duration of RTV administration in this study is insufficient to achieve steady-state; however, the duration is adequate to assess full CYP inhibition by RTV.

Reviewer Comment
The sponsor's dose selection rationale is reasonable.

Formulation

- T-20 was supplied as a lyophilized powder within a glass vial. Each vial contained 106 mg and delivered 90 mg of T-20 when reconstituted. The lot number of T-20 used during this study was C199820-011.
- Ritonavir was supplied as Norvir® 100 mg capsules for oral administration. The lot number of ritonavir used in this study was 806662E21.

Blood Samples
Blood samples were collected on Days 3 and 7 at the following time points: Pre-dose (0 h), 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 24h.

Assay
Analytical Method for T-20 and Ro 50-6343
Plasma samples were analyzed for T-20 and its metabolite (Ro 50-6343) with a validated ——— method by ——————————. The lower limit of quantitation was — ng/mL for T-20 and the T-20 metabolite. Inter-assay precision was assessed by CV: range was from 5.92% to 10.36% for T-20 and 4.81% to 9.41% for Ro 50-6343. The accuracy was assessed by the relative error: ranged from 0.90% to 3.17% for T-20 and -0.80% to 1.05% for the T-20 metabolite. The assay performance was acceptable.

Analytical Method for Ritonavir
Plasma samples were analyzed for ritonavir by ——————————. using a validated ——— method. The lower limit of quantitation was — ng/mL. Inter-assay precision was assessed by CV: range was from 10.2% to 12.9%. The accuracy was assessed by relative error: range was from –0.6% to 8.6%. The assay performance was acceptable.

PK Assessments
The following PK parameters were calculated on day 3 and day 7:

- For T-20: Cmax, C_{trough}, AUC_{12h}, T_{max}, K_{el}, and $T1_{/2}$.
- For T-20 metabolite: C_{max}, C_{trough}, AUC_{12h} and the ratio of AUC_{12h} T-20 metabolite/T-20.
- For ritonavir (day 7 only): C_{max}, C_{trough} and AUC_{12h}.

These PK parameters were calculated using model-independent techniques (WinNonlin Pro Version 3.2):

Pharmacodynamic Assessments
Pharmacodynamic parameters were CD4 cell count and HIV-1 viral load.

Safety Assessments
Safety assessments included adverse events, injection site reactions (ISRs), clinical laboratory parameters (hematology, clinical chemistry, and urinalysis) and vital sign

Statistical Model

Standard pharmacokinetic-statistical methods were used to assess drug-drug interactions.

Results

Disposition of Patients

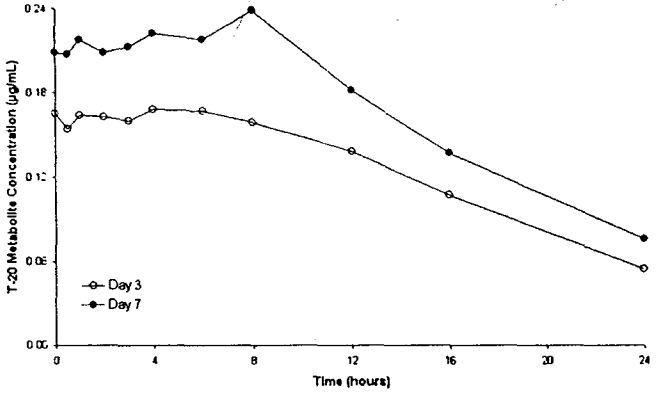
All 12 patients enrolled in the study completed the study as planned. There were no premature withdrawals. No patients or data were excluded from any of the analyses. Some noteworthy demographic data and baseline characteristics were equal number of male and female subjects, all subjects were of Asian/Pacific Island ethnicity, and the age range of subjects was 27-48 years. Additional demographic information is included in the appendix.

Pharmacokinetic Results

- T-20

As shown in the figure below, the mean steady-state T-20 plasma concentrations in the presence of ritonavir were higher than those with the control profile (T-20 alone).

Mean Steady-State T-20 Plasma Concentration-Time Profiles without (day 3) and with (day 7) Ritonavir



Differences in the plasma concentration-time profiles were greater in the initial (absorption) phase than in the terminal (elimination) phase. This finding suggests that RTV may affect the absorption of T-20. The mean steady-state T-20 PK parameters and exposure comparisons are summarized in Table I.

Table I: T-20 Mean ± SD Steady State Pharmacokinetic Parameters

PK Measure	No Ritonavir (Day 3)	With Ritonavir (Day 7)	Geometric Mean ratio (%)	90% Confidence Intervals
AUC_{12h}, h·µg/mL	61.3 ± 9.73	75.8 ± 19.7	122	108-137
C_{max}, µg/mL	6.73 ± 0.88	8.51 ± 2.34	124	109-141
C_{trough}, µg/mL	3.34 ± 0.81	3.83 ± 1.04	114	102-128
T_{max}, h	5.11 ±1.18	4.09 ± 0.67	-	-
$t_{1/2}$, h	4.46 ± 0.52	4.80 ± 0.62	-	-
K_{el}, h^{-1}	0.158 ± 0.021	0.147 ± 0.018	-	-

The GMR and associated 90 % confidence intervals indicate that RTV caused changes in T-20 exposure (approximately 20 % increase in AUC, C_{max} and C_{min}), 1-hour decrease in T_{max}, but had

a minimal effect on $t_{1/2}$ (4.8 vs. 4.5 hr). It is noted that the inter-patient variability in each of the T-20 exposure parameters (C_{max}, C_{trough}, and AUC_{12h}) was increased in the presence of RTV. All patients experienced an increase of T-20 exposure in the presence of ritonavir, although the exposure increases were of different magnitudes. According to the sponsor, the increase in T-20 exposure is not clinically significant.

Reviewer Comment
The apparent lack of significance of the increased T-20 exposure is supported in part by the findings in the Phase III trials. Most subjects in the Phase III trials received T-20 with ritonavir, potentially, having increased T-20 exposure; however, the safety profile of these subjects was considered acceptable. The main limitation of using data from the Phase III trials to support lack of clinical significance of increased T-20 exposure is the fact that subjects received additional medications other than RTV in these studies. Another reason for exercising caution in concluding the RTV-T-20 interaction results are not clinically significant is the fact that the mechanism of the interaction is unknown. It would be useful to identify the mechanism of interaction to allow prediction of other potential drug-drug interactions.

Potential Interaction Mechanism (Role of Transporters)
Ritonavir inhibits CYP3A4, CYP2D6, CYP2C9, and CYP2C19 to varying degrees. The effect of RTV inhibition of CYP-mediated metabolism is profound for compounds metabolized by CYP enzymes. For example, when RTV is coadministered with protease inhibitors (PIs) and other medications the following results are obtained:

- Increased AUC of PIs: 2-fold with amprenavir and 17-fold with saquinavir
- Increased AUC of other medications: 2.5 fold with alprazolam and 11-fold with [redacted]

RTV presence increased the other exposure measures for the above compounds, and in all but one case the half-life of the drug was increased. It should be noted that the magnitude of the inhibition, and resultant exposure increases reported above, are affected by the bioavailability of the compounds. The exposure increase with T-20 was not as great as previously reported for the above compounds, suggesting that the RTV-T-20 mechanism of interaction is not likely via a CYP pathway. Furthermore, because T-20 is a peptide it is unlikely to undergo a CYP-based interaction; thus, the observed T-20 exposure increases are unlikely due to a CYP-based interaction with RTV.

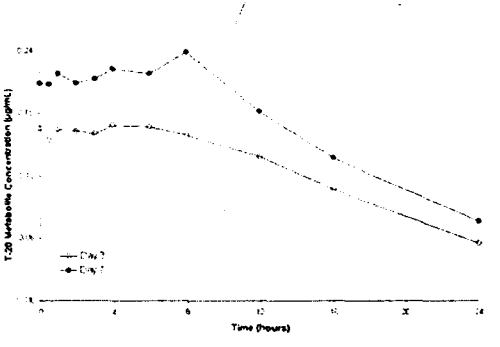
Apart from the CYP inhibition, RTV inhibits P-glycoprotein (PGP). An interaction via PGP is feasible because PGP is a cell-membrane associated ATP-dependent drug efflux pump that transports a variety of drug substrates including peptides. PGP is expressed in the capillary endothelial cells of many tissues. According to the sponsor, reports indicate that expression of the PGP transporter in the endothelial cell has been shown to be a limiting factor for drug entry into the capillary system from the lumen. Additionally, some *in vitro* studies indicate that PGP transports hormones and peptides in Caco-2 cells. It is not known whether T-20 is a substrate for PGP or other kinds of peptide/protein transport systems. If T-20 interacts with RTV via a transport pathway, RTV potentially affects T-20 PK by inhibiting its efflux from the systemic circulation. The sponsor will be asked to evaluate the transport pathways of T-20 to elucidate potential interaction mechanisms.

In this study, a booster dose of RTV increased the AUC_{12h} of T-20 by 22%. This increase in exposure was considerably less than what has been reported when RTV is administered with CYP substrates. Although the increase in T-20 exposure is relatively small using a RTV booster dose it is unknown if higher doses of RTV will cause further increases in T-20 exposure. The sponsor indicates that "results of this study are inconsistent with the data obtained from several other studies". These other studies are

- [redacted] study: 10-day pre-treatment with rifampicin, a strong enzyme inducer, did not cause any change in the C_{max}, C_{trough} or AUC_{12h} of T-20
- Population pharmacokinetic analysis (sponsor's analysis) of sparsely sampled data from two large Phase III clinical trials (T20-301/ NV16054 and T20-302/ BV16052) revealed that cytochrome P450 inducers and inhibitors commonly administered in the HIV+ patient population did not appear to markedly alter the pharmacokinetics of T-20.

In this reviewer's opinion the findings in this study are important because they reveal that there is an interaction pathway by which RTV and other drugs can potentially alter T-20 pharmacokinetics. This pathway should be elucidated as it may play a vital role in potential drug-drug interactions during therapy with T-20.

Figure 2: Mean Steady-State T-20 Metabolite Plasma Concentration-Time Profiles without (day 3) and with (day 7) Ritonavir



- T-20 Metabolite/Ro 50-6343 (T-20-M)

As with the parent drug (T-20), a 4-day treatment with RTV increased the mean plasma concentrations of the T-20 metabolite (figure 2).

The mean exposure of the T-20 metabolite (T-20M) were also increased in the presence of ritonavir relative to exposures observed when only T-20 was administered

Table: Ro 50-6343 Mean ± SD Steady-State PK Parameters and M/P* AUC 12h Ratios

PK Parameter	No RTV (Day 3)	With RTV (Day 7)	Geometric Mean Ratio (%)	90 % CIs
AUC_{12h}, h·µg/mL	1.89 ± 0.340	2.58 ± 0.651	134	123-146
C_{max}, µg/mL	0.186 ± 0.033	0.254 ± 0.063	134	123-147
C_{trough}, µg/mL	0.151 ± 0.028	0.195 ± 0.044	128	116-141
M/P* Ratio of AUC12h (%)	3.1 ± 0.6	3.5 ± 0.9	-	-

* M/P=T-20 metabolite/Parent ratio

As with the parent compound, inter-patient variability in the PK exposure parameters for Ro 50-6343 was higher when T-20 was given with ritonavir than when it was given alone. Interestingly, metabolite/parent AUC_{12h} ratios were comparable, 3.1% vs. 3.5% irrespective of the absence or presence of ritonavir. These results suggest that ritonavir may affect an elimination pathway other than the one leading to formation of Ro 50-6343 or that it inhibits to the same extent both the formation and elimination pathways of Ro 50-6343. The GMRs indicate that the increase in T-20-M exposure was approximately 30 %. The clinical significance of this increased exposure is unknown. It is noted that the T-20 metabolite accounts for < 10 % of T-20 exposure (AUC) consequently it is unlikely to impact overall activity of T-20 despite its comparable *in vitro* activity to T-20.

T-20 PK Comparison in Asian versus Caucasian Populations

The current study was conducted in an Asian population. The main steady-state T-20 exposure parameter (AUC_{12h}) in this study is higher than that obtained in previous studies with Caucasians (61 μg.h/ml in this study vs. 43 to 56 μg.h/mL in Caucasians), but consistent with that found in another study performed in Asian patients (table 2). On average, the 90 mg dose of T-20 is equivalent to 1.60 mg/kg in the Asian patients in this study and equivalent to 1.17 - 1.35 mg/kg in other studies with Caucasian patients. After adjusting the exposure parameters to a body weight-normalized dose, the difference in AUC_{12h} between the two populations was minimal (39 to 45 μg.hr /mL in Asian vs. 37 to 41 μg.hr/mL in Caucasian). The sponsor concluded that the observed race difference in AUC_{12h} can be largely attributed to the difference in the mean body weight between the two populations. This conclusion appears reasonable in this reviewer's opinion. However, the impact of increased exposure in patients with low body weight can not be determined from this short term trial.

Table: Comparison of Mean ± SD Steady State AUC_{12h} in Asian and Caucasian Populations

Reference	Caucasian	Asian	Female /Male	Age	BW kg	AUC_{12h}, hr·μg/mL	Dose mg/kg	*Adjusted AUC_{12h}, hr·μg/mL
This study	0%	100%	6/6	34±6	58± 10	61± 10	1.60 ± 0.29	39
NV 16334	0%	100%	8/4	32±6	56±10	74 ± 17	1.65 ± 0.29	45
NP16370	92%	0%	0/12	45±6	78±11	43 ± 11	1.17 ± 0.16	37
T20-208	82%	0%	0/11	42±8	76±11	49 ± 19	1.21 ± 0.16	40
NP16220	100%	0%	3/9	38±8	68±10	56 ± 12	1.35 ± 0.22	41

Comparison was made for dose group of 90 mg BID and subcutaneously injected in abdomen

* Adjusted AUC_{12h}=observed AUC_{12h}/(90mg/Body Weight)

- Ritonavir

Plasma concentrations of ritonavir exhibited high inter-individual variability at each blood sampling time with CV values ranging from 32 to 60%. The mean steady-state C_{max}, C_{trough} and AUC_{12h} were 5.4 ± 1.6 μg/mL, 1.3 ± 0.7 μg/mL and 33.3 ± 12.2 h·μg/mL, respectively, consistent with previously reported values obtained after 200 mg ritonavir q12h dosing at steady-state.

Safety Results

According to the sponsor, the adverse event profile of the 3 patients (0005, 0006, 0007) with a greater than 50% increase in AUC_{12h} of T-20 in the presence of ritonavir was "unremarkable". Patient 0005 had no adverse events. Patient 0006 experienced mild abdominal distention and Patient 0007 experienced a mild headache. Both events occurred on Day 4, the first day of T-20 in the presence of ritonavir; both were considered unrelated to trial treatment.

Conclusions

A booster dose of ritonavir increased the systemic exposure of T-20; the increase in exposure does not appear to be clinically significant, as most subjects (>80 % of subjects in the Phase III trials) receiving a booster dose of ritonavir had acceptable safety profiles.

Appendix

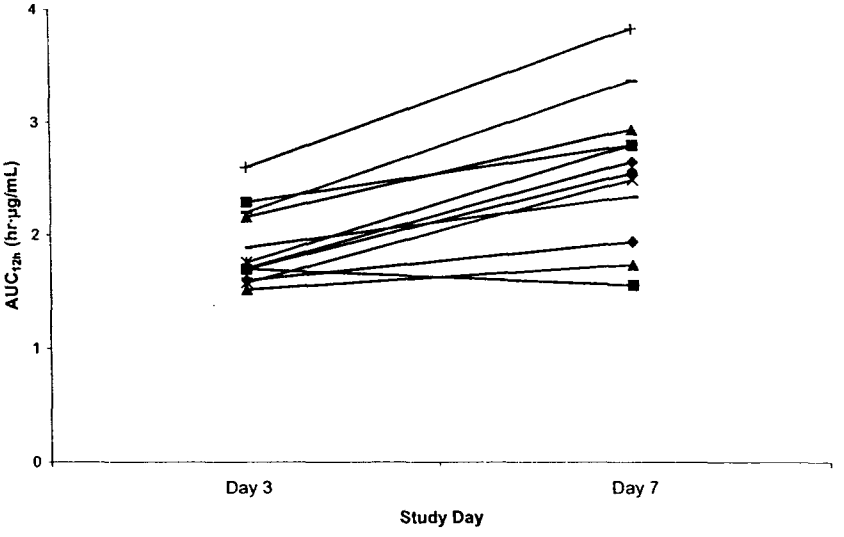
Summary of Demographic Data

	ALL TREATMENTS N = 12
Sex	
MALE	6 (50%)
FEMALE	6 (50%)
n	12
Race	
CAUCASIAN	-
BLACK	-
ORIENTAL	-
OTHER	12 (100%)
n	12
Age	
Mean	33.7
SD	5.50
SEM	1.59
Median	33.5
Min-Max	27 - 48
n	12
Weight in kg	
Mean	58.09
SD	10.501
SEM	3.031
Median	56.95
Min-Max	44.6 - 75.5
n	12
Height in cm	
Mean	160.9
SD	10.02
SEM	2.89
Median	159.5
Min-Max	150 - 176
n	12
Body mass index in kg/m2	
Mean	22.33
SD	2.786
SEM	0.804
Median	21.85
Min-Max	18.7 - 27.3
n	12

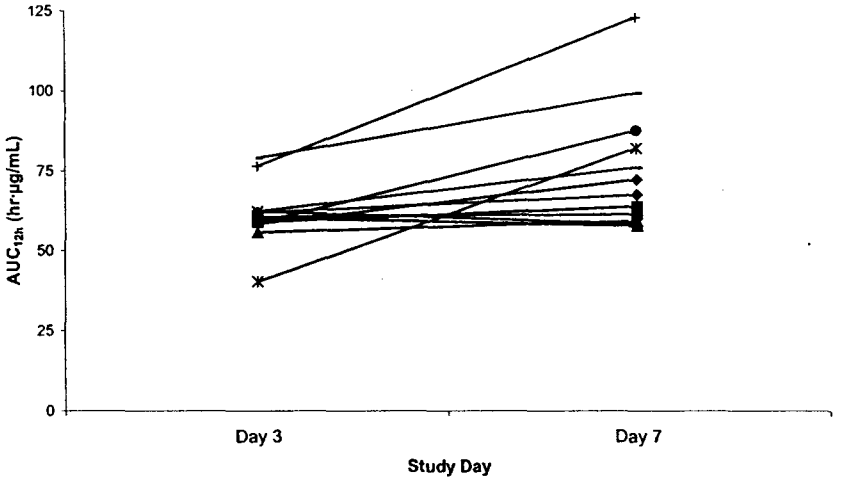
n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

APPEARS THIS WAY
ON ORIGINAL

T-20 metabolite exposure in individual patients



T-20 exposure in individual patients



APPEARS THIS WAY
ON ORIGINAL

Title:	Study to determine the metabolic inhibitory effect of saquinavir (Fortovase®) combined with a minidose of ritonavir (Norvir®) on the pharmacokinetics of enfuvirtide in HIV-infected patient volunteers.
Study:	T20-503 (NP16324)
Investigators/centers:	[redacted]
Study Period:	03/2002 – 05/2002

Study Rationale

During HIV therapy T-20 may be coadministered with protease inhibitors (PIs), such as saquinavir. In clinical practice, PIs are often coadministered with a minidose of ritonavir, as a metabolic inhibitor, to increase the exposure of the PI. Potential benefits of the boosting approach include decreasing pill burden, minimizing the food effect, and decreasing dosing frequency. Thus it was important to investigate the effect of a representative ritonavir-boosted protease inhibitor regimen on the pharmacokinetics (PK) of T-20.

Objective

To determine the metabolic inhibitory effect of saquinavir combined with a minidose of ritonavir on the pharmacokinetics of enfuvirtide in HIV-infected patient volunteers.

Study Design

This study was an open-label, multi-dose, sequential crossover study. Twelve HIV-1-infected adults took part in the study and received the following medications:

- Days 1 –3: T-20 90 mg subcutaneously (SC) every 12 hours (BID or twice daily), except on Day 3* when only the morning dose was given
- Days 4- 7: T-20 90 mg SC every 12 hours, except on Day 7* when only the morning dose was given.
- Days 4 – 7: Ritonavir (Norvir®) 100 mg was orally administered every 12 hours (BID)
- Days 4 – 7: Saquinavir (Fortovase®) 1000 mg was orally administered every 12 hours (BID)

All study medication was administered by study staff only. T-20 was administered by study staff into the SC tissue of the abdomen. The site of injection was rotated around the SC tissue of the abdomen in the event of injection-site-related reactions. On days 4 -7, the protease inhibitors and T-20 were administered at the same time as a meal or up to two hours after a meal.

* on these days, evening dose of T-20 on days was not administered in order to further characterize the T-20 plasma concentration-time profile over a 24-hour period

Dosing Rationale

In general, the doses selected by the applicant were suitable to determine if ritonavir/saquinavir (RTV/SQV) affected the PK of T-20. T-20 concentrations achieve steady-state levels within 3 days and the RTV/SQV (100/1000 mg) every 12 hour dosing regimen has been evaluated by other investigators [redacted] The RTV/SQV regimen will not be at steady-state after four days of dosing, particularly the RTV levels, because RTV induces it's own metabolism. Generally, RTV levels achieve steady state after approximately 12 days of dosing. Steady-state RTV levels (Day 12) will be lower than those obtained after 4 days of dosing. Thus, the chosen schedule will not reflect the steady-state (achieved following chronic administration) effect of the PI-regimen on the PK of T-20. Despite this shortcoming, the study will give an indication if T-20 metabolism is inhibited by this PI combination.

Concomitant Medication/Treatment

Patients were to be off ARV therapy for at least four weeks or on stable doses of NRTIs for at least six weeks. Several drugs and medications were not allowed during and before treatment to minimize the chance of misinterpretation (confounding factors) of drug-drug interaction results. These agents included anti-fungals, herbal remedies, and enzyme inhibitors and inducers. However, All patients received at least one other treatment: eight patients received ARV agents; 4 patients received sulfonamides; 3 patients received mild analgesics and 8 other patients received various individualized treatments.

Reviewer Comment

Ideally, concomitant medications should be absent, but it is difficult to obtain drug-free patients for such trials. Nevertheless, none of the agents are expected to affect the study results because the metabolic pathway of these agents is different from that of T-20, ritonavir, and saquinavir.

Formulation

- T-20 (enfuvirtide)- lyophilized powder within a glass vial. Each vial contained 106 mg and delivered 90 mg of T-20 when reconstituted and injected. Lot numbers: C199820-012, C199810
- Ritonavir (Norvir®) was supplied as 100 mg capsules for oral administration. Lot Number: 806662E21
- Saquinavir (Fortovase®) was supplied as 200 mg soft gel capsules for oral administration. Lot number: B1387

Pharmacokinetic Procedures

Blood samples were collected on day 3 (approximately 5 mL) and on day 7 (approximately 10 mL) at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the morning dose of T-20.

Assay

Plasma samples were analyzed for T-20 and its metabolite (Ro 50-6343), SQV and RTV. An ——— method was used to measure the concentrations of T-20 and its active metabolite ——————— The assay was accurate and precise (% relative error and coefficient of variation for QC samples were within ± 15 %). RTV and SQV concentrations were determined by a validated ——— method ←——————— The assay was accurate and precise (% relative error and coefficient of variation for QC samples were within ± 15 %).

Pharmacokinetic Parameters

The following PK parameters were calculated on Day 3 and/or Day 7.
For T-20: C_{max}, C_{trough}, AUC_{12h}, T_{max}, K_{el}, and $T_{1/2}$
For T-20 metabolite: C_{max}, C_{trough}, AUC_{12h} and the ratio of AUC_{12h} T-20 metabolite/T-20
For saquinavir and ritonavir: plasma concentrations were summarized descriptively and C_{max}, C_{trough} and AUC_{24h} (from time 0 to 24 hour) on day 7 were calculated.
The PK parameters were calculated using model-independent techniques (WinNonlin Pro Version 3.2):

Statistical Model

Standard pharmacokinetic-statistical analyses were used to compare (T-20 + RTV/SQV vs. T-20 alone) drug exposures.

Results

Disposition of Subjects

Thirteen patients were enrolled in this study, and 12 patients completed the study. One patient was withdrawn from this study due to the patient's noncompliance. All patients were Asian/Pacific Islander (Other) with a mean age of 38.4 years. Approximately equal numbers of male and female patients participated in the trial. Additional demographic data and baseline characteristics are included in the appendix.

PK Results

- T-20

Based on inspection of mean steady-state T-20 plasma concentration-time profiles (T-20 plus combination PI vs. T-20 alone- profile not shown), the protease inhibitors increased T-20 exposure. The mean steady-state T-20 and T-20 metabolite PK parameters are summarized in Table I.

Table I: T-20 and T-20 Metabolite Mean (±SD) Steady-State PK Parameters

Drug	PK Parameter	No PIs	With PIs
T-20	C_{max}, μg/mL	9.83 ± 2.09	10.6 ± 2.49
	C_{trough}, μg/mL	4.12 ± 0.93	5.17 ± 1.17
	AUC_{12h}, hr·μg/mL	82.3 ± 18.1	94.0 ± 19.9
	T_{max}, hr	5.26 ± 1.43	5.5 ± 1.51
	$T_{1/2}$, hr	4.49 ± 0.45	5.06 ± 0.74
	K_{el}, hr^{-1}	0.156 ± 0.015	0.139 ± 0.017
T-20 Metabolite	C_{max}, μg/mL	0.265 ± 0.045	0.368 ± 0.122
	C_{trough}, μg/mL	0.200 ± 0.045	0.279 ± 0.075
	AUC_{12h}, hr·μg/mL	2.62 ± 0.515	3.64 ± 0.963
T-20 Metabolite/Parent	AUC_{12h} Ratio,%	3.2 ± 0.6	3.96 ± 1.1

The exposure comparisons for T-20 and its metabolite are summarized in Table II.

Table II: Geometric Mean Ratio (T-20 + RTV/SQV Day 13: T-20 alone Day 3) and 90% Confidence Intervals for T-20 and T-20 metabolite

Drug	PK Parameter	GMR (%)	90 % CI
T-20	C_{max}	107	94.3 – 121
	C_{trough}	126	117 – 135
	AUC_{12h}	114	105 – 124
T-20 Metabolite	C_{max}	134	120 – 150
	C_{trough}	138	128 – 148
	AUC_{12h}	137	127 – 148

Based on the GMR and resulting 90 % confidence interval, RTV/SQV has an effect on T-20 PK. The C_{trough} and AUC increase by approximately 20 %; whereas the change in C_{max} is not statistically significant. However, these changes are unlikely to be clinically significant because the upper bound of the confidence interval exceeds the no effect boundary by only a small amount (≤ 10 %). Although, there is no validated T-20 exposure-response relationship that

supports this claim of lack of clinical significance, empirical evidence from the pivotal clinical trials and other studies, suggest that T-20 is well-tolerated at exposures greater than those obtained with the 90 mg dose. It should be noted that the AUCs obtained in this drug-drug interaction study are higher than has been typically seen in other trials. Inspection of the individual exposure data indicates that most patients had T-20 exposure increases in the presence of the PI combination.

- T-20 Metabolite

Similar to the parent drug, the presence of the PI combination resulted in a significant increased exposure (30 – 40 %) of the T-20 metabolite (Table II). The clinical relevance of the increase exposure of the metabolite is unclear. However, the overall exposure percentage of the metabolite appears negligible (< 4 % of T-20 exposure) and is unlikely to have a clinical impact. The metabolite to parent ratio was comparable in the presence and absence of PIs.

- Protease Inhibitor Combination (RTV/SQV).

Saquinavir

Mean SQV AUC_{24h}, C_{max}, and C_{trough} were 57.0 ± 29.7 hr·μg/mL, 7.56 ± 3.87 μg/mL, and 2.91 ± 2.0 μg/mL, respectively. No appropriate historical data are available to make comparisons to the results obtained in this study. However, the applicant indicates that Kilby *et al* have shown that the boosting effect of RTV on SQV is independent of dose over the 100 to 400 mg RTV dose range. It is noted that the SQV data were highly variable in this study, which is contrary to what one might anticipate when SQV is given with RTV. Most studies show that coadministration of RTV with PIs results in decreased PK variability of the boosted PI.

Ritonavir

Mean RTV AUC_{24h}, C_{max}, and C_{trough} were 14.2 ± 4.5 hr·μg/mL, 2.06 ± 0.81 μg/mL , and 0.74 ± 0.3 μg/mL, respectively.

Discussion

The applicant concludes the RTV/SQV (100 mg/1000 mg BID) did not affect overall T-20 exposure. This conclusion is reasonable based on the AUC and C_{max} exposure comparisons (Table II). However, the increases in T-20 C_{min} and all exposures of the metabolite suggest that T-20 interacts with RTV/SQV). Information from other studies (*in vitro* metabolism, Pittsburgh cocktail, rifampin, population PK analyses) suggest that CYP enzymes are not involved in T-20 metabolism and T-20 does not alter the activity of these enzymes. However, this study and the ritonavir study (Study 16325) indicate that T-20 exposure is affected by RTV coadministration. Data obtained in these two studies are insufficient to elucidate the mechanism by which the T-20 exposure is increased. Potentially, a transporter-based mechanism may be involved in the observed interaction.

In summary, results of this study demonstrate that T-20 exposure is marginally increased by coadministration with the RTV-SQV combination. Although these studies were conducted in Asian subjects, they are expected to be applicable to members of the Caucasian, Asian and Black populations.

T-20 PK Comparison in Asian versus Caucasian Population

This study was conducted in an exclusively Asian or Pacific Island population. Most of the other T-20 studies were conducted mainly in the Caucasian population. Steady-state T-20 PK parameters obtained in this population are compared to those obtained in other T-20 studies (Table III).

Table III: Comparison of Mean ± SD Steady-State T-20 PK Parameters

Reference	White	Asian	Female/ Male	Age (years)	Weight kg	AUC_{12h}[a] hr·μg/mL	Dose mg/kg	Adjusted AUC_{12h} hr·μg/mL
NP 16324 (this study)	0 %	100 %	7/5	39 ± 9	58 ± 8	82 ± 18	1.67 ± 0.24	49
NP16325	0 %	100 %	6/6	34± 6	58 ± 10	61 ± 10	1.60 ± 0.29	39
NP16334	0%	100%	8/4	32±6	56 ± 10	74 ± 17	1.65 ± 0.29	45
NP16370[b]	92%	0%	0/12	45±6	78 ± 11	43 ± 11	1.17 ± 0.16	37
T20-208	82%	0%	0/11	42±8	76 ± 11	49 ± 19	1.21 ± 0.16	40
NP16220	100%	0%	3/9	38±8	68 ± 10	56 ± 12	1.35 ± 0.22	41

[a] Adjusted AUC_{12h}=observed AUC_{12h}/(90mg/body weight)
[b] Comparison was made for dose group of 90 mg bid subcutaneously injected in abdomen

Pharmacokinetics differed between Caucasians and Asians (Thai). In general, the T-20 mean AUC_{12h}, was higher (61 to 82 hr·μg/mL in Asian *vs.* 43 to 56 hr·μg/mL in Caucasian) indicating that the apparent clearance CL/F in Asian subjects was lower than in Caucasian subjects. As seen from Table III, the Thai patient population in this study was demographically different from the Caucasian population in other studies. Specifically, patients in this drug-drug interaction study were predominantly female (67% *vs.* <25%) and had a lower body weight (mean: 58 kg *vs.* 68-78 kg). According to the applicant, the observed race difference in AUC_{12h} is mainly explained by the difference in the body weight between the two populations. Thai patients received, on the average, a 1.67 mg/kg dose of T-20 compared to a 1.17 to 1.35 mg/kg dose of T-20 in other studies with Caucasian patients. After adjusting the exposure parameters with body weight-normalized dose, the difference in AUC_{12h} between the two populations was less pronounced (49 hr·μg/mL in Asian *vs.* 37 to 42 hr·μg/mL in Caucasian). The applicant concluded that the observed race difference in AUC_{12h} could be largely attributed to the difference in the mean body weight between the two populations. This conclusion appears reasonable in this reviewer's opinion. However, the impact of increased exposure in patients with low body weight can not be determined from this short term trial.

Safety and Adverse Events (applicant's summary)

All adverse events were judged by the investigator as either mild or moderate in intensity. Headache and dizziness were the only events considered by the investigator as related (remotely) to study medication. The most frequent manifestations of injection site reactions were erythema (83.3%) and induration (75.0%). For additional details on safety, see Medical Officer's review.

Conclusions

A booster dose of ritonavir (100 mg) with saquinavir (1000 mg) marginally increased (26 %) the C_{min} of T-20 (no effect on AUC and C_{max}) and the T-20 metabolite; the increase in exposure does

not appear to be clinically significant, as most subjects (> 80 % in the Phase III trials) receiving a booster dose of ritonavir had acceptable safety profiles.

Appendix

Table 2 Summary of Demographic Data by Trial Treatment, All Patients

	All Treatments N = 12
Sex	
MALE	6 (46%)
FEMALE	7 (54%)
n	13
Race	
CAUCASIAN	-
BLACK	-
ORIENTAL	-
OTHER	13 (100%)
n	13
Age	
Mean	38.4
SD	8.19
SEM	2.27
Median	41.0
Min-Max	21 - 48
n	13
Weight in kg	
Mean	55.54
SD	7.593
SEM	2.106
Median	57.80
Min-Max	42.0 – 65.0
n	13
Height in cm	
Mean	159.7
SD	9.28
SEM	2.57
Median	159.0
Min-Max	148 - 175
n	13

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

Title:	Study to investigate the influence of rifampicin (Rifadin®) on the pharmacokinetics of T-20 in HIV-infected patient volunteers
Study:	NP16334/T20-505
Investigators/centers:	
Study Period:	11/2001 to 01/2002

Study Rationale

Rifampin (rifampicin) is approved for the treatment of tuberculosis (TB). Rifampin use is frequently required for HIV patients because tuberculosis is a complication in patients infected with HIV. However, rifampin is a potent inducer of cytochrome P450 enzymes and some transferases; consequently coadministration of rifampin may cause a substantial decrease in blood levels of antiretroviral (ARV) drugs. Several studies show that rifampin reduces the exposure of several antiretroviral agents, consequently, rifampin is contraindicated for use with all ARV apart from ritonavir, nevirapine, and efavirenz. Thus, it was important to investigate the effect of enzyme induction caused by rifampicin on the pharmacokinetics (PK) of T-20.

Objective

To determine the metabolic inducer effect of rifampicin (Rifadin®) on the PK of T-20

Study Design

This study was a single-center, open-label, sequential crossover study. Twelve HIV-1-infected adults took part in the study and received the following medications:

- Days 1 - 3: T-20 90 mg subcutaneously (SC) every 12 hours (BID), except on Day 3* when only the morning dose was given
- Days 4 - 13: Rifampicin (Rifadin®) 600 mg was administered orally, once per day, for ten consecutive days.
- Days 11 - 13: T-20 90 mg SC BID, except on Day 13* when only the morning dose was given)

Study staff administered all study medication. T-20 was administered into the SC tissue of the abdomen. The site of injection was rotated around the SC tissue of the abdomen in the event of injection-site-related reactions. On day 13, rifampicin was administered within 5 minutes of the morning dose of T-20. During the study, a standard regimen of meals was given at scheduled times in the morning, noon and evening. Rifampicin was administered orally on days 4 to 13 either 1 hour before or 2 hours after a meal with a full glass of water. Water was allowed *ad libitum*.

* on these days, evening dose of T-20 on days was not administered in order to further characterize the T-20 plasma concentration-time profile over a 24-hour period

Concomitant Medication/Treatment

All 12 patients received an ARV regimen of NRTIs during this study with the majority of patients receiving 2 NRTIs. Additionally, some subjects received non-ARV treatments (see Appendix). However, neither the ARV agents nor the non-ARV agents are expected to affect the study results. Several medications were not allowed during and before treatment to minimize the chance of misinterpretation of drug-drug interaction results. These agents included anti-fungals, herbal remedies, and enzyme inhibitors and inducers.

Dosing Rationale

The doses selected by the applicant were suitable to determine if rifampin affected the PK of T-20. T-20 concentrations achieve steady state levels within 3 days and 600 mg once daily dosing regimen is an accepted regimen for the treatment and prophylaxis of tuberculosis. According to the applicant, previous studies show that nine days of rifampicin administration at 600 mg per day is sufficient to demonstrate the inducer effect on the metabolism of other drugs. Some literature reports affirm this time and dosage required for induction by rifampin; however, a definite time is not recorded in the product label. In this reviewer's opinion the 10-day treatment period seems adequate to detect the effect of rifampicin on the PK of T-20.

Formulation

- T-20- lyophilized powder within a glass vial. Each vial contained 106 mg and delivered 90 mg of T-20 when reconstituted and injected. The batch number was Lot C 199820-010
- Rifampicin (Rifadin®) was supplied as 300 mg capsules for oral administration.

Blood Samples

Blood samples were collected on Day 3 and Day 13 at the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the morning dose of T-20.

Assay

Plasma samples were analyzed for T-20 and its metabolite (Ro 50-6343) and rifampin. Assay details are summarized in the table below.

Analyte	T-20	Ro 50-6343 (metabolite)	Rifampin
Method			
LOQ (ng/mL)			
Accuracy (% nominal)			
Inter-assay Precision (CV %)			
Specificity			
Overall Assessment			

Pharmacokinetic Parameters

The following PK parameters were calculated on Day 3 and/or Day 13.

- For T-20: C_{max}, C_{trough}, AUC_{12h}, T_{max}, K_{el}, $T_{1/2}$ (Days 3 and 13)
- For T-20 metabolite: C_{max}, C_{trough}, AUC_{12h} and the ratio of AUC_{12h} T-20 metabolite/T-20 (Days 3 and 13).
- For rifampicin: C_{max}, C_{trough} and AUC_{24h} (Day 13)

The PK parameters were calculated using model-independent techniques (WinNonlin Pro Version 3.2):

Statistical Model

Standard pharmacokinetic-statistical methods were used to compare (T-20 + rifampin vs. T-20 alone) drug exposures.

Results

Disposition of Subjects

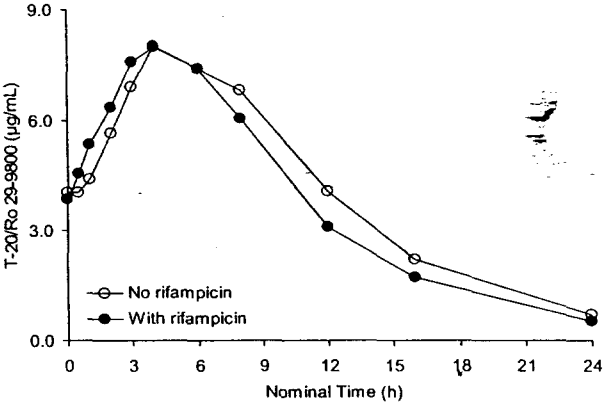
Twelve patients were enrolled in this study and all patients completed the study. All patients were Asian/Pacific Islander (Other) with a mean age of 32.1 years. The majority of patients were female (67%). Additional details on the demographic data and baseline characteristics are included in the appendix.

PK Results

- T-20

Based on inspection of mean steady-state T-20 plasma concentration-time profiles (10-day pretreatment with rifampicin vs. T-20 alone), rifampin did not affect T-20 PK. The plasma concentration time profiles are shown in figure 1.

Figure 1: Mean Steady-State T-20/Ro 29-29800 Plasma Concentration-Time Profiles with and without rifampicin



The mean steady-state T-20 and T-20 metabolite PK parameters are summarized in Table I.

Table I: T-20 and T-20 Metabolite Mean (±SD) Steady-State PK Parameters

Drug	PK Parameter	No Rifampicin	With Rifampicin
T-20	C_{max}, µg/mL	8.12 ± 1.89	8.26 ± 1.60
	C_{trough}, µg/mL	4.06 ± 1.08	3.47 ± 1.02
	AUC_{12h}, hr·µg/mL	74.2 ± 17.3	72.2± 16.3
	T_{max}, hr	5.26 ±1.67	3.93 ± 0.79
	$T_{1/2}$, hr	4.74 ± 0.77	4.64 ± 0.82
	K_{el}, hr^{-1}	0.150 ± 0.023	0.153 ± 0.022
T-20 Metabolite	C_{max}, µg/mL	0.178 ± 0.054	0.198 ± 0.052
	C_{trough}, µg/mL	0.139 ± 0.041	0.128 ± 0.032
	AUC_{12h}, hr·µg/mL	1.76± 0.49	1.90 ± 0.51
T-20 Metabolite/Parent	AUC_{12h} Ratio,%	2.42 ± 0.58	2.67 ± 0.57

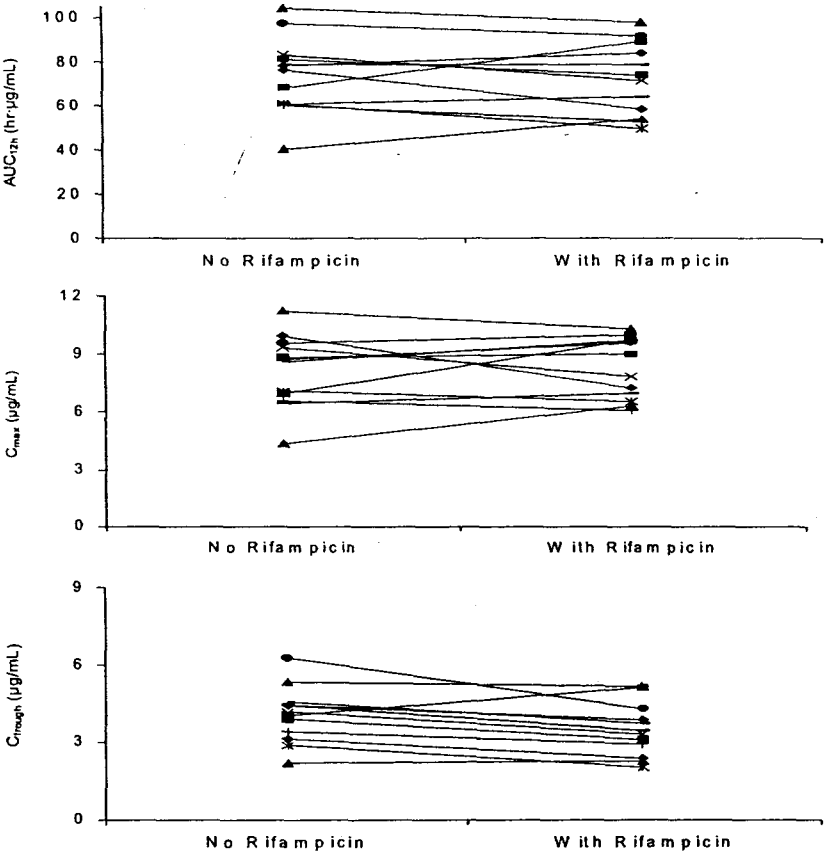
The exposure comparisons for T-20 and its metabolite are summarized in Table II.

Table II: Geometric Mean Ratio (T-20 + rifampin Day 13: T-20 alone Day 3) and 90% Confidence Intervals for T-20 and T-20 metabolite

Drug	PK Parameter	GMR (%)	90 % CI
T-20	AUC_{12h}	97.5	89.3 - 106
	C_{max}	103	92.9 - 114
	C_{trough}	84.9	77.8 - 92.8
T-20 Metabolite	AUC_{12h}	108	101 - 116
	C_{max}	112	103 - 123
	C_{trough}	92.9	88.6 - 94.7

Based on the geometric mean ratio associated 90 % confidence interval, rifampin does not have an effect on T-20 or the T-20 metabolite's AUC or C_{max}, but slightly decreases the C_{min} of T-20 and its metabolite. The clinical significance of the decrease in C_{min} is unclear. The match stick plots of individual subject data also showed minimal effect of rifampicin on T-20 exposure parameters in individual subjects (figure 2)

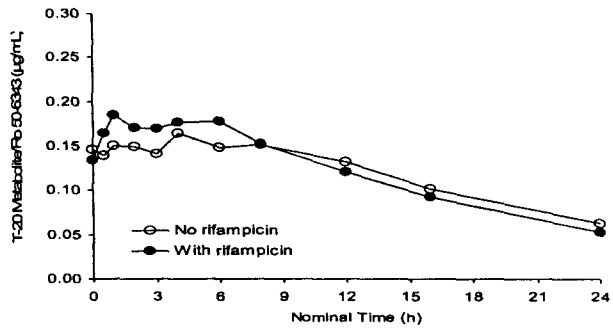
Figure 2: Match Stick Plots for T-20 Exposure Measures



- T-20 Metabolite

Similar to the parent drug, a 10-day pretreatment with rifampicin produced minimal changes in the mean plasma concentration-time profile of the T-20 metabolite. Additionally, the exposure of the metabolite was comparable in the presence and absence of rifampin (figure 3). This finding suggests that rifampin does not affect metabolic conversion of T-20 to this T-20 metabolite.

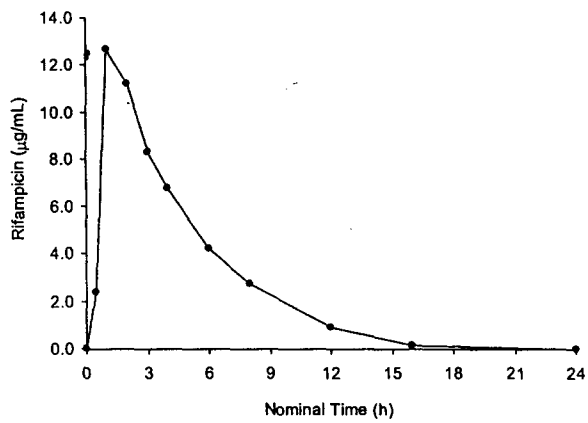
Figure 3: Mean Steady-State T-20 Metabolite Plasma Concentration-Time Profiles with and without Rifampicin



- Rifampicin

Mean steady-state rifampicin plasma concentration-time profiles are displayed in figure 4.

Figure 4: Mean Steady-State Plasma Concentration-Time Profile of Rifampicin in the Presence of T-20 (N=12)



Mean steady-state AUC_{24h} and C_{max} are 61.8 ± 18.5 hr·µg/mL and 14.1 ± 4.2 µg/mL, respectively. The Rifadin label does not include multiple dose PK data for oral administration, thus it was not possible to compare the results obtained in this study with acceptable historical data.

T-20 PK Comparison: Asian versus Caucasian Population

This T-20 study was conducted in an exclusively Asian or Pacific Island population. Most of the other T-20 studies were conducted mainly in the Caucasian population. Steady-state T-20 PK parameters obtained in this population are compared to those obtained in three previous studies (Table III).

Pharmacokinetics differed between Caucasians and Asians (Thai). In general, the T-20 mean AUC_{12h}, was higher (74.2 hr·µg/mL in Asian *vs.* 43 to 56 hr·µg/mL in Caucasian) and the total clearance CL/F was lower (1.3 L/hr in Asian *vs.* 1.7 to 2.4 L/hr in Caucasian) in this study compared to other studies. As seen from table, the Thai patient population in this study was demographically different from the Caucasian population in other studies. Specifically, patients

in this rifampin study were predominantly female (67% *vs.* <25%), with a lower body weight (56 kg *vs.* 68-78 kg), and younger age (32 years *vs.* 38-45 years). According to the applicant, the observed race difference in both AUC_{12h} and CL/F is predominantly explained by the difference in the body weight between the two populations. Thai patients received, on the average, a 1.65 mg/kg dose of T-20 compared to a 1.17 to 1.35 mg/kg dose of T-20 in other studies with Caucasian patients. After adjusting the exposure parameters with body weight-normalized dose, the difference in mean AUC_{12h} between the two populations was minimal (45 hr·μg/mL in Asian *vs.* 37 to 42 hr·μg/mL in Caucasian). After normalizing total clearance by body weight, the CL/F in Asians (23 mL/hr/kg) was comparable to the values obtained in Caucasians (25 to 33 mL/hr/kg).

Table III: Comparison of Mean ± SD Steady-State T-20 PK Parameters

Reference	White	Asian	Female/ Male	Age (years)	Weight kg	AUC_{12h}[a] hr·μg/mL	CL/F L/hr	Dose mg/kg	Adjusted AUC_{12h} hr·μg/mL	Normalized CL/F mL/hr/kg
This study	0%	100%	8/4	32±6	56±10	74 ± 17	1.3 ± 0.4	1.65 ± 0.29	45 ± 7	23 ± 7
NP16370[b]	92%	0%	0/12	45±6	78±11	43 ± 11	2.2 ± 0.6	1.17 ± 0.16	37 ± 10	28 ± 6
T20-208	82%	0%	0/11	42±8	76±11	49 ± 19	2.4 ± 1.0	1.21 ± 0.16	42 ± 19	33 ± 16
NP16220	100%	0%	3/9	38±8	68±10	56 ± 12	1.7 ± 0.4	1.35 ± 0.22	41 ± 6	25 ± 4

[a] Adjusted AUC_{12h}=observed AUC_{12h}/(90mg/body weight)
[b] Comparison was made for dose group of 90 mg bid subcutaneously injected in abdomen

Discussion

Effect of Rifampicin on T-20 PK

The results of this study demonstrate that the elimination (metabolism/catabolism) of T-20 was not induced by concomitant administration of rifampicin. Numerous publications have documented the enzyme induction effect of rifampicin on the metabolism of many drugs. Rifampicin induces metabolism of various drugs in members of the Caucasian, Asian and Black population; thus, the enzyme induction effect of rifampicin is not likely to be race-dependent and the results from this study should be applicable to other populations.

Effect of Body Weight on T-20 PK

The study findings suggest that patients with low body weight (cut-off to be determined) could receive lower doses than subjects with higher body weight. If an appropriate weight cut-off is determined, unnecessarily high exposures can be avoided, if high exposures will increase the incidence of adverse events. The applicant's population PK analyses indicated that body weight was a significant covariate in affecting T-20 clearance, thus the findings from this study are consistent with the population PK findings.

Adverse Events (applicant's summary)

All adverse events were judged by the investigator as either mild or moderate in intensity. Headache and dizziness were the only events considered by the investigator as related (remotely) to study medication. The most frequent manifestations of injection site reactions were erythema (83.3%) and induration (75.0%). For additional details on safety, see Medical Officer's review.

Reviewer Comment

It is not clear if this short-term study is predictive of long-term safety for patients that have a low body weight with the potential to achieve high T-20 exposures (Population PK results).

Conclusions/Recommendations

The results of this study support the following conclusions:

- Rifampicin does not affect the PK (metabolism/catabolism) of T-20. This finding suggests that T-20 is not a substrate for most of the common CYP enzymes. Therefore, T-20 can be administered with rifampin and other CYP inhibitors/inducers or substrates with limited potential for undergoing a drug-drug interaction.
- Patients with low body weights, at a yet to be determined cut-off, will experience higher T-20 exposure than subjects with higher body weights.

Appendix

Non-ARV agents

included sulfonamides (3 patients; 25%), mild analgesics (2 patients; 17%), vitamins and minerals (2 patients; 17%), anti-anxiety agents (1 patient; 8%), antihistamines (1 patient; 8%), and steroids (1 patient; 8%). Two patients (17%) received concomitant medications for treatment of an adverse event. Patient 0007 received paracetamol for treatment of dysmenorrhoea and Patient 0009 received chloramphenicol for treatment of conjunctivitis not elsewhere classified.

Table Summary of Demographic Data by Trial Treatment, All Patients

	All Treatments N = 12
Sex	
MALE	4 (33%)
FEMALE	8 (67%)
n	12
Race	
CAUCASIAN	-
BLACK	-
ORIENTAL	-
OTHER	12 (100%)
n	12
Age	
Mean	32.1
SD	5.63
SEM	1.63
Median	30.5
Min-Max	28 - 48
n	12
Weight in kg	
Mean	56.06
SD	10.081
SEM	2.910
Median	54.75
Min-Max	40.6 - 77.3
n	12
Height in cm	
Mean	161.04
SD	7.393
SEM	2.134
Median	161.25
Min-Max	150.0 - 170.0
n	12

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

APPEARS THIS WAY ON ORIGINAL

Title:	A study to investigate the influence of T-20 on the metabolic activities of cytochrome P450 enzymes using a five-drug phenotyping cocktail in HIV-infected patients
Study:	NP16221/T20-502
Investigators/centers:	[redacted]
Study Period:	11/2001 to 03/2002

Rationale for Current Study

Study NP16221 was designed to investigate the potential of T-20 to influence the *in vivo* metabolic activities of the following major CYP450 enzymes: 3A4, 2D6, 2C19, 1A2 and 2E1. According to a report by Humprey *et al.*, these enzymes account for metabolism of over 90 % of drugs in clinical use. The cocktail approach allows one to conduct a single study, rather than performing several studies, to examine the effect of a study drug (e.g. T-20) on several enzymes simultaneously. The sponsor conducted this study to confirm the findings from an *in vitro* human microsomal study that suggested that T-20 is neither metabolized by nor an inhibitor of CYP450 enzymes. This study was deemed necessary because it was unclear if the findings from *in vitro* microsomal systems, which are commonly used and highly predictive of *in vivo* behavior in humans for small molecules, will be applicable or predictive for macromolecules such as T-20. A literature search conducted by this reviewer yielded limited information on such applications of *in vitro* systems to macromolecules.

Objectives

- to determine the phenotypic index parameters and pharmacokinetics (PK) of a five-drug phenotyping cocktail in the absence and presence of steady-state concentrations of T-20.
- to determine the effect of T-20 on the metabolic activities of N-acetyltransferase and the following CYP450 isozymes: CYP1A2, CYP2E1, CYP3A4, CYP2D6 and CYP2C19.

Study Design

This was a multi-center, open-label, two-way sequential crossover study. Twelve HIV-infected subjects were enrolled in the study. Drug treatments were given on day -15 and days 1-7. Patients received the phenotyping cocktail (see Table below) on day - 15 and T-20 90 mg twice daily (every 12 h) SC. on days 1-7. On day 6, the phenotyping cocktail and T-20 were administered simultaneously by investigational site personnel. T-20 was not self-administered by any patient during this study. Investigational site personnel at the study unit dispensed the phenotyping cocktail to patients with approximately 200 mL of water. Patients were required to fast from approximately midnight of the evening prior to administration of the phenotyping cocktail until approximately four hours after cocktail administration.

Table 1: Phenotyping Cocktail: Lot Number, Dose and Isozyme Target

Drug	Isozyme Target	Dose	Lot Number
caffeine	CYP1A2	100 mg	C203981-001
chlorzoxazone	CYP2E1	250 mg	1233A1
dapsone	CYP3A4	100 mg	Supplied by site
debrisoquine	CYP2D6	10 mg	[redacted]383
mephenytoin	CYP2C19	100 mg	[redacted]19082601

Reviewer Comment

The components of the Pittsburgh cocktail are not ideal, particularly the use of dapsone as the 3A4 substrate. However, at the time the study was initiated these substrates were considered acceptable by the FDA; therefore, results from the study will be considered adequate for

regulatory action, although additional studies may be required at a future date. Dapsone is metabolized to some extent by 2E1 and 2C9. Chlorzoxazone has been reported to have 1A1, 1A2, and 3A metabolic components.

The doses chosen by the sponsor are adequate:

1. *Drugs administered at highest or standard therapeutic doses*
2. *For T-20, the 7-day regimen of T-20 is considered adequate to be at steady state and will show inhibitory or inducing effect of T-20 on the metabolism of model substrates.*

Concomitant Medications

Ten of 12 patients received previous and concomitant treatments including testosterone, caffeine/codeine and Trizivir. It should be noted that the impact of coadministration of these non-cocktail components was not evaluated in this study.

Formulations

- T-20- Lyophilized powder for injection. Each vial delivered up to 90 mg of T-20 when reconstituted. T-20 lot numbers: C199820-009, C199760-008 and C202321-01.
- Phenotyping Cocktail- Drugs in cocktail were obtained from commercial stock (Table I)

Sampling

Blood and urine samples were collected on Day –15 and Day 6 at the following times:

- Blood samples: predose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after administration of the phenotyping cocktail
- Urine Samples: predose, 0 to 4 h and 4 to 8 h intervals following cocktail dosing

Assay

Plasma and urine samples were analyzed for analytes listed in Table II using various validated methods. In general, all assays used in this trial performed acceptably, as summarized in the table below.

Table II: Summary of Assay Performance

Name	Sample Matrix	LLOQ (ng/mL)	Inter-assay Precision (%)	Overall Accuracy (%)
T-20	Plasma		2.3 to 12.4%	-0.2 to 0.8
T-20 Metabolite	Plasma		3.5 to 4.8	-1.9 to 2.0
Caffeine	Plasma		7.6 to **17.4**	-2.2 to 5.3
Paraxanthine	Plasma		2.3 to **19.1**	-2.3 to 9.0
Chlorzoxazone	Plasma		4.9 to **12.7**	-3.1 to 4.3
6-hydroxychlorzoxazone*	Plasma		4.2 to **19.2**	-4.9 to 9.2
Dapsone	Plasma		4.4 to 11.3	-3.0 to 2.0
Monoacetyldapsone	Plasma		4.3 to **15.7**	-2.1 to 3.5
Debrisoquine	Plasma		4.8 to **18.6**	-8.4 to 3.7
S-mephenytoin	Plasma		4.8 to 8.8	-4.0 to 5.0
R-mephenytoin	Plasma		5.7 to 9.3	-4.4 to 5.0
Dapsone	Urine		2.6 to **16.7**	-10.7 to 5.3
Dapsone hydroxylamine	Urine		3.0 to 12.2	-14.2 to 3.9
Debrisoquine	Urine		3.9 to 9.4	-4.8 to 3.5
4-hydroxydebrisoquine	Urine		3.6 to 11.2	-10.7 to 0.7
4-hydroxymephenytoin*	Urine		3.1 to 9.7	-2.6 to 2.7

*Total amount of free and conjugated; LOQ- lower limit of quantitation

Reviewer Comment on Assays

The interassay precision measures of individual runs were ≤ 15 % for most drugs; however, the information indicates that some runs (shown in bold) exceeded the recommended 15 % limit. It should be noted that the data above include all samples and runs. Inspection of the mean data for QC samples (precision and accuracy assessments) showed that the assays performed acceptably. The reported LLOQs are consistent with values reported in the literature for the various analytes.

Pharmacokinetic Parameters (Phenotypic Index Parameters)

The primary PK parameters for this study were the phenotypic index parameters (PIPs). Each PIP was calculated using the criteria listed in Table III. However, the sponsor indicates that the sampling schedule was not adequate to calculate all the parameters listed in the protocol.

Other PK parameters were considered secondary and included the following:
C_{max}, T_{max}, and AUC_{last} for each phenotyping cocktail drug and its respective metabolite; C_{max}, C_{trough} and AUC_{12h}, for T-20 and T-20 metabolite; and CL_{ss}/F for T-20 ratio of AUC_{12h} for T-20 metabolite/T-20.

Reviewer's Comment on PK Parameters

The calculations employed by the sponsor are acceptable, as they are consistent with standard calculations that evaluate enzymatic activity.

Table III: Calculation of Phenotypic Index Parameters

Isozyme	Phenotypic Index Parameter	PK Parameters
CYP1A2	Ratio of paraxanthine/caffeine	AUC_{last} C_{8h}
CYP2E1	Ratio of 6-hydroxychlorzoxazone/chlorzoxazone	AUC_{last} C_{4h}
CYP3A4	Dapsone urinary recovery ratio	HDA/(HDA+DDS)[1]
CYP2D6	Debrisoquine urinary recovery ratio	HDB/(HDB+DB)[2]
CYP2C19	4'-hydroxymephenytoin total urinary recovery Ratio of S-mephenytoin/R-mephenytoin	Amount of metabolite in urine AUC_{last}
N-acetyltransferase	Ratio of monoacetyldapsone/dapsone	AUC_{last} C_{8h}

[1]HDA=total amount of dapsone hydroxylamine; DDS=total amount of dapsone.
[2]HDB=total amount of 4-hydroxydebrisoquine; DB=total amount of debrisoquine

Subject Demographics (n = 12)

Sex: 10 male, 2 female
Race: 10 Caucasian, 1 Black, 1 Other
Age in years: 42.8 ± 11.5 (mean ± SD); range, 22 –67
Weight in kg: 80.74 ± 11.22 (mean ± SD)

Data from all 12 patients were included in the plasma PK analysis, whereas, analysis of urine data was limited to information from 9 patients. The three patients excluded from the urine analysis had missing urine collection or samples were mislabeled. Exclusion of these data is acceptable.

Pharmacokinetic Results

- **Pharmacokinetics of CYP substrates and their metabolites**

Plasma pharmacokinetic time profiles (n = 5 from interim study report) for the cocktail components and relevant metabolites in the absence (Day –15) and presence (Day 6) of T-20 are depicted in the appendix. It should be noted that the profiles of the five subjects accurately reflect the profiles of all 12 subjects. In the absence and presence of T-20 the profiles were virtually superimposable for all drug-metabolite-combinations apart from for chlorzoxazone and caffeine. Selected PK measures of the individual cocktail components and their respective metabolites are summarized in Table IV.

Table IV: Summary of Mean PK Parameters (± SD) for Phenotyping Drugs and Metabolites in the Presence and Absence of Steady-State Concentrations of T-20

Drug	C_{max} (µg/mL)		T_{max} (hour)		AUC_{last} (hr·µg/mL)	
	Control	T-20	Control	T-20	Control	T-20
Caffeine	3.2 ± 1.8	2.9 ± 1.9	2.8 ± 4.7	4.5 ± 10	61 ± 63	52 ± 49
Paraxanthine	1.1 ± 0.7	0.91 ± 0.55	16 ± 15	11 ± 9.2	31 ± 27	27 ± 25
Chlorzoxazone	2.9 ± 1.7	4.2 ± 1.8	2.2 ± 1.1	1.6 ± 1.1	8.2 ± 3.1	10 ± 4.0
6-hydroxychlorzoxazone[a]	2.3 ± 0.7	2.6 ± 0.8	2.4 ± 1.2	1.9 ± 0.9	9.0 ± 2.0	9.2 ± 2.0
Dapsone	1.5 ± 0.3	1.6 ± 0.3	3.7 ± 2.8	2.6 ± 1.4	35 ± 8	35 ± 9
Monoacetyldapsone	0.64 ± 0.47	0.66 ± 0.49	2.5 ± 0.9	2.6 ± 1.9	14 ± 10	14 ± 10
Debrisoquine	0.0091 ± 0.0004	0.0089 ± 0.0062	1.9 ± 0.9	1.7 ± 0.7	0.10 ± 0.07	0.11 ± 0.11
S-Mephenytoin	0.16 ± 0.14	0.17 ± 0.20	3.3 ± 2.0	2.6 ± 1.1	1.4 ± 2.0	1.3 ± 2.1
R-Mephenytoin	0.51 ± 0.11	0.48 ± 0.13	5.3 ± 6.0	4.6 ± 3.2	15 ± 3.6	15 ± 2.8

[a]Unconjugated 6-hydroxychlorzoxazone was used for calculation.

Determination and Assessment of Phenotypic Index Parameters (PIP)

The sponsor assessed phenotypic index parameters for CYP1A2, CYP2E1, and NAT by two methods:
1) the single concentration validated approach (commonly reported in the literature)
2) using truncated AUC (non-validated approach, in bold font in Table V)
The PIPs of the remaining enzymes were calculated by standard procedures. Calculated PIPs are summarized in Table V.

Table V: Phenotypic Index Parameters (Mean ± SD)

Isozyme	Substrate	Trend[1]	No T-20 (Day –15)	With T-20 (Day 6)	Geometric Mean Ratio (90 % CI)	Arithmetic Mean ± SD Change (range %)
CYP1A2	Caffeine					
AUC_{last}		↓	0.71 ± 0.35	0.70 ± 0.34	0.99 (0.86 – 1.13)	3.1 ± 30
C_{8h}		↓	0.81 ± 0.55	0.76 ± 0.53	0.94 (0.71 – 1.17)	2.0 ± 42
CYP2E1	Chlorzoxazone					
AUC_{last}		↓	1.2 ± 0.4	1.0 ± 0.4	0.83 (0.70 – 0.97)	-15 ± 26
C_{4h}		↓	1.2 ± 0.3	1.3 ± 0.4	1.08 (0.87 – 1.29)	15 ± 48
CYP2D6 (DeRR)	Debrisoquine[1]	↓	0.70 ± 0.20	0.69 ± 0.23	1.02 (0.97 – 1.06)	1.0 ± 8.9
CYP2C19	Mephenytoin					
Urine Recovery[2], µmol		↓	81.8 ± 60.6	93 ± 60	1.13 (0.98 – 1.28)	21.3 ± 40.2
S/R Ratio, AUC_{last}		↑	0.085 ± 0.113	0.087 ± 0.130	1.02 (0.82 – 1.22)	
CYP3A4 (DaRR)	Dapsone[2]	↓	0.34 ± 0.15	0.33 ± 0.16	0.99 (0.88 – 1.09)	-2.1 ± 16.4
N-Acetyltransferase	Dapsone					
AUC_{last}		↓	0.38 ± 0.25	0.37 ± 0.23	0.98 (0.94 – 1.03)	1.1 ± 10.4
C_{8h}		↓	0.39 ± 0.27	0.35 ± 0.23	0.90 (0.82 – 0.98)	-8.5 ± 15

[1]Trend of index parameter change if enzyme is inhibited.
[2]Total amount of free and conjugated drug
DeRR- total amount of 4-OH-debrisoquine/(total amount of 4-OH-debrisoquine + total amount of debrisoquine
DaRR- total amount of dapsone hydroxylamine/(total amount of dapsone hydroxylamine + total amount of dapsone

The PK results from this study (n = 12 for non-urine data) indicate that generally T-20 had no relevant PK effects on any of the PIPs evaluated. Thus, T-20 does not inhibit or induce the metabolic activities of the enzymes investigated. The sponsor used both validated and non-validated PIPs to evaluate the drug-drug interaction potential of T-20. In Table I, non-validated parameters are in bold font. Based on GMR, the mean changes in PIP values upon T-20 coadministration were less than 15 % with both the validated and non-validated PIPs. Use of non-validated parameters is reasonable for exploratory analyses; however, the conclusions in this review are based on the validated measures, the plasma concentrations at a given time. Exposure changes less than 20 %, based on 90 % confidence intervals are generally considered pharmacokinetically insignificant when drug-drug interactions are evaluated. Consequently, these data are consistent with results of *in vitro* human microsomal studies. The only statistically significant changes in exposure were the 10 % decrease in C_8 (validated parameter) for NAT and 17 % decrease in chlorzoxazone AUC_{last} (non-validated parameter).

Reviewer Comment on Influence of Caffeine-intake and Apparent Change in PIP
The sponsor indicates that inconsistent compliance with protocol restrictions on caffeine intake during the study may have contributed to the variability in the study. This explanation is reasonable as chlorzoxazone reduces the elimination of caffeine from the body; additionally, caffeine could impact the dapsone results.

Discussion: Potential Shortcomings of Cocktail Approach
Interpatient Variability
It should be noted that the above conclusions are based on data from a limited number of subjects (n = 12) who exhibited high interindividual variability (last column of Table V). The variability associated with the means may be reduced if more subjects were included in the study, but the use of 12 subjects in a drug-drug interaction trial is generally reasonable. Most CVs exceeded ——— The source of variability is unclear. A comparison of the results obtained using the typical GMR and 90 % CIs vs. arithmetic mean data demonstrate the following:

- Changes in PIP may be obscured by log-transformation, because large differences are minimized or reduced on log scale, relative to a linear scale
- Patients had varied changes in PIP values for a given substrate in the absence and presence of T-20: results were (0 % change) to significant increase and decrease in PIP value.

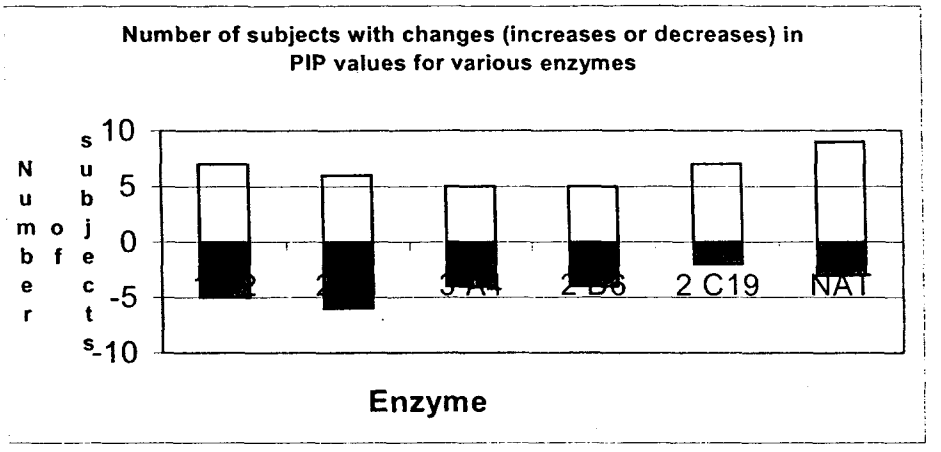
Overall the listed observations suggest that evaluation of PIP changes in a small number of individuals may lead to conflicting conclusions regarding the inhibiting or inducing status of T-20. Overall changes in PIP (increase implying inhibition, decrease implying in induction or no change implying T-20 is neither an inhibitor or inducer of a given substrate).

In most drug-drug interaction studies with potent enzyme inhibitors or inducers, exposure changes (measured by PIP for the enzyme substrate) in individuals occur in one direction and are consistent with the mean:

- positive ⇒ increased exposure, signifying enzyme inhibition or
- negative ⇒ reduced exposure, signifying enzyme induction

Alternatively, the exposure may hover about zero or be evenly distributed about zero, if the compound being evaluated is not an enzyme inhibitor or inducer. In the current study only the NAT and CYP2C19 study yielded consistent results in a given direction in that more than 60 % of the data were in one direction. The exposure distribution is depicted in figure 1.

Figure 1: Distribution of PIP values



Number of subjects: subjects with positive values indicate an increase in PIP and subjects with negative values indicate decrease in PIP values

However, the mean data will tend to serve as a poor predictor with respect to individual response (apparent metabolic inhibition/induction or lack effect).

Use of Dapsone as CYP3A4 substrate

As mentioned previously, dapsone is not an ideal CYP3A4 substrate , therefore definitive conclusions regarding this CYP enzyme can not be made on the basis of this study alone.

Role of Concomitant Medications

Interpretation of the study results may be further complicated by the underlying drug-drug interactions with concomitant medications. In this study concomitant medications were prohibited; however, some subjects received concomitant medications. The impact of these medications on this study was not assessed.

Collectively, the listed study limitations suggest that the conclusions drawn from this Pittsburgh cocktail study should be interpreted with caution.

Phenotypic Index Parameters: Comparison to Literature Values

The sponsor compared the baseline phenotypic index parameters (PIP) obtained in this study to those obtained by other investigators. From Table VI, the baseline PIP values for all enzymes, except for CYP2E1, were comparable to those reported in the literature for the cocktail study. The reason for the difference in the CYP2E1 enzyme activity is unclear.

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Table VI: Comparison of Mean Phenotypic Index Parameters (± SD) with Literature Data

Enzyme[a]	Present Study		Study Reference (see Appendix*)			
			6704*	6741*	6744*	6743*
	cocktail	cocktail+T-20	cocktail	cocktail	cocktail	1-drug
CYP1A2	0.81 ± 0.55	0.76 ± 0.53	0.73 ± 0.21	0.75 ± 0.61	0.35 ± 0.13	NA
CYP2E1[b]	1.2 ± 0.3	1.3 ± 0.4	0.80 ± 0.33	NA	0.62 ± 0.32	NA
CYP3A4	0.34 ± 0.15	0.33 ± 0.16	0.60 ± 0.08	0.53 ± 0.12	0.40 ± 0.13	NA
CYP2D6	0.71 ± 0.15	0.69 ± 0.23	0.61 ± 0.14	0.68 ± 0.17	0.60 ± 0.29	NA
CYP2C19 Urine (μmol)[c]	81.8 ± 60.6	93 ± 60	131.1 ± 25.9	75.7 ± 46.9	99.2 ± 17.4	150 ± 39 (EMs) 1.9 ± 1.4 (PMs)
CYP2C19 (S/R Ratio)	0.085 ± 0.113	0.087 ± 0.130	NA	NA	NA	0.16 ± 0.12 (EMs) 0.99 ± 0.01 (PMs)
NAT*	0.38 ± 0.26	0.35 ± 0.23	0.17 ± 0.02	NA	NA	NA

[a]The listed data for 1A2, 2E1 and NAT (N-acetyltransferase) are single concentration ratio data (not AUC_{last}).
[b]CYP2E1 index from present study was calculated based on concentrations of unconjugated 6-hydroxychlorzoxazone.
[c]CYP2C19 urine index from present study was calculated from concentrations of unconjugated 4'-hydroxymephenytoin (molecular weight =220).
PM - poor metabolizer
EM - extensive metabolizer
NA—Not applicable

The sponsor indicates that the mean PIP data obtained in this cocktail study suggest that there were no poor metabolizers for CYP2D6 or CYP2C19. This conclusion appears reasonable, based on the data provided.

Pharmacokinetics of T-20 and T-20 Metabolite

The pharmacokinetic measures for T-20 and the T-20 metabolite in this study are summarized in the table below.

Table VII: T-20 and T-20 Metabolite Mean ± SD (CV%) Steady-State Pharmacokinetic Parameters at Day 6

PK Parameter	T-20	T-20 Metabolite
C_{max}, μg/mL	5.7 ± 1.8 (32)	0.21 ± 0.02 (11)
C_{trough}, μg/mL	2.7 ± 0.8 (29)	0.16 ± 0.03 (22)
AUC_{12h}, hr·μg/mL	48 ± 17 (27)	2.0 ± 0.4 (21)
CL_{ss} F, L/hr	2.0 ± 0.5 (25)	NA
Metabolite/Parent AUC_{12h} Ratio (%)	5.0 ± 1.8 (37)	

NA— Not Applicable

The T-20 PK parameters C_{max}, C_{trough} and AUC_{12h} from this study are in close agreement with parameter values reported in other clinical studies of T-20.

Comparison of T-20 PK Parameters (± SD) with Other Study Results

Reference	Injection site	C_{max} (μg/mL)	C_{trough} (μg/mL)	AUC_{12h} (hr·μg/mL)
Present Study	Abdomen	5.4 ± 1.8	2.8 ± 1.1	48 ± 17
T20-506 (NP16370)	Abdomen	5.4 ± 1.3	2.7 ± 0.9	43 ± 11
	Thigh	4.7 ± 1.2	3.0 ± 0.7	44 ± 10
	Arm	5.6 ± 2.1	3.7 ± 1.5	53 ± 22
T20-208	Abdomen	5.0 ± 1.7	3.4 ± 1.6	49 ± 19
T20-206	Abdomen	5.0 ± 0.8	2.6 ± 1.2	49 ± 8

Summary and Conclusions

The data from this Pittsburgh cocktail study were highly variable and suggested that use of mean data may not be appropriate to characterize the CYP enzyme inhibitory or inducing potential of T-20. Interpretation of the data may have been confounded by the presence of concomitant medications and foods that alter the activity of some of the studied enzymes. The assessment of the CYP3A4 effect is not ideal because the substrate (dapsone) used for this evaluation has other metabolic pathways. Due to the study shortcomings, this reviewer recommends cautious interpretation of the study results. Ideally, additional studies or supportive evidence should have been provided to confirm the findings of the study. However, based on the mean data, the following conclusion can be made regarding this study:

T-20 does not appear to alter (inhibit or induce) the metabolic activities of CYP450 isozymes 1A2, 2E1, 3A4, 2D6, and 2C19, but marginally inhibits (10 %) the metabolism of N-acetyltransferase. Consequently, the potential for T-20 to interact with other concomitantly given drugs via common metabolic pathways is extremely low.

Appendix

Reference List

6704- Frye RF, Matzke GR, Adedoyin A, Porter JA, Branch RA. Validation of the five-drug "Pittsburgh Cocktail" approach for assessment of selective regulation of drug-metabolizing enzymes. *Clin. Pharmacol. Ther.* 62: 365-376, 1997.

6741 - Adedoyin A, et al. All-trans-retinoic acid modulation of drug-metabolizing enzyme activities: investigation with selective metabolic drug probe. *Cancer Chemother Pharmacol.* 1998;41:133-139.

6743 - Wedlund P, et al. Mephenytoin hydroxylation deficiency in Caucasians: frequency of a new oxidative drug metabolism polymorphism. *Clin Pharmacol Ther.* 1984;36(6): 773-780.

6744 - Zhu B, et al. Assessment of cytochrome P450 activity by a five-drug cocktail approach. *Clin Pharmacol Ther.* 2001;70 (5): 455-461.

Title:	A phase I/II pharmacokinetic and safety study of T-20 in combination with an optimized antiretroviral regimen in HIV-infected children and adolescents.
Study	NP16056/T-20-310
Investigators/Centers:	Multiple investigators/multiple sites in USA
Study Period:	08/01 – 03/02

Introduction

The applicant indicates that this report contains interim data available as of March 6th, 2002 from this ongoing trial. The final report will be submitted for review once all subjects complete 24 weeks of treatment. Pharmacokinetic (PK) results presented in this report are not subject to change; however, additional PK information will be available in the final report. Specifically, PK information from five additional subjects will be available.

Study Rationale

Previously, a pilot study (Study T20-204/PACTG 1005) in thirteen children aged 3 to 12 demonstrated that T-20 was relatively safe and exhibited antiviral activity at a dose of 60 mg/m^2 subcutaneous (SC) twice daily (BID) for up to 24 weeks. The pharmacokinetics of T-20 at this dose suggested the following:

- Target C_{min} was obtained in most subjects
- AUC in pediatrics was comparable to that in adults receiving the standard adult dose

Objectives

- to assess the exposure properties of T-20 in combination with at least three other antiretrovirals (ARVs) at therapeutic doses in HIV-1 infected children and adolescents.
- to evaluate the safety and tolerability of T-20

This study was designed to evaluate a mg/kg dosing regimen that is comparable to the studied 60 mg/m^2 regimen.

Overall Study Design

This is an open-label, single arm/non comparative study of T-20, in combination with an optimized ARV regimen, for 48 weeks. HIV-1 infected children aged 3 through 16 years are participating in this trial. The patients were stratified into two age groups

Group 1: children ≥ 3 and < 12 years of age (n = 7)

Group 2: adolescents ≥ 12 and < 17 years of age (n = 13)

Each subject received a dose of 2 mg/kg. The first 12 patients enrolled per age group underwent intensive PK sampling performed at week 1. Adjustments to the T-20 dose were to be allowed for a particular age group if the group exposures ($AUC_{0\text{-}12\ hr}$) were higher or lower than targeted AUC (43.6 μg·hr/mL). If dose adjustment was required, intensive PK sampling was repeated one week after dose adjustment. If a patient failed to achieve an acceptable T-20 drug level after dose adjustment, the patient was discontinued from the study. Changes in body weight also prompted T-20 dose adjustment to ensure adequate dosing during the course of the trial. Dose modifications and changes in concomitant medications were employed under prespecified conditions (see Medical Review). It is noted that each patient was on an optimized background regimen comprising antiretrovirals from all drug classes. Overall, the most frequently chosen drug in each ARV class, was didanosine (56%) for NRTIs, lopinavir/ritonavir (56%) for PIs, and efavirenz (56%) for NNRTIs. T-20 was administered SC BID at 2.0 mg/kg per dose, up to the adult maximum of 90 mg per dose. T-20 was administered into the SC tissue of the abdomen, deltoid,

or the anterior aspect of the thigh. Sites for injection were to rotated for each dose to minimize local reactions. [redacted] cream was applied prior to injections was to be permitted to minimize discomfort, and was not expected to alter drug absorption. Dosing guidelines were provided for the two types of T-20 vials (see Appendix)

Concomitant Medications

- Drugs prohibited during the course of the trial: HIV vaccines (e.g., Remune); PRO-542; adefovir; and investigational agents (e.g. tenofovir) when adequate pediatric safety information were absent.
- Drugs discouraged during the course of the trial: chemotherapy, except for maintenance treatment of Kaposi's Sarcoma; all medications that may interfere with concomitant medications (including ARVs) as specified in the package inserts; and Hydroxyurea.

Reviewer Comment on Study Design and Concomitant Medications
In general, the study design is acceptable. Additional variability in T-20 PK may be introduced by the concomitant antiretroviral medications if a drug-drug interaction occurs between T-20 and antiretroviral (ARVs) agents. The results from the RTV-T-20 and RTV/SQV-T-20 drug interaction study suggest that T-20 exposure is increased in the presence of RTV (RTV/SQV). Thus, subjects who receive T-20 and RTV may have higher exposures than subjects receiving T-20 alone. Despite the potential complications in data interpretation, the results from this study provide useful PK information for the pediatric population. However, the label should indicate that PK were obtained in the presence of ARVs.

Formulation and Packaging
T-20 was supplied as a white, lyophilized powder in molded glass vials. The clinical lot numbers of T-20 used during this study were as follows:

T-20 Vial Name/label	Lot Numbers
45 mg vial	C202211-1, C202211-2
90 mg vial	C199820-1, C199820-2, C199790-1 and 2

Blood Sampling
First 12 patients enrolled per age group
Week 1- blood samples were drawn at pre-dose (time 0) and 2, 4, 8 and 12 hours after the morning T-20 administration.

- Week 1- blood sample collected 4 hours after the morning T-20 dose to determine protein binding (in the first 12 patients enrolled per age group)

All patients

- Weeks 2, 8, 16, and 24 - a single blood sample was drawn from every patient immediately prior to T-20 administration.

Assay
Plasma samples were analyzed for T-20 parent compound and T-20 metabolite concentration with a validated [redacted]nethod. The lower limit of quantification was [redacted]ng/mL for both T-20 and the T-20 metabolite. For T-20, the inter-assay precision was assessed by the CV: ranged from 6% to 8%. The accuracy was assessed using relative error: range was –3% to 2%.

For the T-20 metabolite, the inter-assay precision ranged from [redacted] for and the overall accuracy was between [redacted]

PK Parameters and Analysis

The following steady state (Day 7) PK parameters were calculated for T-20 and the T-20 metabolite: C_{max}, C_{trough}, T_{max}, AUC_{12h}. The parameters were calculated using standard non-compartmental PK methods and the computer program WinNonlin Pro v3.2 [redacted]. All PK parameters were summarized descriptively. Simple linear regression was used to evaluate the relationship of T-20 and computed parameters with Tanner stage, age, body weight, and body surface area.

Exploratory Efficacy Assessments

Plasma HIV-1 RNA levels were assessed at every study visit when possible. Additionally, CD4 and CD8 T cell counts and percentages were determined at every study visit.

Results

Disposition of Patients in Clinical Trial

A total of 25 patients were enrolled in the study as of March 6, 2002, and data from these patients are presented in this preliminary report. Highlights of the demographic data are as follows:

- The majority of patients were adolescents (aged ≥ 12 to < 17 years).
- There was an approximate even distribution of males to females and black to white subjects.
- Adolescents were more immunosuppressed than children <12 years old- based on baseline CD4 values and HIV classification of clinical symptoms

For additional demographic information, please see the appendix to this study.

Four adolescents withdrew from the study by March 6, 2002. According to the applicant none of the premature withdrawals were for safety reasons. Reasons for the withdrawals were: refusal of treatment (30225/2502), aversion to injections (30225/2501), non-compliance (30225/2506) and failure to return (30286/8604).

PK Results

Subject Demographics

Twenty subjects, 7 children and 13 adolescents, completed the intensive PK part of the study and were included in the PK analysis. Demographic characteristics in these children (n = 20) were comparable to that of the overall study population (n = 25) as might be expected. The demographic information for the two age groups is listed below:

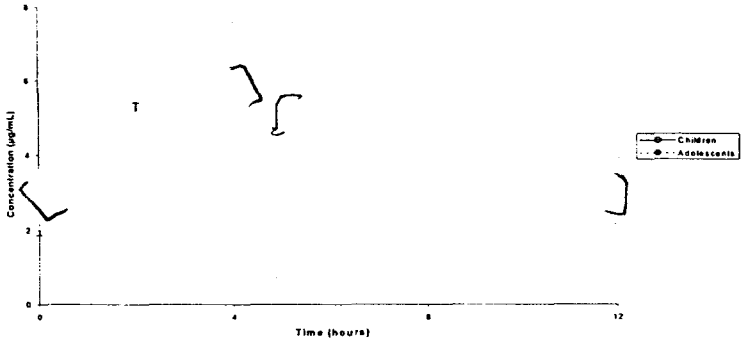
- Mean and age (range) in children: < 12 years, 8 (5-11) years vs. > 12 years, 14 (12-16) years
- Mean body weight in children: < 12 years, 23.2 (13.8 - 38.3) kg vs. > 12 years, 47.2 (35.7 - 68.9) kg

The applicant reports that intensive PK sampling for three patients (2801, 2802, and 8602) were repeated since the initial profiles indicated sampling or labeling errors. The second set of assay values for all three patients was used in the analysis.

T-20 Plasma Concentrations

Plasma concentrations of T-20 exhibited relatively high inter-individual variability at each blood sampling time, with CV% values ranging from ———— However, the mean steady-state T-20 plasma concentration-time profiles obtained from children and adolescents were comparable (figure 1).

Figure 1: Mean (± SE) T-20 Plasma concentration Over Time (By Age Group)



As summarized in Table I the mean exposure measures for T-20 were comparable in children < 12 years and in adolescents (12 – 17 years old).

Table I: T-20 Mean ± SD Steady-State PK Parameters

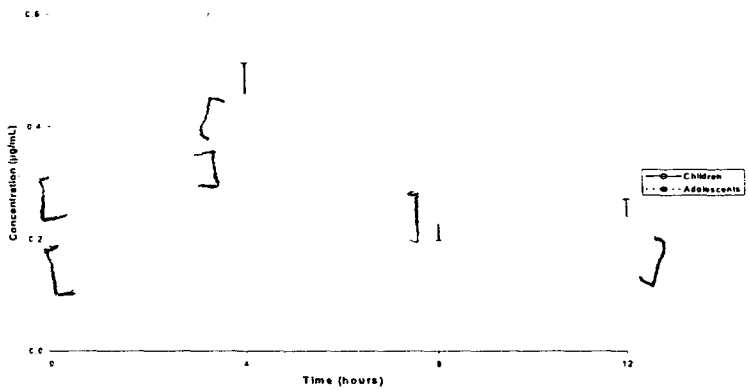
PK Parameter	Age Groups		All Subjects
	Children ≥ 3 to < 12 years (n=7)	Adolescents ≥ 12 to < 17 years (n=13)	(n=20)
C_{max}, µg/mL	5.68 ± 1.30	5.88 ± 2.81	5.81 ± 2.35
T_{max}, hr	3.98 ± 0.06	5.05 ± 2.67	4.68 ± 2.19
C_{trough}, µg/mL	2.51 ± 1.04	2.98 ± 1.66	2.82 ± 1.46
AUC_{12h}, µg•hr/mL	49.1 ± 11.3	52.7 ± 27.4	51.4 ± 22.8

The degree of interindividual variability in adolescents was greater than that in children under 12 years old, despite the smaller number of subjects in the younger age group. However, the exposure results suggest that dosing by body weight will provide comparable T-20 exposure throughout the age groups.

T-20 metabolite Plasma Concentrations

Similar to the parent compound, plasma concentrations of the T-20 metabolite exhibited high inter-individual variability at each time point (CV% range, ————————. The mean steady-state T-20 metabolite plasma concentration-time profiles (figure 2) obtained from children and adolescents differed in two respects: 1) plasma concentrations were higher in adolescents at early time points (< 6 hours) and 2) the concentrations in children exhibited minimal fluctuation (C_{minss} and C_{maxss} approximately 0.2 µg/mL) vs. (C_{minss} 0.2 and C_{maxss} 0.4 µg/mL) in adolescents. The reason for these apparent differences in steady state levels between the two groups is unclear.

Figure 1 Mean (± SE) T-20 Metabolite Plasma concentration Over Time (By Age Group)



Numerically, the mean exposure data for the T-20 metabolite was greater in adolescents than in children (Table II).

Table II: T-20 metabolite Mean ± SD Steady-State PK Parameters and Metabolite/Parent AUC_{12h} ratios

PK Parameter	Age Groups		All Subjects
	Children ≥ 3 to < 12 years (n=7)	Adolescents ≥ 12 to < 17 years (n=13)	(n=20)
C_{max}, µg/mL	0.261 ± 0.146	0.450 ± 0.341	0.384 ± 0.298
C_{trough}, µg/mL	0.170 ± 0.064	0.242 ± 0.146	0.217 ± 0.126
AUC_{12h}, hr·µg/mL	2.54 ± 1.35	3.41 ± 2.09	3.10 ± 1.87
Metabolite/Parent Ratio of AUC_{12h} (%)	5.17 ± 2.34	7.12 ± 3.98	6.43 ± 3.56

Tanner Stage Evaluation

The applicant conducted an exploratory analysis to evaluate the effect of Tanner stage on pharmacokinetic exposures of T-20 and its metabolite. Patients were grouped by baseline Tanner stage into group 1 (Tanner stage 1-3) or group 2 (Tanner stage 4-5). Nineteen patients (6 children and 13 adolescents) were included in the analysis; one patient who did not have Tanner stage assessed at baseline was excluded from this analysis. Grouping into Tanner stages caused redistribution of the patients as follows: Fourteen children had a Tanner stage between 1 and 3 (group 1), and 5 children had Tanner stage of 4 or 5 (group 2). Because there are a limited number of subjects in Tanner Group 2, Group comparisons may not be appropriate. With this caveat in place, the following observations were made:

1) The mean steady-state T-20 and T-20 metabolite plasma concentration profiles were comparable between the two groups as illustrated in the figures below.

Mean (± SE) Plasma Concentration Over Time By Tanner Stage Groups

Figure 2: T-20

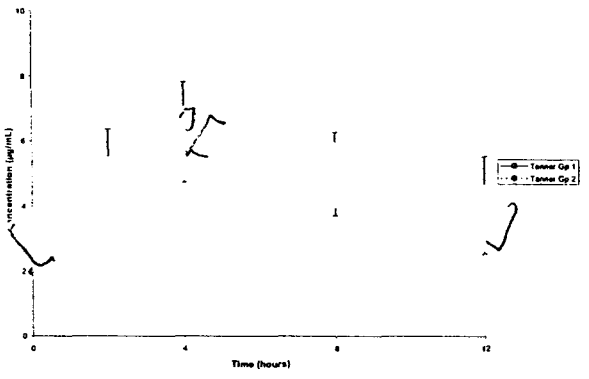
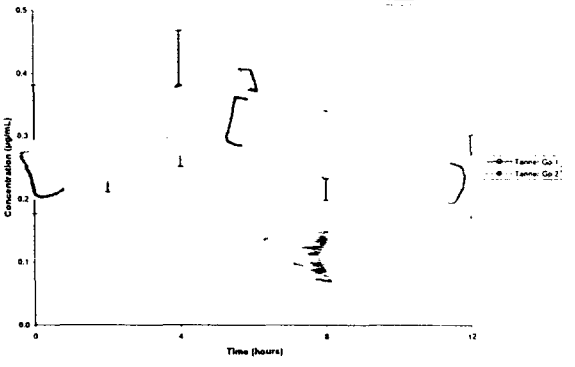


Figure 3: T-20 Metabolite



2) There did not appear to be any correlation between Tanner Stage and T-20 exposure measures, as shown in figures 4 and 5.

Figure 4: T-20 C_{max} vs. Tanner Stages

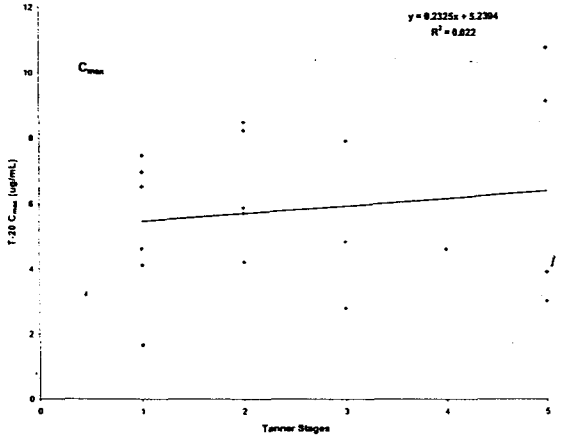
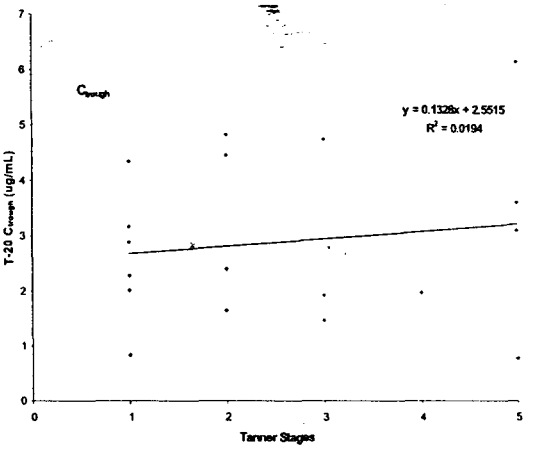


Figure 5: T-20 C_{trough} vs. Tanner Stages



The AUC vs. Tanner stage plot (not shown) was similar to that for the C_{max}. The exposure and Tanner stage data indicate that within any given Tanner stage data were highly variable. The source of this variability is unclear. Mean exposure measures obtained with the Tanner groupings are tabulated in Table III.

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Table III: T-20 and T-20 metabolite Mean ± SD Steady-State PK Parameters and Metabolite/Parent $AUC12_h$ Ratios by Tanner Stage Groups

PK Parameter	Tanner Stage*	
Parent	Group 1 (n=14)	Group 2 (n=5)
C_{max}, µg/mL	5.67 ± 2.07	6.30 ± 3.45
T_{max}, hr	4.70 ± 2.44	4.74 ± 1.83
C_{trough}, µg/mL	2.81 ± 1.30	3.12 ± 2.01
AUC_{12h}, ·µg•hr/mL	50.0 ± 20.4	57.6 ± 32
Metabolite		
C_{max}, µg/mL	0.381 ± 0.336	0.419 ± 0.219
C_{trough}, µg/mL	0.204 ± 0.109	0.257 ± 0.186
AUC_{12h}, ·µg•hr/mL	3.07 ± 2.05	3.32 ± 1.68
Metabolite/Parent Ratio of $AUC12_h$ (%)	6.45 ± 3.97	6.46 ± 2.99

*Patients were grouped by baseline Tanner scores into Group 1 (Tanner Stage 1-3) or Group 2 (Tanner Stage 4-5).

Additional Exploratory Analyses

The applicant conducted additional exploratory analyses to determine if the AUC obtained with 2.0 mg/kg T-20 dosing was affected by age, body weight, or body surface area. Plots of the various covariates with AUC are shown in the figures on the next page. No trend was apparent between any of the listed covariates and AUC. It is noted that the data were highly variable, and as noted previously, it is difficult to identify the source(s) of variability in the study. However, the potential sources include:

- Incorrect dosing amount and/or frequency
- Inherent interpatient PK variability (absorption/elimination)
- Drug-drug interactions (role of concomitant medications)
- Number of subjects

Insufficient data are available to confidently evaluate these possible sources of variability. The study was conducted on an outpatient basis, so patient compliance may not have been adequately controlled. Because adherence to the dosage regimen impacts PK it is unclear if the results obtained in this trial accurately reflect T-20 PK in the pediatric population.

Reviewer Comment

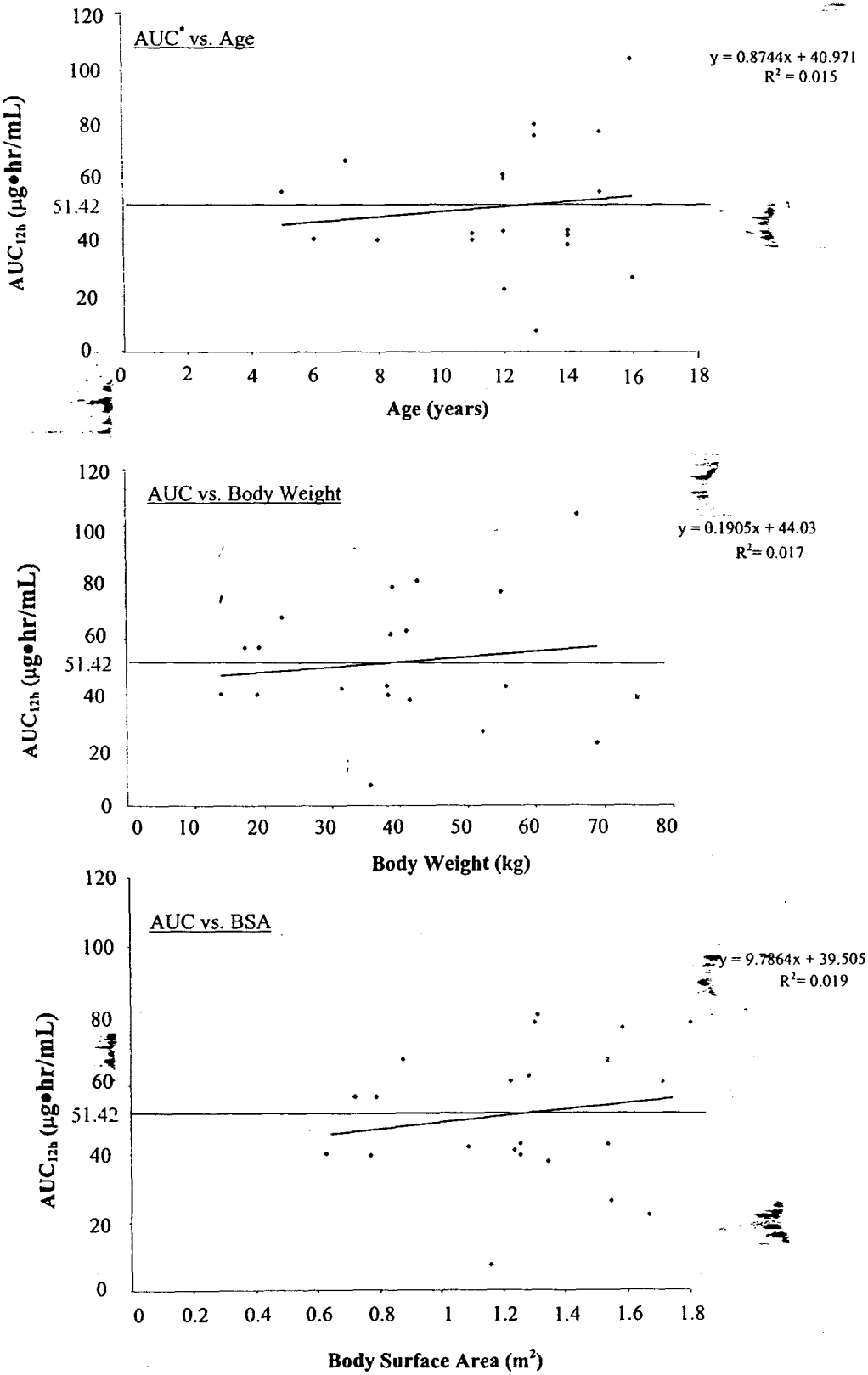
It is well recognized that it is often difficult to recruit pediatric patients for PK trials therefore certain allowances have to be made in conducting such studies. However, the limited control of extrinsic factors should be documented in any labeling comments or claims.

Gender does not appear to affect T-20 PK parameters in children and adolescents

Table T-20 Mean ± SD Steady-State PK Parameters and Metabolite/Parent AUC_{12h} Ratios by Gender

PK Parameter	Gender	
Parent	Male (n=13)	Female (n=7)
C_{max}, µg/mL	5.77 ± 2.45	5.87 ± 2.35
T_{max}, hr	5.04 ± 2.67	3.99 ± 0.02
C_{trough}, µg/mL	2.72 ± 1.35	3.00 ± 1.75
AUC_{12h}, ·µg•hr/mL	49.9 ± 22.9	54.3 ± 24.0

Figure 2 T-20 Average AUC_{12h} vs. Age, Body Weight and Body Surface Area
(* = average AUC_{12h} of 51.4 µg•hr/mL in the study is shown with a straight line)



Safety (Adverse Events)- applicant's summary

The most frequently (≥ 3 patients) reported adverse events were nausea, upper respiratory tract infection, and diarrhea. The majority of patients (72.0%) overall, had at least 1 local injection site reaction. Fewer children (≥ 3 to < 12 years) reported pain and discomfort associated with ISRs than adolescents (≥ 12 to < 17 years). For additional details see Medical Officer's review.

Comparability of PK Pediatrics vs. Adults

The mean AUC_{12h} in this study (51 μg•hr/mL) is higher than the originally targeted adult AUC value of 43.6 μg•hr/mL. However, the AUC in this study is comparable to the AUC obtained in some other adult studies (in studies 206 and 208 mean AUC ≈ 50 μg•hr/mL) in which 90 mg of T-20 was administered SC BID. The PK data from this study indicate that the 2.0 mg/kg dose achieves adequate exposure for activity. Based on AUC_{12h} ratios, T-20 metabolite was 6.4% of the parent compound, a finding similar to that observed in adults, where the T-20 metabolite ranged from ——————— (Table IV). These ratios suggest that T-20 metabolite was a minor species in plasma.

Table IV: Mean Ro 50-6343 (±SD) Steady-State PK Parameters Following SC Administration in Adults

Reference	Study	Pharmacokinetic parameter			
		Cmax (μg/mL)	C_{trough} (μg/mL)	AUC_{12h} (μg·h/mL)	Metabolite/parent AUC_{12h} Ratio %
NP16220	501	0.784 (0.32)	0.371 (0.18)	6.44 (2.54)	15.2 (5.72)
NP16221	502	0.21(0.02)	0.16 (0.03)	2.0 (0.4)	4.6 (2.0)
NP16334	505	0.178 (0.054)	0.139 (0.041)	1.76 (0.49)	2.42 (0.58)

Conclusion

The pharmacokinetic data indicate that body weight based twice daily dosing of T-20 at a dose of 2.0 mg/kg is appropriate in HIV infected children and adolescents.

Appendix

Patient Demography

Children (Age ≥ 3 and <12 years)

Patient	Age (years)	Height (cm)	Weight (kg)	BSA (m2)	Gender	Tanner Stage
2301	8	112	19.1	0.77	M	1
2504	7	116	19.4	0.79	M	1
2508	6	102	13.8	0.63	F	NA
2601	5	107	17.3	0.72	M	1
2703	11	150	38.3	1.26	F	3
2803	7	121	22.8	0.88	F	1
3001	11	137	31.5	1.09	F	1
Mean	8	121	23.2	0.88	3 M/4F	
SD	2.3	17.1	8.7	0.22		

Adolescents (Age ≥ 12 and < 17 years)

Patient	Age (years)	Height (cm)	Weight (kg)	BSA (m^2)	Gender	Tanner Stage
2502	12	140	38.8	1.23	M	2
2503	15	154	55.8	1.54	F	5
2701	12	146	41.2	1.29	M	2
2801	16	156	66.4	1.7	F	5
2802	13	164	55.2	1.59	M	5
2901	14	157	41.6	1.35	M	4
3002	14	148	37.7	1.24	M	2
3003	13	146	42.9	1.32	M	2
8601	14	150	38.2	1.26	F	2
8602	13	136	35.7	1.16	M	1
8603	16	165	52.2	1.55	M	5
8604	12	146	68.9	1.67	M	3
8701	15	158	39.1	1.31	M	3
Mean	14	151	47.2	1.40	10M/3F	
SD	1.4	8.7	11.28	0.18		

NA: Not Assessed

Summary of Demographic Data by Age Group (Safety Population)

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

Summary of Optimized ARV Regimen by Age Group (Safety Population)

	Aged >= 3y to <12y N (%)	Aged >=12y to <17y N (%)	All Patients N (%)

NUMBER OF PATIENTS	7	18	25
NUMBER OF DRUGS IN OB			
3 DRUGS	2 (28.6%)	9 (50.0%)	11 (44.0%)
4 DRUGS	4 (57.1%)	6 (33.3%)	10 (40.0%)
5 DRUGS		1 (5.6%)	1 (4.0%)
6 DRUGS		2 (11.1%)	2 (8.0%)
MISSING	1 (14.3%)		1 (4.0%)
MEAN(STD DEV)	3.7 (0.5)	3.8 (1.0)	3.8 (0.9)
NUMBER OF PIs IN OB			
0-1 DRUGS	4 (57.1%)	13 (72.2%)	17 (68.0%)
2-3 DRUGS	2 (28.6%)	5 (27.8%)	7 (28.0%)
MISSING	1 (14.3%)		1 (4.0%)
NUMBER OF NRTIs IN OB			
0-1 DRUGS	1 (14.3%)	3 (16.7%)	4 (16.0%)
2-3 DRUGS	5 (71.4%)	14 (77.8%)	19 (76.0%)
4-5 DRUGS		1 (5.6%)	1 (4.0%)
MISSING	1 (14.3%)		1 (4.0%)
NUMBER OF NNRTIs IN OB			
0 DRUGS	3 (42.9%)	6 (33.3%)	9 (36.0%)
1 DRUG	3 (42.9%)	12 (66.7%)	15 (60.0%)
MISSING	1 (14.3%)		1 (4.0%)

Note: Only drugs that start in the first 3 days are included

Title: Plasma protein binding and blood distribution studies with ^{3}H-T20
Study number: [redacted] /03

Objectives

- To determine the extent of plasma protein binding of ^{3}H-T-20 in human plasma
- To assess the potential for co-administered compounds to displace protein bound T-20 *in vitro*
- To determine the distribution ^{3}H-T-20 between blood cells and plasma in whole blood

The plasma protein binding and blood distribution studies were conducted in two stages.

Stage 1

Ultracentrifugation was used to determine plasma protein binding of ^{3}H-T-20 in human plasma. T-20 concentrations evaluated were as follows: [redacted] and [redacted] µg T-20/g plasma. Additionally, the extent of protein binding of ^{3}H-T-20 to human serum albumin [redacted] and α-1 acid glycoprotein [redacted] was determined at concentrations of 10 and 100 µg T-20/g plasma. The potential for displacement of protein-bound T-20 (10 µg/g plasma) in the presence of saquinavir, efavirenz and nevirapine were evaluated. Concentrations of these compounds were 10 µg/g plasma. Control samples containing only T-20 in plasma were included in the study. Pooled human blood (3 subjects) was collected by venipuncture from healthy volunteers. Non-specific binding of radioactive T-20 to the device and membrane was determined.

Stage 2

Whole blood from two healthy volunteers was used in this study. Aliquots of the whole blood were incubated with ^{3}H-T-20 at three concentrations for 30 minutes at approximately 37 °C. The distribution of radioactivity between cells and plasma was determined.

Drugs used in trial

Drug	Batch Number	Supplier
^{3}H-T-20	99/BDR/121-17/12/99	[redacted]
T-20	800426	
Saquinavir	71132036U	
Nelfinavir	N970164	
Efavirenz	[redacted] 06-000	
Nevirapine	[redacted] 0036	

Results

The extent of plasma protein binding was independent of concentration over the concentration range studied (Table I).

Table I: Protein binding of T-20

T-20 Plasma Concentrations (μg/g)	% Bound ± SD
[redacted]	99.06 ± 0.00
	98.32 ± 0.14
	97.53 ± 1.75
	97.96 ± 1.47
	97.30 ± 3.93
	ND

ND- not determined because radioactivity levels in ultrafiltrate below detection limit

T-20 was more highly bound to human serum albumin than to α-1 acid glycoprotein (Table II). These data suggest that T-20 is mainly bound by albumin in human plasma.

Table II: Binding of T-20 to Human Plasma Proteins

Human Plasma Protein	T-20 Plasma Concentrations (μg/g)	% Bound ± SD
Human serum albumin	[redacted]	94.78 ± 0.08
		95.53 ± 0.68
α-1 acid glycoprotein		36.57 ± 1.43
		59.17 ± 0.51

The data (Table III) on protein-binding displacement indicate that T-20 binding was not affected by the presence of SQV, NFV, EFV or NVP.

Table III: Effect of four drugs on plasma protein binding of T-20

Drug *	T-20 Drug Concentration (μg/g plasma)	% of T-20 Bound ± SD
None	[redacted]	98.16 ± 0.40
Saquinavir		97.93 ± 0.66
Nelfinavir		97.95 ± 0.27
Efavirenz		98.55 ± 0.34
Nevirapine		98.53 ± 0.42

* Nominal concentration of each drug was 10 μg/g and for drug = none, concentration was 0 μg/g

The hematocrit values for Donors A and B were 44.4 and 47.8 %, respectively, which are consistent with typical hematocrit values. Unlike plasma protein binding, the binding of T-20 to blood cells was concentration-dependent, as shown in Table IV.

Table IV: T-20 Concentrations in blood cells and whole blood following incubation ^{3}H-T-20 in whole blood

Donor	Nominal T-20 concentration (μg/g)	Replicate #	Concentration (μg equivalents) in		% of blood T-20 concentration associated with cells
			Blood Cells	Whole Blood	
A	100	1	39.32	80.22	49.02
		2	51.15	97.60	52.41
	10	1	5.72	9.61	59.52
		2	5.74	9.64	59.54
	1	1	0.90	1.32	68.18
		2	0.95	1.30	73.08
B	100	1	63.74	93.87	67.90
		2	55.69	91.96	60.56
	10	1	6.78	8.97	75.59
		2	6.97	11.16	62.46
	1	1	0.82	1.22	67.21
		2	0.84	1.04	81.77

Overall, binding increased inversely with concentration, suggesting that a saturable process may be involved in the binding. The range of binding to blood cells was approximately 50 – 80 % over the 100 – 1 μg/g concentration range. At physiologically relevant concentrations (C_{minss} = 2 μg/mL and C_{maxss} = 5 μg/mL; ≈ 1 and 10 μg/g), T-20 was approximately 65 % bound by the blood cells. This value indicates that T-20 binding to blood cells is generally within the value expected for general distribution within the blood components.

Conclusions

- T-20 is highly bound by plasma proteins (> 97 %) and appears to be bound primarily by albumin
- T-20 binding is not affected by the presence of SQV, NFV, EFV or NVP
- Binding of T-20 to blood cell components is less than 65 % at clinically relevant concentrations

Title: The in vitro binding of Ro 29-9800 (T-20) to human plasma protein in healthy volunteers and patients with human immunodeficiency virus (HIV+), and displacement effects of concomitant medications in healthy volunteers.

Study No: D01034

Study Procedure

The *in vitro* binding of T-20 to human plasma proteins in normal healthy volunteers and patients with HIV was determined. Additionally, the protein-binding displacement effects of some concomitant medications on T-20 binding were evaluated. The concomitant medications were warfarin, midazolam, itraconazole, amprenavir, lopinavir, and efavirenz. Equilibrium dialysis was used in this study.

Reviewer Comment

The study procedure adopted is acceptable.

Results

Time to equilibrium at 37°C was 20 hours and 4 hours for T-20 and the concomitant drugs, respectively (data not shown).

Protein binding of ^{3}H-T-20 in healthy and HIV+ human plasma is summarized in Table I. The data indicate that T-20 was highly bound to plasma proteins and is comparable to the findings from another binding study [redacted]

Table I: Plasma Protein Binding of T-20 and Concomitant Medications using Equilibrium dialysis

	Concentration (μg/g)	Donor Side	% Bound	% Free
^{3}H-T-20	5	healthy	95.3 ± 0.0	4.7 ± 1.0
	2	HIV	92.5 ± 0.8	7.5 ± 9.6
	5	HIV	92.0 ± 0.3	8.0 ± 3.3
	10	HIV	92.1 ± 0.1	7.9 ± 1.2

The plasma protein binding of T-20 was not significantly affected by coincubation with highly bound medications and vice versa.

Table II: Displacement effect of coincubated medications on T-20 binding

	Test Drug	Concentration (μg/mL)	% Bound	% Free
T-20	None	None	95.3 ± 0.0	4.7 ± 1.0
	Warfarin	2	95.1 ± 0.1	4.9 ± 2.1
		4	95.1 ± 0.4	4.9 ± 8.3
	Midazolam	0.1	95.1 ± 0.3	4.9 ± 5.2
		0.2	94.9 ± 0.6	5.1 ± 11.0
	Itraconazole	3	95.3 ± 0.0	5.7 ± 4.4
		6	94.1 ± 0.3	5.9 ± 4.6
	Lopinavir	10	95.0 ± 0.4	5.0 ± 8.6
		20	94.8 ± 0.3	5.2 ± 5.8
	Amprenavir	8	94.0 ± 1.6	6.0 ± 24.8
		16	93.2 ± 0.2	6.8 ± 3.1

Table III: Displacement effect of T-20 on binding of coincubated medications

Drug	Drug Concentration (μg/mL)	T-20 Concentration (μg/mL)	% Bound	% Free
^{3}H-Warfarin	2 μg/mL	0	98.7 ± 0.1	1.3 ± 6.4
		2	98.8 ± 0.0	1.2 ± 2.6
		5	98.5 ± 0.4	1.5 ± 27.5
		10	98.8 ± 0.0	1.2 ± 4.1
^{3}H-Midazolam	0.1 μg/mL	0	88.5 ± 0.7	11.5 ± 5.0
		2	88.8 ± 0.4	11.2 ± 3.3
		5	89.8 ± 0.1	10.2 ± 0.8
		10	89.5 ± 0.4	10.5 ± 3.6
^{3}H-Amprenavir	8 μg/mL	0	91.3 ± 1.1	8.7 ± 11.1
		2	91.3 ± 0.5	8.7 ± 5.3
		5	91.7 ± 0.2	8.3 ± 1.7
		10	91.0 ± 0.2	9.0 ± 1.6
^{14}C-Efavirenz	5 μg/mL	0	99.2 ± 0.0	0.8 ± 5.6
		2	99.2 ± 0.0	0.8 ± 2.2
		5	99.2 ± 0.0	0.8 ± 1.3
		10	99.2 ± 0.1	0.8 ± 6.6

Overall the result from this study are comparable to those obtained in a previous study using ultrafiltration.

Conclusions

- T-20 is highly bound to plasma proteins
- T-20 plasma protein binding is not affected by coincubation with highly bound study medications
- The plasma protein binding of highly bound drugs, such as warfarin, midazolam, amprenavir and efavirenz is not affected by coincubation with T-20

Title:	A controlled phase 2 trial assessing three doses of T-20 in combination with abacavir, amprenavir, ritonavir and efavirenz in HIV-infected adults
Study:	T-20-206
Investigators/Sites	Multiple investigators/multiple sites within in USA
Study Period:	06/1999 – 04/2001

Pharmacokinetic Objectives

- To determine the pharmacokinetics (PK) of T-20 in combination with background antiretrovirals (ARVs)
- To assess the T-20 trough concentrations over a 48-week treatment period
- To evaluate the potential effect of concomitant T-20 administration on plasma concentrations of background ARV at steady state.

Study Design

The PK substudy was conducted as part of a larger safety and efficacy study. The main PK methodology involved blood sample collection in HIV infected subjects receiving a background antiretroviral regimen (abacavir, amprenavir, ritonavir and efavirenz) with or without T-20. The doses for the drugs were as follows: abacavir (300 mg BID), amprenavir (1200 mg BID), ritonavir (200 mg BID), efavirenz (600 mg QD), and T-20 (50, 75 or 100 mg BID).

Blood Samples

- For trough: blood samples were collected from all patients at baseline and study weeks 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48
- Intensive: blood samples were collected at week four from two sets of patients*. Blood samples were collected at pre-T-20 dose (morning), and at 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dosing.

* patients randomized to control group (no T-20) and group receiving T-20

PK Analyses

- For T-20

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

- For ARVs

The applicant indicates that PK parameters were not included for the background regimens because the parameters could not be estimated accurately. The estimates would have been inaccurate because blood samples for the background regimens were obtained relative to the time of T-20 administration, rather than the time the background regimen was administered. Essentially the PK data would be limited by the variable relationship between the dose time of a particular drug and would not be representative of a true full profile at steady state (unequal dosing intervals). This reviewer agrees with the applicant's conclusions that determination of PK measures for the OB will not be accurate; subsequently, it will be difficult to make definitive conclusions about drug exposure changes in the OB regimen components.

- T-20 Trough Sample Analyses

All patients with at least one reliable measured trough concentration were included in summary tables. Trough samples included in the summary are those obtained within the window 12 ± 4 hours post dose. Values below the assay limit of quantitation were set as zero in the summaries.

The approaches adopted by the applicant in the trough analyses are acceptable; however, the time collection window will introduce additional variability in trough measurements.

Assays

The assays employed in this study are summarized in the table below.

Analyte	Interassay Precision of QC (%)	Accuracy (%)	LLOQ/Linear Range (ng/mL)	Assay Method/
T-20	8.3 – 10.3	101- 103	5/ 7.5 – 120	ECLIA/ IGEN
Amprenavir	4.3 - 4.8	89.5 – 90	10/ 30 – 1500	LC/MS/MS/ BAS Analytics
Ritonavir	4.1 – 4.5	90.8 – 94.6	50/ 150 - 7500	LC/MS/MS/ BAS Analytics
Efavirenz	3.3 – 5.8	96.7 – 102.6	50/ 120 - 8000	HPLC/UV/ Covance
Abacavir	13.3 – 15.0	96.6 – 107.3	25/ 75 – 4000	LC/MS/MS/ CEDRA

Reviewer Comment

The assays performed acceptably.

Results

T-20 Pharmacokinetics

PK data were available from 33 subjects who underwent intensive blood sampling. The mean parameter measures for these patients are presented in Table I.

Table I: Mean (CV%) T-20 PK Parameters following twice daily administration of 50, 75 or 100 mg of T-20 for 28 days.

T-20 Regimen	N	C_{max} (µg/mL)	C_{min} (µg/mL)	$AUC_{0\text{-}12hr}$(µg·hr/mL)	CL/F (L/hr)	T_{max}* (hr)
50 mg BID	12	2.58 (32)	1.04 (54)	23.1 (31)	2.36 (31)	4.0
75 mg BID	12	4.63 (31)	2.22 (33)	42.8 (27)	1.89 (31)	4.0
100 mg BID	9	4.99 (16)	2.60 (48)	48.6 (16)	2.11 (18)	4.0

* median value reported

The mean apparent clearance was comparable across all T-20 dose groups (approximately 2 L/hr) suggesting that T-20 PK exhibit dose independence. T-20 exposure (C_{min} , C_{max}, AUC increased with increasing dose; however, the exposure increases were not dose-proportional. The reason for the lack of dose-proportionality even though clearance was comparable is unclear. It should be noted that the lack of dose-proportionality is mainly due to data from the 75 mg dose group (supraportional increases in exposure at 75 mg dose group). Results from other T-20 studies indicate that exposure increases in an approximately dose-proportional manner over the 45 to 180 mg range following single dose administration.

According to the applicant, reliable trough concentrations were available from 45 patients. Selected trough concentrations collected from baseline to week 48 are summarized in Table II.

T-20 Dose	Week 4 (n)	Week 16	Week 32	Week 48
50 mg BID	0.972 (n = 4)	1.05 (n = 14)	1.14 (n = 12)	1.28 (n = 11)
75 mg BID	2.75 (n = 7)	2.27 (n = 15)	2.63 (n = 14)	2.19 (n = 10)
100 mg BID	3.63 (n = 3)	2.10 (n = 8)	2.72 (n = 6)	2.03 (n = 6)

(n) number of subjects

Trough data were highly variable (CV generally [redacted] range [redacted]), and were primarily likely due to variability in blood collection time. Other factors that may have influenced the variability were interindividual PK variability, small number of subjects, drug dosage and the influence of concomitant medications. Trough concentrations were lower in the 50 mg dose group (approximately 1

μg/mL) compared to the 75 and 100 mg dose groups (> 2 μg/mL). The trough concentrations in the 75 and 100 mg groups overlapped substantially (range ——— and ——— μg/mL for 100 and 75 mg dose groups, respectively) over the 48-week period.

Pharmacokinetics of antiretroviral (ARV) drugs in the optimized background regimens

It is difficult to make definitive conclusions regarding the role of T-20 on the exposure of drugs in the OB regimens for reasons previously outlined (see PK analyses for ARVs). Thus, data on the ARVs will not be discussed in detail in this report. Inspection of mean plasma concentration-time profiles for all the background drugs by T-20 dose group did not show definitive evidence for marked changes in background drug concentrations. The profiles of the control regimens (OB without T-20) were comparable to the OB regimens including T-20 in the two respects:

- Control regimen's profile was bracketed by T-20-containing regimen
- Control regimen's profile comparable in shape to T-20 containing regimens

Conclusions

- Plasma T-20 exposure increased with increasing dose
- Plasma T-20 trough concentrations were sustained over a 48 week period in the presence of antiretroviral agents