, GPGR=3) and missing values (GPGR=0) were treated either as "negative" or evaluated as a separate category in the population pharmacokinetic analysis. For the assessment using PCTG, "positive" antibody responses were further classified into maximum percent change from baseline categories. Percent change from baseline was calculated as

$$\%Change = 100 \cdot \frac{on\text{-}treatment\ numerical\ value - baseline\ numerical\ value}{baseline\ numerical\ value}$$

Percent change in antibody titer was calculated only for patients with positive values at baseline and at least one follow-up visit. PCTG group classification consisted of 3 grades: ≥ 30% decrease from baseline (PCTG=1), <30% decrease to <30% increase from baseline (PCTG=2), and ≥ 30% increase from baseline (PCTG=3).

Urine protein (UPRO) was determined by a dipstick test and recorded in the Case Report Form as a categorical covariate with values of 0 (absent), +1 (trace), +2 (positive), or +3; +4 (strong positive). For the population analysis this was coded to 0 (absent), 1 (trace), or 2 (positive or strong positive).

Concomitant Medications: Several commonly co-administered drugs used in the treatment of HIV and associated co-morbidities were evaluated for their effect on enfuvirtide pharmacokinetics. These agents were evaluated as individual covariates, and using a group assignment for known cyctochrome p450 inhibitors and inducers (Table 6). The purpose of this investigation was to screen for large effects of concomitantly administered drugs on enfuvirtide pharmacokinetics. Concomitant medication data indicated only the presence or absence of each medication; dose information was not assessed in this analysis.

A one-compartment open model with first-order input and first-order elimination was used to model the time course of enfuvirtide concentrations in this analysis. Other structural models were investigated early in the model development process, but were rejected on the basis of high objective function values, poor residual plots, or unidentifiable parameters.

4.1.2. Covariate Model:

Continuous covariates such as age or weight were modeled using a general slope function (equation 1) or an intercept slope function equation 2:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} cov_i^{\theta_i} \qquad \text{Equation 1}$$

$$TVP = P_{pop} + \sum_{i=1}^{n} \text{cov}_i \cdot \theta_i \qquad \text{Equation 2}$$

TVP represents the model predicted pharmacokinetic parameter (CL/F, V/F) for the "typical" individual with covariate value(s) cov_i, P_{pop} represents the population central tendency for the pharmacokinetic parameter TVP in equation 1 and intercept value for the pharmacokinetic parameter TVP, cov_i represents the individual value for that covariate normalized by the approximate median value for the patient population, and θ_i represents a scale factor.

Categorical covariates (e.g., gender, AWS, urine protein, and race) were modeled using the general equation:

$$TVP = P_{pop} \cdot (1 + \text{cov}_i \cdot \theta_i) \qquad \text{Equation 3}$$

In this equation, cov_i is either 0 (for the standard or reference patient), or 1 for the comparative patient. TVP is the typical value of the parameter, P_{pop} represents the value for the pharmacokinetic parameter when cov_i is 0, and θ_i represents a scale factor for the influence of that covariate such that if θ_i is less than 0, the net effect is a decrease in the typical value, and if θ_i is greater than 0, the net effect is an increase in the typical value of the parameter.

For categorical covariates that could take on more than one value (e.g. urine protein), these parameters were first tested using a bivariate case comparing the most common value or the most physiologically normal value against all other values for that covariate (e.g., negative urine protein versus all positive values). If the covariate model was statistically significant and if the scale factor was estimated as being potentially clinically relevant (e.g. a greater than 20% change in the parameter value), then a function treating each covariate value separately was tested.

The relative impact of these covariates on the pharmacokinetics of enfuvirtide was ultimately assessed by the associated decrease in objective function together with the magnitude of the covariate effects and any associated reduction in inter-individual variability. Initial covariate selection was conducted using the base model. All covariates were initially modeled individually

on each parameter and were then combined on parameters based on the results of the log likelihood ratio test.

Only those covariates that individually influenced the PK parameters were added in descending order of magnitude ("forward addition" method). The covariate was retained in the final model if it resulted in at least 10 points change in the objective function from the previous model. In the evaluation of alternate models, together with significant reductions in the objective function ($\geq$ 10 points), the goodness-of-fit criteria included (1) improvement in the prediction of the observed concentrations, reduction of the standard errors with respect to the parameter estimates, (2) improvement in the random scatter of weighted residuals around the line of identity in plots of weighted residuals versus predicted concentrations, (3) minimization of the inter-individual variances and an improvement in their prediction, and (4) a reduction in the magnitude of the residual variability. In addition, covariate factors had to have clinical or physiological relevance. If the magnitude of the change of the parameter due to a covariate influence was less than 20%, the covariate factor was not considered relevant.

4.1.3. Pharmacostatistical Model:

4.1.3.1. Inter-Individual Variability:

Inter-individual variability was described using the following error model:

$$P_j = TVP \cdot e^{\eta_j} \qquad \text{Equation 4}$$

In this equation P_j is the individual value for the pharmacokinetic parameter in the *jth* individual and η_j is an independent random variable with a mean of zero and variance ω_P^2.

4.1.3.2. Residual Variability:

The residual variability was described using a combined additive and constant coefficient of variation (CCV) model

$$Cs_{ij} = \hat{C}s_{ij} \cdot \exp(\varepsilon_{ij_1}) + \varepsilon_{ij_2} \qquad \text{Equation 5}$$

In this equation Cs_{ij} is the *i*th concentration measured in the *j*th patient, $\hat{C}s_{ij}$ is the model predicted Cs_{ij}, and ε_{ij1} and ε_{ij2} are error terms with means of zero and variances σ_1^2 and σ_2^2.

4.2. Model Validation:

The two methods that were employed in the present analysis were the generation of log likelihood profiles and

4.2.1. Log Likelihood Profiling:

Conditional 90% confidence intervals for CL/F, V/F and Ka were estimated by profile mapping. Briefly, to obtain the upper and lower confidence limits for the θ value of interest, the estimate for θ is "fixed" at a percentage of the final model estimate and the model is re-run, allowing all other θ values to be re-estimated. The resultant change in objective function (ΔM) is then plotted against the fixed θ value. This procedure is repeated for a range of values above and below the final model θ estimate, such that a bowl-shaped curve is obtained with the minima at ΔM equal to

0 (usually corresponding to the original, final model θ estimate). The two points at which the curve intersects a horizontal line drawn with y-intercept 3.84 represent the approximate, conditional upper and lower 90% confidence limits for the θ value of interest. Since it was impractical to repeat a large number of runs to determine the exact θ value at which ΔM is equal to 3.84, linear interpolation was used between the 2 closest fixed θ values that span the ΔM value of 3.84.

4.2.2. Maximum A Posteriori Analysis:

Maximum a posteriori analysis of the final model was carried out by two methods. First, the final model was re-fitted to the validation dataset to obtain an independent set of "test" estimates for the pharmacokinetic parameters. Consistency between the estimates obtained for the model building dataset and the "test" estimates was examined to confirm model robustness. Secondly, the final model, together with the final population parameters from the model building dataset, was applied to the test dataset to obtain estimates of enfuvirtide plasma concentrations for the typical patient as well as the individual Bayesian estimates using the NONMEM command MAXEVALS=0 (maximum *a posteriori* Bayesian assessment). These predictions were graphically compared to the actual observed concentrations. Agreement between the predicted and observed concentrations was evaluated to verify the reliability of the model predictive capacity.

4.3. Derived Pharmacokinetic Parameters:

After the final population pharmacokinetic model was determined, individual estimates of area under the enfuvirtide plasma concentration time curve at steady state (AUC12h), and steady state trough concentrations of enfuvirtide (Ctrough) were calculated for all patients (i.e., Model Building and Validation Datasets) in the population pharmacokinetic analysis for use in further exploratory analyses.

AUC12h was calculated as:

$$AUC12h = \frac{F \cdot Dose}{CL}$$

where CL is the individual estimate for CL from the final population model, F is assumed to be 1, and Dose is the administered enfuvirtide dose of 90 mg.

Ctrough was calculated as:

$$Ctrough = \frac{F \cdot Dose \cdot Ka}{V \cdot (Ka - \frac{CL}{V})} \left[\left(\frac{1}{1 - e^{-\frac{CL}{V} \cdot \tau}} \right) e^{-\frac{CL}{V} \cdot \tau} - \left(\frac{1}{1 - e^{-Ka \cdot \tau}} \right) e^{-Ka \cdot \tau} \right]$$

These parameters were obtained from the final model for the model building database and the estimated run for the validation database. The results for both were pooled. All derived

parameters were calculated for each occasion sampled within an individual. Since it was desirable to have one parameter estimate per individual, the mean value across all occasions within an individual was reported.

5. RESULTS:

The demographic of the study was summarized in Table 4.

5.1. Base Model:

The best base model was a one-compartment open model with first order input and first order elimination. This model was consistently superior to the two-compartment model. The model had terms for inter-individual variance on all parameters and no covariance terms. Inter-occasion variability was estimated for CL/F and V/F. The residual error was best described using a combined CCV and additive model. The model was run using the default first order conditional estimation (FOCE) method.

Several special input functions were tested during model development because previous analysis of Phase I data suggested an inverse Gaussian model best described the input. None of the special input functions that were tested resulted in any improvement over the simple first order input function. This finding is consistent with expectations given that these data were collected at steady state and consequently, such data would not have a great deal of information about drug absorption.

Parameter estimates for the base model are given in Table 5 and the goodness of fit figure is presented in Figure 1. The plot of observed versus predicted concentrations shows a reasonable uniform distribution of observations about the line of unity. The plot of individual predicted versus observed concentrations shows that the individual predictions are estimated well, with no observable bias. The plot of absolute value of individual weighted residuals versus individual predicted concentrations indicate that there is a slight tendency for the model to over predict very low concentrations. The plot of weighted residuals versus time shows that there is no obvious bias in the model over time.

5.2. Final Model:

The final model was a one-compartment model with first order input and first order elimination, with total body weight and sex covariates on CL/F. The model was parameterized for CL/F, V/F and Ka with terms for inter-individual variability on all parameters and a term for covariance between CL/F and V/F. The inter-individual variability term for Ka was fixed to 20%. IOV was estimated for CL/F and V/F. The model used a combined CCV and additive residual error model.

Covariates identified to contribute to inter-individual variability in CL/F included total body weight and sex. Over the reported weight range of 33.6 to 112 kg, CL/F varies from 1.34 L/h to 2.17 L/h. Females exhibited CL/F values that were 20% lower than that observed in males of the same weight. The final model parameterization is presented below. Parameter estimates for the final model are given in Table 6.

$$\frac{CL}{F} = \left[\theta_1 + \left(\frac{WT}{70}\right) \cdot \theta_4\right] \cdot (1 + SEX \cdot \theta_5)$$

$$\frac{V}{F} = \theta_2$$

$$KA = \theta_3$$

The parameter estimates for CL/F and V/F are in generally good agreement with parameters reported previously. For a 70 kg male patient, the model estimated CL/F was 1.82 L/h. The standard errors of the parameter estimates are reasonable and the random residual variance is fairly low. The additive portion of the residual error function is negligible and could conceivably have been removed to simplify the model slightly. Inter-individual variability and inter-occasion variability for CL/F are also reasonably low, although both terms remained high for V/F.

The diagnostic plots for the final model are given in Figure 2. Compared to the base model, there is a minor improvement in the plot of observed (DV) versus predicted (PRED) enfuvirtide concentrations in that the data are no longer 'clumped' into two sections as they were in the base model. The observations are evenly distributed about the line of unity, although there is a tendency for the model to under-estimate very high concentrations. The plot of observed versus individual predicted concentrations shows no overt improvement. However, the plasma concentrations are estimated well in this plot and no overt bias is evident. The high concentrations are well estimated in this figure. The plot of absolute value of individual weighted residuals versus individual predicted concentrations shows that there is a tendency for higher individual weighted residuals at the lowest concentrations. The plot of weighted residuals versus time did not suggest that there were any changes in model performance over the several occasions observed.

5.3. Covariate Influences on Pharmacokinetic Parameters:

Covariates identified to contribute to inter-individual variability in CL/F included total body weight and sex. Clearance increased with increasing weight. Over the reported weight range of 33.6 to 112 kg in both male and female patients, CL/F varies from 1.34 L/h to 2.17 L/h.

Females exhibited CL/F values that were 20% lower than observed in males of the same weight. A plot of the final model estimates of individual clearance versus weight stratified by patient sex is given in Figure 3. The reason for this finding is not clear, but this finding is not expected to be clinically relevant as the magnitude is relatively small (20%).

The influence of race on the pharmacokinetic parameter is presented in Figure 4. The histogram of baseline renal and hepatic function covariates is presented in Figure 5 and the relationship between renal and hepatic function and the pharmacokinetic parameters is presented in Figures 6 and 7, respectively.

Several commonly co-administered drugs used in the treatment of HIV and associated co-morbidities were evaluated for their effect on enfuvirtide pharmacokinetics. Based on the metabolic profile of enfuvirtide, no interactions were anticipated. This analysis was conducted as a "screen" for major effects of commonly administered concomitant medications on enfuvirtide pharmacokinetics. These agents were evaluated as individual covariates, and grouped by

predisposition to induce or inhibit cytochrome p450 isozymes. In all cases, the magnitude of any observed effect was small (less than 15% change in clearance). Therefore, cytochrome p450 inducers and inhibitors commonly administered in this patient population do not appear to markedly alter the pharmacokinetics of enfuvirtide. A graphical representation of the lack of effect noted with the group comparison is presented in Figure 8.

The presence of circulating anti-enfuvirtide reactive antibodies did not influence the pharmacokinetics of enfurvidite in this patient population, as presented in Figure 9.

5.4. Model Validation:

5.4.1. Log-Likelihood Profiles

Log likelihood profiles were generated for all parameters estimated in the final model. Because the models were run under FOCE estimation method, the assumption of chi-square distribution is acceptable without a permutation test to define the change in objective function associated with $p < 0.05$. Therefore, an increase in the objective function of 3.84 would mark the 95% confidence interval for that parameter. The 95% confidence intervals estimated by profile mapping are given in Table 7. The log-likelihood profile plot for θ_1 (intercept value for CL/F) is presented in Figure 10. In general, the Log Likelihood profiles suggest that the parameters identified in the present analysis are reasonably well identified.

5.4.2. Maximum A Posteriori Bayesian Estimate:

The results of the [redacted] assessment are shown in Figures 11. In the plot of observed versus predicted enfuvirtide concentrations, the observations are evenly distributed about the line of unity but have the same tendency to under-estimate high concentrations that was seen in the model building data set. The plot of individual predicted concentrations versus observed concentrations indicates that the individual estimates are good, and that there is no obvious bias.

During the actual estimation of parameters from the validation data set, the estimates of IOV on V/F were not identifiable. Therefore, the parameters associated with IOV on V/F were removed and the model was re-run. The parameter estimates from this slightly modified model are given in Table 8. As can be seen, the parameter for the intercept of CL/F (θ_1) became negligible, suggesting that the model could be simplified to a slope model for the effect of weight. In addition, the variance terms for V/F are larger than were estimated in the model-building database. Otherwise, the parameter estimates are very similar, again supporting the observation that the parameter estimates obtained in the present analysis are reasonably well defined.

5.5. Outlier Runs:

Once the final model was established and qualified, all measurable concentrations that had been removed from the database because of high weighted residuals, or due to questionable dose or sample time information, were restored to the database and the final model control stream was re-run to assess the effect of removing these data from the database on the parameter estimates. As might be expected with the addition of questionable data, the model did not converge successfully. Therefore, standard errors on the parameter estimates cannot be provided. However, the parameter estimates are very similar to those obtained in the final model, suggesting that the removal of the outlier data did not alter the parameter estimates.

5.6. Derived Parameters

A summary of derived parameters is provided in Table 9 and the distribution of the parameters are shown in Figure 12.

To assess the potential clinical significance of the covariate influence identified in this analysis, the final population model was used to calculate pharmacokinetic parameter values for patients representative of the extremes of covariate influences within this study population. The effects of these covariates on CL/F are given in Table 10. It showed that using 70 kg male as reference, the CL was increased by only 26 % for the 110 mg male and the CL was decreased by 36% in 40 kg female.

6. CONCLUSION:

- The pharmacokinetics of enfuvirtide in HIV-infected patients was well described by a one-compartment open model with first order absorption and first order elimination from the central compartment.
- The population mean estimates for clearance and volume of distribution for a 70 kg male reference patient were 1.82 L/h and 4.43 L, respectively, and were in agreement with previously reported values.
- Total body weight and sex were the only covariates found to significantly contribute to inter-individual variability in clearance. Using a 70 kg male as the reference, the clearance of a 40 kg female was about 36% lower and clearance of a 110 kg male was about 26% higher.
- The clearance of enfuvirtide was similar in the patients with creatinine clearance ≥ 35 ml/min. The pharmacokinetic of enfuvirtide across patients with creatinine clearance < 35 mL/min is unknown.

Table 4. Pharmacokinetic Sampling Schedule for NV16054/T20-301 and BV16052/T20-302

Study Visit Week	-3 to 0 hours pre-dose	1 to 4 hours post-dose	5-8 hours post-dose
1 or 2			2 samples separated by at least 1 hour
8	2 samples separated by at least 1 hour		
24		2 samples separated by at least 1 hour	
48	1 sample collected at any time during visit		

Table 5. Covariates Assessed in Population Pharmacokinetic Analysis

Covariate	Abbreviation	Unit	Value	Type
Demography				
Patient Age at baseline	AGE	yr	numeric	Continuous
Patient Weight	WT	kg	numeric	Continuous
Patient Height at baseline	HT	cm	numeric	Continuous
Body Surface Area	BSA	m^2	numeric	Continuous
Patient Gender	SEX	---	1=female 0=male	Categorical
Patient Race	RACE	---	1=White 2=Black 3=Asian or Pacific Islander 4=Other	Categorical
AIDS wasting syndrome	AWS	---	1=yes 0=no	Categorical
Renal Function:				
Creatinine Clearance	CRCL	mL/min	numeric	Continuous
Urine Protein	UPRO		0=Absent 1=Trace 2=Positive/Strong Positive	Categorical
Hepatic Function:				
Albumin[a]	ALB	g/dL	numeric	Continuous
SGOT[a]	SGOT	IU/L	numeric	Continuous
SGPT[a]	SGPT	IU/L	numeric	Continuous
Total Bilirubin[a]	BILT	mg/dL	numeric	Continuous
Prothrombin time[a]	PT	s	numeric	Continuous
Cirrhosis[a]	CIRR	---	1=yes 0=no	Categorical
Concomitant Medications[b]	---[b]	---	0=not taking 1=taking	Categorical
Anti-Enfuvirtide Reactive Antibodies				
Antibody Status	GPGR	---	1=pos 2=neg 3=non-quantifiable 0=missing	Categorical
Antibody Change from Baseline (BL)	PCTG	%	1=≥30% decrease from BL 2=<30% decrease to <30% increase from BL 3=≥30% increase from BL 0=neg/missing	Categorical

[a]Evaluated individually.

[b]i.e. abacavir, amprenavir, delavirdine, didanosine, efavirenz, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, stavudine, tenofovir, zalcitabine, zidovudine, carbamazepine, clarithromycin, erythromycin, fluconazole, fluoxetine, itraconazole, ketoconazole, phenytoin, rifabutin, sulfamethoxazole_trimethoprim, phenobarbital

Table 6. Concomitant Medication Classification for Group Assessment of Cytochrome p450 Inducers and Inhibitors

Drug	Predominant CYP Activity	Classification (0=renal, 1=inhibitor, 2=inducer, 3=other)
Abacavir	Metabolized by ROH-dehydrogenase, glucuronyl transferase, renal elimination of metabolites	0
Amprenavir	Inhibitor(3A4)	1
Carbamazepine	Inducer (2C19, 3A4)	2
Clarithromycin	Substrate(3A4), inhibitor(3A4)	1
Delavirdine	Inhibitor(3A4)	1
Didanosine	Renal excretion 50%	0
Efavirenz	Inducer(3A4), inhibitor(3A4, 2C9, 2C19), MIXED	3
Erythromycin	Substrate(3A4), inhibitor(3A4)	1
Fluconazole	Inhibitor(2C19,3A4)	1
Fluoxetine	Substrate(2C9, 2D6), inhibitor(2C19,2D6,3A4 (via norfluoxetine))	1
Indinavir	Substrate(3A4), inhibitor(3A4)	1
Itraconazole	Inhibitor(3A4)	1
Ketoconazole	Inhibitor(2C19,3A4)	1
Lamivudine	Excreted unchanged in urine	0
Lopinavir	Substrate(3A4), inhibitor(2D6, 3A4)	1
Nelfinavir	Substrate(2C19, 3A4), inhibitor(3A4)	1
Nevirapine	Inducer(3A4)	2
Phenobarbital	Inducer(2B6, 3A4)	2
Phenytoin	Substrate(2C9, 2C19), inducer(3A4)	2
Rifabutin	Substrate(3A4), inducer(3A4)	2
Ritonavir	Substrate(3A4), inhibitor(2D6, 3A4)	1
Saquinavir	Substrate(3A4), inhibitor(3A4)	1
Stavudine	Renal excretion 50%	0
Sulfamethoxazole trimethoprim	Substrate(2C9-SMZ), inhibitor(2C9-TMP)	1
Tenofovir	Primarily filtered and secreted	0
Zalcitabine	Renal excretion 70%	0
Zidovudine	Metabolized to zidovudine glucuronide, renal excretion of g-zidovudine	0

Table 4. Summary of Baseline Demographic, Patient Status and Concomitant Medication Information. Model Building Data Set (n=534)

Baseline Characteristic	Mean (SD)	Median	Range
Age (y)	42.3 (7.92)	41.0	16.0 – 67.0
Height (cm)	176 (8.21)	176	33.6-112
Weight (kg)	72.2 (12.7)	71.7	33.6 – 112
Body Surface Area (m^2)	1.87 (0.18)	1.87	1.09 – 2.35
Creatinine Clearance[a] (mL/min)	112 (26.6)	112	34.5 – 150
SGOT (IU/L)	46.0 (29.0)	37.0	12.0-178
SGPT (IU/L)	47.8 (35.3)	35.0	7.00-229
Albumin (g/dL)	4.10 (0.45)	4.20	2.10-5.20
Serum creatinine (mg/dL)	0.88 (0.24)	0.85	0.40-2.50
Bilirubin (mg/dL)	0.48 (0.27)	0.40	0.18-2.5
Prothrombin Time (s)	12.4 (1.61)	12.1	10.6-26.3
Sex	Males = 476; Females = 55		
Race	Caucasian=476; non Caucasian = 58		
Aids Wasting Status (AWS)	No AWS = 441; AWS =93		
Cirrhosis	No Cirrhosis 534; Cirrhosis 0		
Urine Protein	0(absent)=379; 1(trace)=127; 2(pos)=28		
GP group	0=178; 1=246; 2=6; 3=104		
PCT group	0=332; 1=131; 2=54; 3=17		
Abacavir Sulfate	Not Taking=382; Taking=152		
Amprenavir	Not Taking=328; Taking=206		
Delavirdine	Not Taking=503; Taking=31		
Didanosine	Not Taking=305; Taking=229		
Efavirenz	Not Taking=448; Taking=86		
Indinavir	Not Taking=488; Taking=86		
Lamivudine	Not Taking=304; Taking=230		
Lopinavir	Not Taking=243; Taking=291		
Nelfinavir	Not Taking=521; Taking=13		
Nevirapine	Not Taking=511; Taking=23		
Ritonavir	Not Taking=115; Taking=419		
Saquinavir	Not Taking=473; Taking=61		
Stavudine	Not Taking=362; Taking=172		
Tenofovir	Not Taking=418; Taking=117		
Zalcitabine	Not Taking=504; Taking=30		
Zidovudine	Not Taking=447; Taking=87		
Carbamazepine	Not Taking=530; Taking=4		
Clarithromycin	Not Taking=514; Taking=20		
Erythromycin	Not Taking=533; Taking=1		
Fluconazole	Not Taking=422; Taking=112		
Fluoxetine	Not Taking=530; Taking=4		
Itraconazole	Not Taking=515; Taking=19		
Ketoconazole	Not Taking=520; Taking=14		
Phenytoin	Not Taking=531; Taking=3		
Rifabutin	Not Taking=530; Taking=4		
Sulfamethoxazole	Not Taking=278; Taking=256		
Phenobarbital	Not Taking=533; Taking=1		

[a] – Predicted creatinine clearance

NB – these are baseline values only. Changes in patient weight, BSA, lab values etc. were recorded in the database.

Table 5. Base Model Parameter Estimates

Model Parameter	Pop. Mean	Inter-Individual Variability**	Inter-Occasion Variability**
CL/F (L/h)	1.78	29.0	25.0
V/F (L)	3.63	77.0	51.0
Ka (h-1)	0.111	30.0	NE
Random Residual CCV Variability as % CV	20.0		
Random Residual Additive Variability (ng/mL)	0.01		
** expressed as % coefficient of variation			
'N.E.' - 'not evaluated'			

Table 6. Final Model Parameter Estimates

		Pop. Mean (s.e.%)	Inter-Individual Variability**	Inter-Occasion Variability**
CL/F (L/h)	θ_1	0.990 (22.1)	27.0	31.6
Effect of weight	θ_4	0.833 (25.5)		
Effect of sex	θ_5	-0.203 (26.8)		
V/F (L)	θ_2	4.43 (9.20)	57.0	54.1
Ka (h-1)	θ_3	0.113 (5.8)	20.0 FIX	NE
Random Residual CCV Variability as % CV		16.2		
Random Residual Additive Variability (ng/mL)		0.188		
** expressed as % coefficient of variation				
'N.E.' - 'not evaluated'				

Table 7. 95% Confidence Intervals for Final Model Parameters

Parameter		Pop. Mean	Lower 95% CI	Upper 95% CI
CL/F (L/h)	θ_1	0.990	0.723	1.24
Effect of weight	θ_4	0.833	0.575	1.09
Effect of sex	θ_5	-0.203	-0.136	-0.266
V/F (L)	θ_2	4.43	3.81	5.41
Ka (h-1)	θ_3	0.113	0.104	0.125

Table 8. Validation Dataset Parameter Estimates

Parameter		Pop. Mean (s.e.%)	Inter-Individual Variability % **	Inter-Occasion Variability %**
CL/F (L/h)	θ_1	-0.186 (259)	31.9	30.6
Effect of weight	θ_4	2.01(23.6)		
Effect of sex	θ_5	-0.241 (58.1)		
V/F (L)	θ_2	5.42 (22.7)	96.3	NE
Ka (h-1)	θ_3	0.0972 (12.2)	20.0 FIX	NE
Random Residual CCV Variability as % CV		16.2		
Random Residual Additive Variability (ng/mL)		0.188		
** expressed as % coefficient of variation				
'N.E.' - 'not evaluated'				

Table 9. Summary Statistics for Individual Derived Area Under the Enfuvirtide Plasma Concentration Time Curve at Steady State (AUC12h), and Steady State Trough Plasma Concentration (Ctrough)

Parameter (n=628)	Mean	Median	Minimum	Maximum
AUC12h (ug.h/L)	54103	50820	[redacted]	[redacted]
Ctrough (ug/L)	2995	2800	[redacted]	[redacted]

Table 10. Effect of Weight and Sex on Enfuvirtide Clearance

Weight (kg)	Clearance Males (L/h)	Percent Change from 70 kg Male	Clearance Females (L/h)	Percent Change from 70 kg Male
40	1.47	-19%	1.17	-36%
50	1.59	-13%	1.27	-30%
60	1.70	-7%	1.35	-26%
70	1.82	reference	1.45	-20%
80	1.94	+7%	1.55	-14%
90	2.06	+13%	1.64	<1%
100	2.18	+20%	1.73	<1%
110	2.30	+26%	1.83	<1%

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Pharmacometrics Review (Place Holder)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-481	Brand Name	Fuzeon
OCPB Division (I, II, III)	DPE III	Generic Name	Enfuvirtide
Medical Division	DAVDP	Drug Class	Fusion Inhibitor
OCPB Reviewer	Robert O. Kumi, Ph.D.	Indication(s)	Treatment of HIV-1 infection
OCPB Team Leader	Kellie S. Reynolds, Pharm.D.	Dosage Form	Lyophilized Powder
		Dosing Regimen	90 mg twice daily
Date of Submission	09/17/2002	Route of Administration	Subcutaneous (SC)
Estimated Due Date of OCPB Review	12/31/2002	Applicant	Hoffmann-La Roche Inc.
PDUFA Due Date	03/17/2003	Priority Classification	Priority
Division Due Date	12/15/2002		

1.1.1.1.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	x	[redacted]	[redacted]	
Tabular Listing of All Human Studies	x	[redacted]	[redacted]	
HPK Summary	x	[redacted]	[redacted]	
Labeling	x	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	x	[redacted]	[redacted]	Two methods used: [redacted] and [redacted] Cross-validation conducted.
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:	x	1		
Blood/plasma ratio:	x	1		
Plasma protein binding:	x	1		
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:	X	2		
multiple dose:	X	4		
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:	X	2		
fasting / non-fasting multiple dose:	x	1		
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
In-vivo effects on primary drug:	X	3		
In-vivo effects of primary drug:	X	2		
In-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				

gender:				
pediatrics:	x	2		There is an additional ongoing study
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:	x	2		Pharmacometrics Consult
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	x	1		
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:	x	1		
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	15		Study on CSI may not be reviewed

Filability and QBR comments		
	"X" if yes	
Application filable ?	X	Applicant will be asked to provide SAS transport files of all available PK data, particularly, data used in population pharmacokinetic analyses.
Comments sent to firm ?		
QBR questions (key issues to be considered)	Is the applicant's population pharmacokinetic analysis adequate to determine if demographic and other patient factors affect T-20 pharmacokinetics?	

Other comments or information not included above	This application is a rolling submission, and the clock started on September 17, 2002. If granted a priority review, the PDUFA deadline would be in March 2003, however, the clinical division intends to take an action on this application by 12/31/2002.
Primary reviewer Signature and Date	Robert O. Kumi, Ph.D.
Secondary reviewer Signature and Date	Kellie S. Reynolds, Pharm.D.

CC: NDA 21-481, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-530 (Yoerg), HFD-880(Reynolds, Lazor, Selen), CDR

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

/s/

Robert Kumi
3/26/03 07:47:38 PM
BIOPHARMACEUTICS

Kellie Reynolds
3/27/03 10:00:15 AM
BIOPHARMACEUTICS

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