CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-705 / S-008

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20-705 (SE7-008)
TYPE:	Standard Review
DRUG:	Rescriptor (delavirdine mesylate) Tablets
APPLICANT:	Agouron pharmaceuticals, Inc.
REVIEWER:	Jenny H. Zheng, Ph.D.
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CLINICAL DIVISION:	530
SUBMISSION DATE:	July 12, 2000
PDUFA GOAL DATE:	May 12, 2001
Briefing:	Not required

Executive Summary

Rescriptor (delavirdine mesylate) 400 mg TID received accelerated approval for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents in 1997. Delavirdine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). The accelerated approval was based on surrogate marker changes at 24 weeks. This NDA supplement seeks traditional approval for delavirdine. The submission also contains 6 additional drug-drug interaction studies, to characterize the pharmacokinetics of protease inhibitors (PI) ritonavir, indinavir, saquinavir, and nelfinavir when coadministered with delavirdine, and the effect of these PIs on the delavirdine exposure.

The study results that have been added to the label are summarized in Tables 1 and 2.

Table 1. Pharmacokinetic Parameters for Coadministered PIs in the Presence of Delavirdine.

Coadministered PI	Dose of Coadministered PI	Dose of RESCRIPTOR	n	Study	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
					Cmax	AUC	Cmin
Indinavir	400 mg tid x 7 days	400 mg tid x 7 days	28	063	↓36* (↓52-↓14)	↔*	↑118* (↑16-↑312)
	600 mg tid x 7 days	400 mg tid x 7 days	28	063	↔*	↑53* (↑7-↑120)	↑298* (↑104-↑678)
Nelfinavir	750 mg tid x 14 days	400 mg tid x 7 days	12	070	↑88 (↑66-↑113)	↑107 (↑83-↑135)	↑136 (↑103-↑175)
Saquinavir	Soft gel capsule 1000 mg tid x 28 days	400 mg tid x 28 days	20	081	↑98‡ (↑4-↑277)	↑121‡ (↑14-↑340)	↑199‡ (↑37-↑553)

↑ Indicates increase
↓ Indicates decrease
↔ Indicates no significant change
* relative to indinavir 800 mg tid without RESCRIPTOR
‡ Saquinavir soft gel capsule 1000 mg tid plus RESCRIPTOR 400 mg tid relative to saquinavir soft gel capsule 1200 mg tid without RESCRIPTOR

Table 2. Pharmacokinetic Parameters for Delavirdine in the Presence of Coadministered PIs

Coadministered PI	Dose of Coadministered PI	Dose of RESCRIPTOR	n	Study	% Change in Delavirdine Pharmacokinetic Parameters (90% CI)		
					Cmax	AUC	Cmin
Indinavir	400 mg or 600 mg tid x 7 days	400 mg tid x 7 days	81	063	No apparent changes based on a comparison to historical data		
Nelfinavir	750 mg tid x 7 days	400 mg tid x 14 days	7	070	↓27 (↓49-↑4)	↓31 (↓57-↑10)	↓33 (↓70-↑49)
Saquinavir	Soft gel capsule 1000 mg tid x 28 days	400 mg tid for 7-28 days	23	081	No apparent changes based on a comparison to historical data		

↑ Indicates increase
↓ Indicates decrease

We removed ritonavir drug interaction results from the applicant proposed labeling, because it was not possible to interpret the pharmacokinetic data in Study 061. In this study, the highest concentration occurred at pre-dose for both delavirdine and ritonavir in about half of the patients.

Study 073A, an open-label randomized study of delavirdine plus nelfinavir, didanosine, and stavudine in triple and quadruple treatment regimens in HIV-1 infected individuals, compared pharmacokinetics of DLV and NFV following the administration of DLV 400 mg TID or 600 mg TID and NFV 750 mg TID. The results agreed with Study 070, and indicated that delavirdine increased nelfinavir concentrations. We decided to include only study 070 in the label.

The pharmacokinetic information from Study ACTG 359 was not incorporated into the labeling, since the drug-drug interaction information in this study is complicated and difficult to interpret. The study contains two PIs in each regimen, and adefovir dipivoxil (nucleotide RTI, HIV NDA received non-approval) in 4 of the 6 regimens.

For the package insert, we made some significant changes in the Clinical Pharmacology, Contraindications, Warnings, and Precautions: Drug interaction sections. The biggest change is that we deleted a lot of text and summarized all of the drug interaction information into 5 tables. The revised tables mimic the KALETRA package insert for consistency of antiviral drug package inserts and for greater ease of use by health care professionals. Other changes include:

[redacted]

[ ]

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cc: HFD-530 /NDA 20705
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Clinical Pharmacology 1a

An open-label study of delavirdine mesylate in combination with zidovudine and two doses of indinavir versus zidovudine, lamivudine, and indinavir in HIV-1 infected individuals
(Protocol M/3331/0063, V3-5)

Objectives: To evaluate the steady-state pharmacokinetic interaction between delavirdine and indinavir in HIV-infected patients.

Subjects: Forty-five patients aged 14 years and older with CD4 counts of > 50 cells/mm^3 and plasma HIV-1 RNA levels of > 20,000 copies/ml enrolled in the study. Fourteen of them (93%) in each group were included in the pharmacokinetic analysis.

Study design: This was an open-label, parallel-group, randomized study. The patients were randomized to receive one of three regimens of triple therapy for 24 weeks:

	DLV	ZDV	IDV	3TC
Group 1	400 mg TID	200 mg TID	400 mg q8h	
Group 2	400 mg TID	200 mg TID	600 mg q8h	
Group 3		200 mg TID	800 mg q8h	150 mg BID

The dose of 3TC was 150 mg once daily if patient's body weight was less than 50 kg. Indinavir was taken one hour before or two hours after a meal. Other medications were taken without regard to meals. This study was optionally extended to 48 weeks if a clinical benefit was seen.

Formulation: 100 mg delavirdine tablets, 100 mg zidovudine capsules, 200 mg or 400 mg indinavir capsules, and 150 mg 3TC tablets.

PK sample collection: Blood samples were collected at predose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7. Single blood samples for trough concentrations were also collected on Weeks 2, 4, 8, 12, 16, and 24.

Analytical methodology: The delavirdine plasma samples were analyzed using a validated sensitive and specific [redacted] The indinavir plasma samples were analyzed using a validated sensitive and specific [redacted]

Pharmacokinetic results and discussions:

Indinavir:

Figure 1 shows the mean steady-state indinavir concentrations with or without concomitant administration of delavirdine to HIV-1 patients (n=14/group). Mean (±SD) steady-state indinavir pharmacokinetic parameters from the three treatments are listed in Table 1. There was considerable inter-individual variability in indinavir pharmacokinetic parameters, with overlapping of parameter values across all treatment groups. The indinavir pharmacokinetic parameter with the greatest relative variability was Cmin, and delavirdine did not reduce the variability in this parameter. Delavirdine significantly

inhibited the clearance of indinavir or increased the absorption of indinavir. Compared to indinavir 800 mg alone, the AUC and C_{ss} of indinavir 400 mg when administered with delavirdine were about the same. However, delavirdine increased indinavir Cmin by 118% (Table 2). The indinavir 600 mg in combination with delavirdine had an AUC value approximately 53% higher than that obtained with indinavir 800 mg alone, with a 298% increase in C_{min} and a similar C_{max} (Table 2).

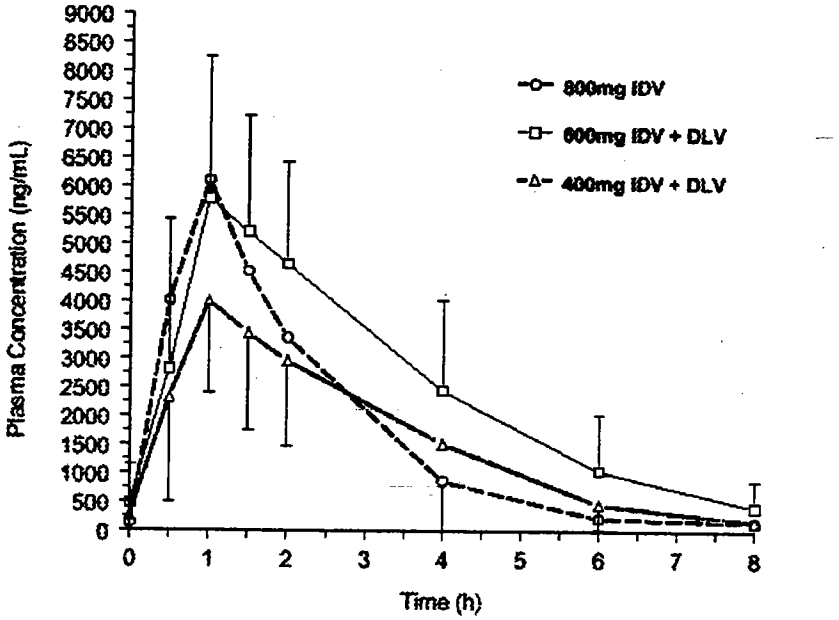

Figure 1

Parameter	Indinavir 400 mg q8h +DLV (A, n=14)	Indinavir 600 mg q8h +DLV (B, n=14)	Indinavir 800 mg q8h (C, n=14)
CLpo (L/h)	41.3 (29.2)	36.6 (17.5)	84.8 (76.1)
AUC$_\tau$ (ng·h/mL)	13089 (7221)	20182 (9830)	13928 (7670)
Css (ng/mL)	1636 (903)	2523 (1229)	1741 (959)
Cmin (ng/mL)	152 (136)	351 (469)	67 (68)
Cmax (ng/mL)	4222 (1512)	6344 (2207)	6965 (2866)
tmax (h)	1.1 (0.3)	1.3 (0.4)	0.9 (0.3)
λz (h^{-1})	0.5308 (0.0982)	0.4983 (0.1739)	0.5627 (0.1315)
t½ (h)	1.4 (0.3)	1.6 (0.7)	1.3 (0.3)

Table 1

Parameter	Indinavir geometric means ratio (90% CI)	
	IDV 400 mg TID with DLV vs. 800 mg TID without DLV	IDV 600 mg TID with DLV vs. 800 mg TID without DLV
Cmax	0.64 (0.48, 0.86)	0.95 (0.69, 1.30)
Cmin	2.18 (1.16, 4.12)	3.98 (2.04, 7.78)
AUC	0.96 (0.65, 1.42)	1.53 (1.07, 2.20)

Table 2

Delavirdine:

Figure 2 shows the mean steady-state delavirdine concentration vs. time profiles from both delavirdine treatment groups. The combination of indinavir (either 400 or 600 mg q8h) with delavirdine resulted in no statistically significant differences in any delavirdine pharmacokinetic parameter between the two groups or as compared to previous Phase I studies in HIV-infected patients on delavirdine alone (Tables 3 and 4). These results indicate that indinavir has no effect on delavirdine pharmacokinetics.

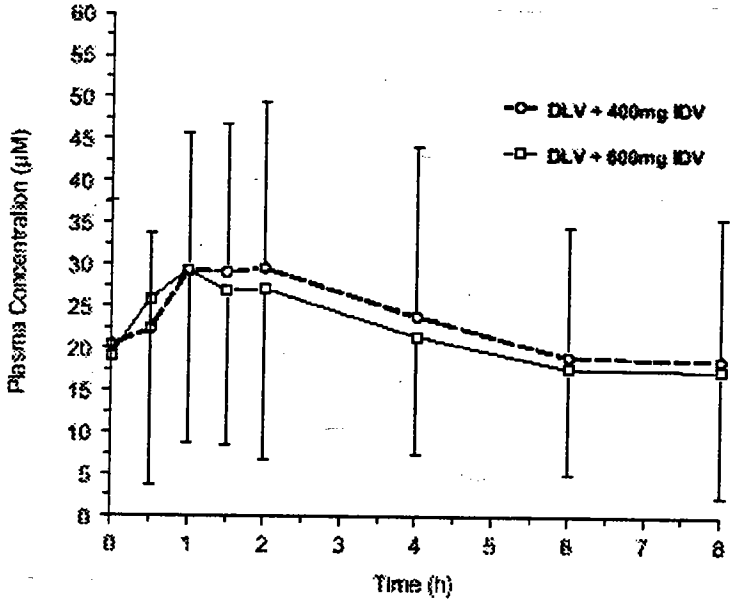

Figure 2

DLV Regimen	Statistic	Cmin (µM)	Css (µM)	Cmax (µM)	Tmax (h)	AUCτ (µM h)	CLpo (L/h)
400 mg TID + IDV 400 mg q8h (n=14)*	Mean ± SD	15 ± 12	24 ± 17	32 ± 19	1.6 ± 1.2	186 ± 137	5.9 ± 4.3
	Median†	15	23	32	1.5	165	3.9
	Range	1.7 – 45	5.4 - 74	13 - 87	0.5 – 4.0	43 - 594	1.2 - 17
400 mg TID + IDV 600 mg q8h (n=14)*	Mean ± SD	16 ± 14	22 ± 16	31 ± 20	1.4 ± 1.4	174 ± 126	6.0 ± 4.0
	Median†	9.7	16	26	1.0	142	5.1
	Range	3.9 – 47	5.1 - 63	7.1 - 87	0.5 – 5.0	41 - 502	1.4 - 16
400 mg TID Without IDV (n=67)**	Mean ± SD	15 ± 10	23 ± 13	35 ± 20	1.4 ± 0.7	180 ± 100	6.0 ± 19
	Median	12	21	33	1.0	165	4.4
	Range	0.69 – 45	0.6 - 64	9 - 109	0.5 - 5.1	9 - 513	1.4 - 156

Table 3

Parameter	Delavirdine geometric means ratio (90% CI) (400 mg TID with IDV 600 mg TID vs. 400 mg TID without IDV)
Cmax	0.89 (0.64, 1.22)
Cmin	1.02 (0.64, 1.63)
AUC	0.97 (0.67, 1.39)

Table 4

Conclusion:

This study demonstrated that concomitant administration of delavirdine 400 mg TID with indinavir (400 mg or 600 mg Q8h) increased the mean systemic exposure to indinavir. Indinavir had no effect on the pharmacokinetics of delavirdine. The applicant should include these results in the updated label.

Delavirdine mesylate (PNU-90152T) and nelfinavir mesylate: a pharmacokinetic drug-drug interaction study in normal healthy adult volunteers (Protocol M/3331/0070, V6-8)

Objectives: To evaluate the steady-state pharmacokinetic interaction between delavirdine and nelfinavir in HIV-infected patients.

Subjects: Twenty-four healthy male and female volunteers aged 18-55 enrolled in the study. Nineteen of them were included in the pharmacokinetic analysis.

Study design: This was an open-label, parallel-group, multiple-dose, randomized study. The subjects were randomized to two groups:

Group A: nelfinavir 750 mg q 8h for 1 week (Days 1-7, morning dose only on Day 7) followed by nelfinavir 750 mg q 8h + delavirdine 400 mg q 8h for 1 week (Days 8-15, morning dose only on Day 14 and only morning delavirdine on Day 15*).

Group B: delavirdine 400 mg q 8 h for 1 week (Days 1-7, morning dose only on Day 7) followed by nelfinavir 750 mg q 8h + delavirdine 400 mg q 8h for 1 week (Days 8-14, morning dose only on Day 14)

* In Group A, the sponsor stated that delavirdine was given q 8h on Day 15 in some places and stated that delavirdine was administered morning only on Day 15 in some other places. However, it is not clear why delavirdine was given on Day 15. In some other occasions, the sponsor only mentioned up to 14 days for drug administration.

All doses were administered with food.

Formulation: 100 mg delavirdine tablets and 250 mg nelfinavir mesylate tablets.

PK sample collection: Blood samples were collected at following schedule:

Tx Group	Day	Time of Blood Draw Relative to Dose																
		pre-dose*	0.25	0.5	0.75	1	1.5	2	2.5	3	4	5	6	8	12	18	24	30
A	7	N†		N		N	N	N	N	N	N	N	N	N	N	N	N	
	11	N‡																
	14	N/D§	D	N/D	D	N/D	N/D	N/D	N	N	N/D	N	N/D	N/D	N	N	N	N
B	7	D	D	D	D	D	D	D			D		D	D				
	11	N*																
	14	N/D	D	N/D	D	N/D	N/D	N/D	N	N	N/D	N	N/D	N/D				

* pre-dose = -10 mins
† N = Nelfinavir
‡ Nelfinavir trough sample
§ D = Delavirdine

Analytical methodology: The delavirdine plasma samples were analyzed using a validated sensitive and specific [redacted] method by [redacted] The nelfinavir and M8 metabolite were analyzed using a validated sensitive and [redacted]

Pharmacokinetic results and discussion:

Nelfinavir:

· Figure 1 shows the mean steady-state plasma nelfinavir concentrations from Group A.

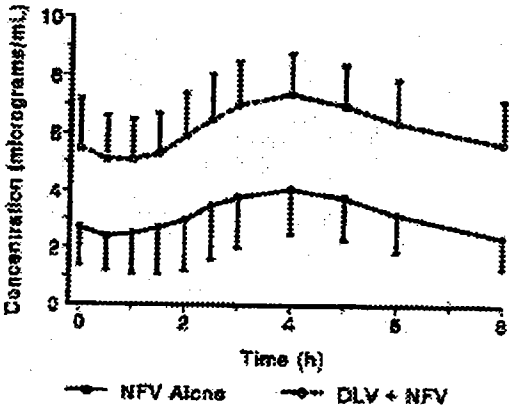

Figure 1

Mean (± SD) nelfinavir and its active metabolite pharmacokinetic parameters are shown in Tables 1 and 2, respectively.

Parameter	Group A (n=12)		Group B (n = 7)
	Nelfinavir alone (Day 7)	Nelfinavir plus delavirdine (Day 14)	Nelfinavir plus delavirdine (Day 14)
C_{max} (µg/ml)	4.2 ± 1.7	7.6 ± 1.4	8.1 ± 1.1
T_{max} (h)	4.0 ± 0.8	4.0 ± 0.8	4.7 ± 1.0
C_{min} (µg/ml)	2.2 ± 1.1	4.9 ± 1.4	5.3 ± 1.6
CL_{po} (l/h)	33 ±10	16 ± 3	14 ± 3
CL_f/CL_m	0.39 ± 0.12	0.11 ±0.04	0.14 ± 0.05
AUC_{0-8} (µg/ml.h)	25.6 ± 11.5	50.3 ± 10.8	53.9 ±10.9
$t_{1/2}$ (h)	3.1 ± 0.6	6.3 ± 1.2	6.6 ± 2.1

Table 1. Summary of nelfinavir pharmacokinetic parameters

Parameter	Group A (n=12)		Group B (n = 7)
	Nelfinavir alone (Day 7)	Nelfinavir plus delavirdine (Day 14)	Nelfinavir plus delavirdine (Day 14)
C_{max} (µg/ml)	1.7 ± 0.3	0.8 ± 0.3	1.1 ± 0.4
T_{max} (h)	4.5 ± 0.8	4.6 ± 0.7	3.3 ± 2.3
C_{min} (µg/ml)	0.6 ± 0.2	0.5 ± 0.2	0.7 ± 0.4
AUC_{0-8} (µg/ml.h)	9.0 ± 1.9	5.2 ± 1.7	7.2 ±2.9
$t_{1/2}$ (h)	4.5 ± 2.0	6.1 ± 1.0	-

Table 2. Summary of nelfinavir active metabolite pharmacokinetic parameters

Delavirdine reduced nelfinavir oral clearance, which resulted in the substantially increased mean steady-state plasma nelfinavir concentrations (Tables 1 and 3). The reduction is consistent with the inhibition of nelfinavir metabolism by delavirdine

through inhibition of CYP 3A4, as evidenced by the reduced the formation clearance of nelfinavir metabolite M8 (decreased CL_f/CL_m value). There were no statistically significant differences in pharmacokinetic parameters between two nelfinavir plus delavirdine groups, which indicated that the sequence of drug treatments had no effect on pharmacokinetics of nelfinavir. Although delavirdine treatment reduced the nelfinavir active metabolite M8, the total amount of nelfinavir plus metabolite increased.

Parameter	Nelfinavir geometric means ratio (90% CI) (750 mg TID with DLV 400 mg TID vs. 750 mg TID without DLV)
Cmax	1.88 (1.66, 2.13)
Cmin	2.36 (2.03, 2.75)
AUC	2.07 (1.83, 2.35)

Table 3

Delavirdine:

Figure 2 shows the mean steady-state plasma delavirdine concentrations from Group B, and Table 3 shows the mean (± SD) delavirdine pharmacokinetic parameters. The combination of delavirdine plus nelfinavir showed a trend of lower plasma delavirdine concentrations, with about a 30% reduction in AUC, Cmin, and Cmax (Table 4). The sponsor suggested that, although it was not observed in previous studies, nelfinavir might have a mild inductive effect on CYP 3A4. Groups A and B did not differ significantly with respect to steady-state delavirdine pharmacokinetic parameters on Day 14.

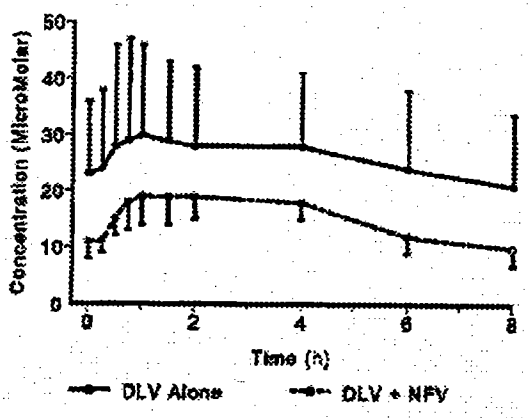

Figure 2

Parameter	Group B (n=7)		Group A (n = 12)
	Delavirdine alone (Day 7)	Delavirdine plus nelfinavir (Day 14)	Delavirdine plus nelfinavir (Day 14)
C_{max} (μM)	32 ± 16	21 ± 5	21 ± 7
T_{max} (h)	1.6 ± 1.2	2.1 ± 1.4	2.3 ±1.4
C_{min} (μM)	21 ± 13	10 ± 3	10 ± 4
CL_{po} (l/h)	5.7 ± 6.4	6.1 ± 1.3	7.0 ± 4.5
CL_f/CL_m	0.17 ± 0.12	0.21 ± 0.08	0.24 ± 0.08
AUC_{0-8} (μM.h)	256 ± 153	122 ± 24	124 ± 40

Table 3

Parameter	Delavirdine geometric means ratio (90% CI) (DLV 400 mg TID with NFV 750 mg TID vs. 400 mg TID without NFV)
Cmax	0.73 (0.51, 1.04)
Cmin	0.67 (0.30, 1.49)
AUC	0.69 (0.43, 1.10)

Table 4

It is interesting to know that five patients were dropped from Group B due to neutropenia (n = 4) or leukopenia (n = 1). The onset of adverse events occurred within 3-6 days of combination treatment with delavirdine and nelfinavir. The sponsor claimed that the abnormalities returned to normal following discontinuation of both drugs. The mean and median delavirdine and nelfinavir concentrations for the dropped subjects were higher than those in subjects who completed the study (Table 5).

Subject (hematology values)	Delavirdine Pharmacokinetic Parameter Values from Day 7			Trough Nelfinavir Concentration (μg/mL) on Day 11
	Cmin (μM)	Css (μM)	Cmax (μM)	
5 (1.16*)	25	30	34	10.7
8 (3.50†)	8.3	14	23	4.4
10 (0.80*)	40	44	48	7.7
11 (0.28*)	68	79	90	15.4
21 (0.91*)	27	34	38	7.8
Statistics for Dropped Subjects				
N	5	5	5	5
Mean ± SD	34± 22	40± 24	47± 26	9.2±4.1
Median	27	35	38	7.8
Range	8-68	14-79	23-90	4.4-15.4
Statistics for Evaluable Subjects				
N	7	7	7	19
Mean ± SD	21 ± 13	26± 14	36± 16	6.4±2.1
Median	19	26	30	6.1
Range	0.7-45	5-51	9-62	2.7-9.9

* Absolute Neutrophil Count, normal range = 1,300-7,000 Thou/μL
† White Blood Cell count, normal range = 4,000-11,000 Thou/μL

Conclusion and recommendations:

The combination of delavirdine plus nelfinavir resulted in lower plasma delavirdine concentrations and higher nelfinavir concentrations and lower M8 concentrations. The applicant should include these results in the updated label.

An open-label randomized study of delavirdine mesylate (DLV, Rescriptor) plus nelfinavir (NFV), didanosine (ddI), and stavudine (d4T) in triple and quadruple treatment regimens in HIV-1 infected individuals (Protocol M/3331/0073A, V9-12)

Background: The study includes two parts. Only data from Part A were submitted. This portion of the study was done to determine the effect of lower DLV concentrations on antiviral response, to determine if the pharmacokinetic parameters of combination therapy with DLV and NFV would support BID dosing. In addition, safety of the treatment regimens was examined before enrolling a large number of patients (Part B).

Objectives: To determine efficacy, safety, and the pharmacokinetics of DLV and NFV following the administration of DLV 400 mg TID or 600 mg TID and NFV 750 mg TID in HIV-1 infected patients.

Subjects: Twenty-two HIV-1 infected patients were enrolled in the study. A total of 20 patients were included in the pharmacokinetic analyses.

Study design: This was an open-label, parallel-group, multiple-dose, randomized study. Patients enrolled in Part A of this study received a four-drug combination consisting of an NNRTI (delavirdine, 400 mg TID or 600 mg TID), two NRTIs (didanosine and stavudine), and a PI (nelfinavir). Patients were treated for 24 weeks, with the option of continuing study participation for one or two additional 24 weeks period at discretion of the investigator. Didanosine was given on an empty stomach and NFV was given with food. Delavirdine and stavudine were given without regard to meals. Didanosine and DLV were given at least 1 hour apart.

Formulation: 100 mg delavirdine tablets, 250 mg nelfinavir mesylate tablets, 100 mg didanosine tablets (two 100 mg tablets for patients who weighed 60 kg or more; one 100 mg tablet and one 25 mg tablet for patients who weighed less than 60 kg), and stavudine capsule (one 40 mg capsule for patients who weighed 60 kg or more and one 30 mg capsule for patients who weighed less than 60 kg).

PK sample collection: Pharmacokinetic (PK) samples were collected at week 4. Blood samples were collected at Pre-dose (-10 min), 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours post-dose. Although the patients were on TID regimens of both delavirdine and nelfinavir, the next doses of both drugs were to be withheld until the 12-hour blood samples were obtained. Trough blood samples for the determination of plasma delavirdine, nelfinavir, and nelfinavir M8 metabolite concentrations were obtained on Day 1 and Weeks 1, 2, and 3.

Pharmacokinetic results and discussion:

Nelfinavir:

Figure 1 shows the mean steady-state plasma nelfinavir concentrations (left figure) and metabolite M8 concentrations (right figures) from both treatment groups.

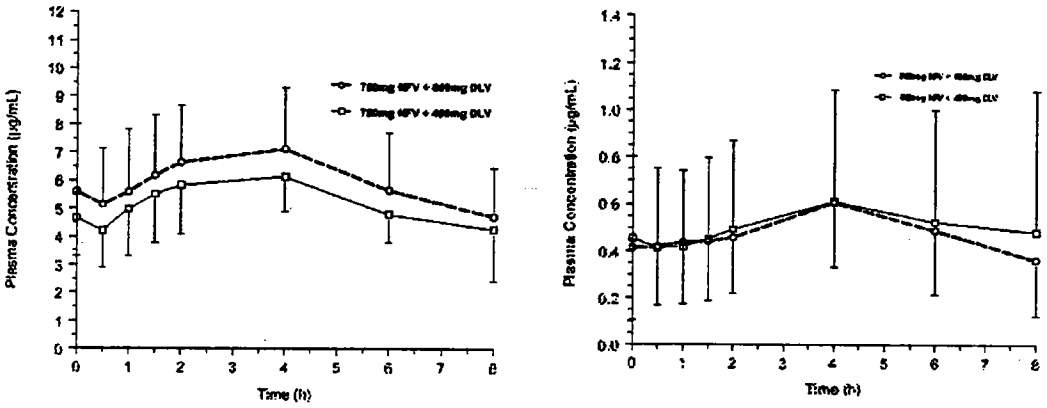

Figure 1

Tables 1 and 2 shows the mean (± SD) nelfinavir and M8 metabolite pharmacokinetic parameters from HIV-1 infected patients in this study, as compared to that from healthy subjects in Study M/3331/0070.

Regimen	Statistic	Cmin (µg/mL)	Css (µg/mL)	Cmax (µg/mL)	Tmax (h)	AUCτ (µg·h/mL)	CL/po (L/h)	λz (h⁻¹)	t½ (h)	C12h
NFV 750 mg TID	Mean ± SD	3.7 ± 1.9	5.3 ± 1.1	6.6 ± 1.5	3.2 ± 2.1	42 ± 9	19 ± 5	0.14 ± .062	5.8 ± 2.6‡	2.9 ± 1.8§
Plus DLV 400 mg TID	Median	3.8	5.6	6.9	3.6	45	17	0.14	5.6	2.4
(n=10)*	Range	2.3 - 5.0	3.5 - 6.8	4.3 - 8.4	1.0 - 5.0	28 - 54	14 - 27	0.07 - 0.24	2.9 - 10.3	0.6 - 6.1
NFV 750 mg TID	Mean ± SD	3.9 ± 2.2	6.0 ± 2.8	7.8 ± 2.1	2.6 ± 1.6	48 ± 16	17 ± 6	0.13 ± .05	6.5 ± 2.9	2.6 ± 1.8§
Plus DLV 600 mg TID	Median	3.5	5.4	8.6	3.0	44	17	0.12	5.8	2.4
(n=10)*	Range	1.2 - 7.7	3.3 - 9.1	4.2 - 10.0	0.0 - 4.0	28 - 73	10 - 29	0.08 - 0.23	3.1 - 13.6	0.6 - 6.0
NFV 750 mg TID	Mean ± SD	4.9 ± 1.4	6.3 ± 1.4	7.8 ± 1.4	4.0 ± 0.8	59 ± 11	16 ± 3	0.11 ± .02	6.5 ± 1.2	3.9 ± 1.1
Plus DLV 400 mg TID	Median	4.5	6.1	7.3	4.0	49	16	0.11	6.3	3.7
(n=12)**	Range	3.3 - 7.6	4.7 - 9.1	5.6 - 9.5	2.5 - 5.0	38 - 73	10 - 20	0.08 - 0.16	4.4 - 8.3	2.7 - 6.0
NFV 750 mg TID	Mean ± SD	2.2 ± 1.1	3.2 ± 1.6	4.2 ± 1.7	4.5 ± 0.5	36 ± 11	33 ± 13	0.23 ± .04	3.1 ± 0.8	1.0 ± 0.7
Alone	Median	1.8	2.7	3.7	4.0	33	35	0.21	3.2	0.9
(n=12)**	Range	1.2 – 5.0	1.9 – 6.8	2.9 – 8.1	2.5 – 5.0	15 – 54	14 - 49	0.17 – 0.33	2.3 – 5.1	0.5 – 3.0

* Protocol M/3331/0073A
** Protocol M/3331/0070 (normal healthy volunteer study)
† p>0.1 by Wilcoxon rank sum test for detectable regimen differences for all nelfinavir pharmacokinetic parameters in study M/3331/0073A.
‡ n = 8
§ Concentration at 12 hours with the next dose delayed in the TID regimen
≈ n = 9

Table 1. Summary of nelfinavir pharmacokinetic parameters

Regimen	Statistic	Cmin (µg/mL)	Css (µg/mL)	Cmax (µg/mL)	Tmax (h)	AUCτ (µg·h/mL)	λz (h^{-1})	t½ (h)
NFV 750 mg TID	Mean ± sd	0.3 ± 0.3§	0.5 ± 0.4§	0.6 ± 0.6§	4.4 ± 2.4§	4.1 ± 3.4§	0.22 ± .02‡	3.2 ± 0.3‡
Plus DLV 400 mg TID	Median	0.18	0.32	0.44	4.0	2.6	0.22	3.2
(n=10)*	Range	0.09 - 0.8	0.30 - 1.3	0.30 - 1.9	3.0 - 8.0	0.8 - 10.3	0.19 - 0.24	2.9 - 3.6
NFV 750 mg TID	Mean ± sd	0.3 ± 0.3	0.5 ± 0.3	0.6 ± 0.3	3.7 ± 2.0	3.8 ± 2.0	0.18 ± .05§	4.2 ± 1.6§
Plus DLV 600 mg TID	Median	0.24	0.45	0.6	4.0	3.6	0.18	3.9
(n=10)*	Range	0.11 - 0.9	0.2 - 1.0	0.3 - 1.1	0.0 - 6.0	1.6 - 8.3	0.08 - 0.25	2.7 - 8.2
NFV 750 mg TID	Mean ± sd	0.5 ± 0.2	0.7 ± 0.2	0.8 ± 0.3	4.6 ± 0.7	5.2 ± 1.8	0.12 ± .02	6.1 ± 1.9
Plus DLV 400 mg TID	Median	0.5	0.6	0.8	5.0	4.8	0.12	6.0
(n=12)**	Range	0.3 - 0.9	0.4 - 1.1	0.5 - 1.3	3.0 - 5.0	3.0 - 8.8	0.09 - 0.16	4.4 - 7.9
NFV 750 mg TID	Mean ± sd	0.6 ± 0.2	1.1 ± 0.2	1.7 ± 0.3	4.5 ± 0.67	9.0 ± 1.9	0.19 ± .08	4.6 ± 2.9
Alone	Median	0.5	1.1	1.8	5.0	8.8	0.18	3.8
(n=12)**	Range	0.4 – 0.9	0.7 – 1.5	1.1 – 2.5	2.5 – 5.0	6 - 12	0.10 – 0.34	2.1 – 7.2

* Protocol M/3331/0073
** Protocol M/3331/0070 (normal healthy volunteer study)
† p<0.1 by Wilcoxon rank sum test for delavirdine regimen differences for all M8 nelfinavir metabolite pharmacokinetic parameters in study M/3331/0073.
‡ n = 4
§ n = 9

Table 2. Summary of nelfinavir M8 metabolite pharmacokinetic parameters

Nelfinavir pharmacokinetic parameters from both groups in study M/3331/0073 generally agreed with the parameters from nelfinavir 750 mg TID plus delavirdine 400 mg TID in healthy volunteers in Study M/3331/0070, showing substantially increased nelfinavir concentrations and half-life when nelfinavir and delavirdine were coadministered. Pharmacokinetic data for the M8 nelfinavir metabolite from study M/3331/0073A agreed less well with data for the metabolite from study M/3331/0070. Median values of nelfinavir M8 metabolite pharmacokinetic parameters from study M/3331/0073A tended to be approximately 50% of the median values from study M/3331/0070.

The applicant started enrolling patients into the Part B portion of study using BID dosing regimens in May 1998.

Delavirdine:

Figure 2 shows the mean steady-state plasma delavirdine concentrations following coadministration with nelfinavir, didanosine, and stavudine. Mean delavirdine pharmacokinetic parameters from these two delavirdine regimens and historic data for delavirdine 300 and 400 mg TID without nelfinavir are listed in Table 3.

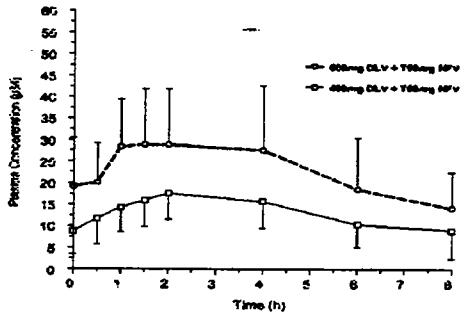

Figure 2

DLV Regimen	Statistic	Cmin (µM)	Css (µM)	Cmax (µM)	Tmax (h)	AUCτ (µM h)	CLpo (L/h)	C12§ (µM)
400mg TID	Mean ± sd	6.6 ± 3.9	13 ± 5	20 ± 8	2.4 ± 2.2	106 ± 40	8.4 ± 5.4	4.3 ± 4.4
Plus NFV	Median	5.8†	14‡	20‡	2.0	116‡	6.3	2.6
(n=18)*	Range	1.4 - 15.1	4.0 - 21	6.7 - 29	0.5 - 8.0	32 - 166	4.4 - 10.2	0.5 - 14.5
300 mg TID	Mean ± sd	9.5 ± 5.9	15 ± 8	23 ± 10	1.1 ± 0.4	122 ± 64	5.8 ± 3.9	-
Without NFV	Median	8.2	14	22	1.0	113	4.7	-
(n=40)**	Range	1 - 28	3.8 - 42	6 - 54	0.5 - 2.5	30 - 338	1.8 - 18	-
600 mg TID	Mean ± sd	13 ± 8	21 ± 11	33 ± 15	2.3 ± 1.2	186 ± 91	7.4 ± 3.7	7.0 ± 7.6#
Plus NFV	Median	11.1	20	30	2.0	162	6.7	4.4
(n=18)*	Range	1.8 - 30	9.9 - 40	16 - 51	1.0 - 4.0	79 - 318	3.4 - 13.7	1.2 - 23
400 mg TID	Mean ± sd	15 ± 10	23 ± 13	35 ± 20	1.4 ± 0.7	180 ± 100	8.0 ± 19	-
Without NFV	Median	12	21	33	1.0	165	4.4	-
(n=67)**	Range	0.09 - 45	0.5 - 64	2 - 100	0.5 - 5.1	5 - 515	1.6 - 156	-

* Protocol M/3331/0073
** Historical database (delavirdine NDA, Item 6, Section E.1.a)
† p<.05 for comparison to the delavirdine 600 mg TID plus nelfinavir group by Wilcoxon rank sum test
‡ .05<p<.10 for comparison to the delavirdine 600 mg TID plus nelfinavir group by Wilcoxon rank sum test
§ Concentration at 12 hours with the next dose delayed in the TID regimen
# n = 8

Table 3

Administration of the two delavirdine regimens (400 and 600 mg TID plus nelfinavir) resulted in a statistically significant difference in the delavirdine Cmin and marginally significant differences (.05<p<.1) in the delavirdine Cmax, Css, and AUXτ. The combination of nelfinavir plus delavirdine 400 or 600 mg TID had similar median CL_{po}, suggesting linear steady-state pharmacokinetics of delavirdine in combination with nelfinavir. The combination of nelfinavir plus delavirdine 400 mg TID resulted in pharmacokinetic parameters in good agreement with Study M/3331/0070, where nelfinavir and delavirdine (400 mg TID) were administered without NRTIs. It is not clear which studies where used as the historical data for comparison. The applicant stated that they had conducted simulations using C_{min}, C_{12} values from this study, and predicted a mean trough delavirdine concentration of 6.2 µM from delavirdine 600 mg BID in combination with nelfinavir, which they were considered to be similar to the Cmin of the 400 mg TID group. However, detailed information was not provided.

Conclusion: Delavirdine increased nelfinavir concentrations and half-life. The results of this study generally agree with results from Study 070.

Delavirdine mesylate: randomized, open-label, parallel group pharmacokinetic comparison of SQV+3TC+DLV twice or thrice daily vs. SQV+3TC+AZT vs. SQV+3TC+AZT +DLV in the treatment of HIV-1 positive patients (Protocol M/3331/0081, V13-14)

Objectives: To evaluate the pharmacokinetics, safety, tolerance and efficacy of the study regimens.

Subjects: Ninety-seven treatment-naïve patients aged 14 years and older with a baseline plasma HIV RNA level of greater than 5000 copies/ml were recruited in this study. Thirty-one patients were included in the pharmacokinetic analyses.

Study design: This was an open-label, parallel group, randomized study of the combination of delavirdine and saquinavir soft gel capsules. Four groups received a combination of the following antiviral agents for 24 weeks:

	SQV	DLV	3TC	AZT
Group 1	1400 mg BID	600 mg BID	150 mg BID	
Group 2	1000 mg TID	400 mg TID	150 mg BID	
Group 3	1200 mg TID		150 mg BID	200 mg TID
Group 4	1400 mg BID	600 mg BID	150 mg BID	300 mg BID

The dose of 3TC was 150 mg once daily if the patient's body weight was less than 50 kg. Saquinavir was taken within 2 hours of a meal. Other medications were taken without regard to meals. Grapefruit juice was not allowed during the study. This study was optionally extended to 48 weeks if a clinical benefit was seen.

Formulation: 200 mg saquinavir soft gelatin capsules, 100 mg delavirdine tablets (these tablets may be replaced by 200 mg tablets after Week 24), 100 mg zidovudine capsules, and 150 mg 3TC tablets.

PK/PD sample collection: In Week 4, the steady-state pharmacokinetics of delavirdine and saquinavir were evaluated. Blood samples were collected at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours postdose for the BID treatment groups (Groups 1 and 4), but only out to 8 hours for the TID treatment groups (Groups 2 and 3). Single blood samples for trough concentrations (6-10 hours after the last doses of saquinavir and delavirdine in Groups 2 and 3, and 8-12 hours after the last doses in Groups 1 and 4) were collected on Day 1, Weeks 1, 2, 4, 8, and 12.

Plasma samples were collected during each clinic visit (Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24) for HIV-1 RNA levels. CD_4 lymphocyte counts were also determined at these times.

Analytical methodology: The plasma samples were analyzed for delavirdine and saquinavir using validated methods at a contract research organization.

Pharmacokinetic results and discussion:

Because the doses and treatment regimens in Groups 1 and 4 were identical for DLV and SQV, and AZT does not interact pharmacokinetically with either DLV or SQV, the pharmacokinetic data for patients from these two groups were pooled for DLV and SQV. Although trough concentration data were obtained at other times during the study, this preliminary report only discusses data from the Week 4 steady-state pharmacokinetic evaluation.

Saquinavir:

The applicant provided median plasma saquinavir concentration-time profiles (Figure 1) due to non-normal distribution and high variability.

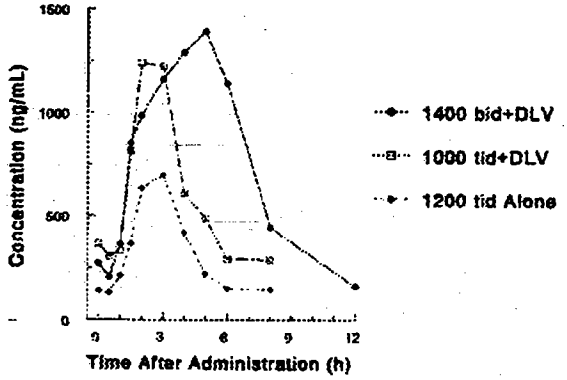

Figure 1

Saquinavir pharmacokinetic parameters are summarized in Table 1. Relative to the control treatment (Group 3), both delavirdine regimens significantly inhibited the oral clearance of saquinavir, and thus increased the saquinavir concentrations. The results of the statistical comparisons of the pharmacokinetic parameters of saquinavir from 1000 mg TID regimens in combination with DLV and 3TC relative to SQV 1200 mg TID and two NRTIs are listed in Table 2. The applicant claimed that the increases in saquinavir concentrations were not associated with increases in the incidence of saquinavir adverse events.

Drug	Dose	Group	statistics	Cmax (µg/ml)	Tmax (h)	Cmin (µg/ml)	AUC_{0-12} (µg/ml.h)
SQV	1400 BID with DLV 600 mg BID	1+4 (n = 11)	Mean	2.1	4.5	0.13	9.6
			SD	1.0	2.9	0.12	5.4
			Median	1.9	4.0	0.09	8.7
	1000 TID with DLV 400 mg TID	2 (n = 10)	Mean	2.2	3.4	0.33	8.4
			SD	2.1	1.8	0.36	8.3
			Median	1.4	3.0	0.18	4.8
	1200 BID without DLV	3 (n = 10)	Mean	0.99	2.5	0.11	3.2
			SD	0.61	0.6	0.09	2.2
			Median	0.85	2.5	0.10	2.9

Table 1

Parameter	SQV geometric means ratio (90% CI) (1000 mg TID with DLV vs. 1200 mg TID without DLV)
Cmax	1.98 (1.04, 3.77)
Cmin	2.99 (1.37, 6.53)
AUC	2.21 (1.14, 4.30)

Table 2

Delavirdine:

Mean plasma delavirdine concentration data from 600 mg BID (Groups 1 and 4) and 400 mg TID (Group 2) are plotted against time in Figure 2. Mean delavirdine pharmacokinetic parameters from the two delavirdine regimens and from historic data (Study M/3331/0019) for delavirdine 400 mg TID without saquinavir are listed in Table 3. Relative to the 400 mg TID regimen, the 600 mg BID regimen resulted in a 63% increase in Cmax and a 13% decrease in Cmin. However, these changes were not statistically significant. Saquinavir had no apparent effect on the pharmacokinetics of delavirdine, based upon similar pharmacokinetic parameters between this study and the previous study where delavirdine administered with food (M/3331/0019, Table 4)

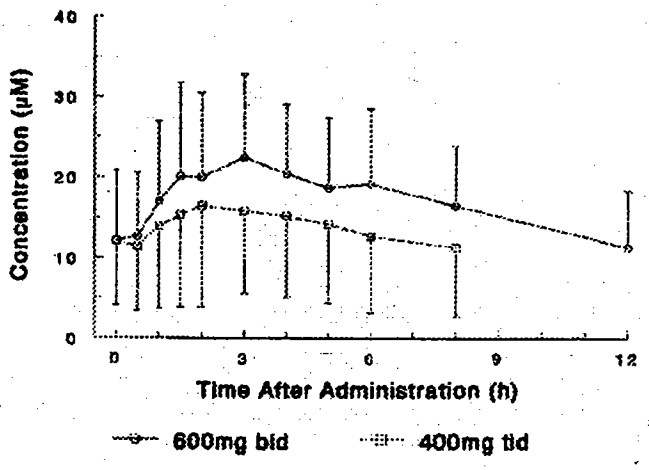

Figure 2

Parameter	Study/Treatment		
	0019 400mg TID n=13	0081 400mg TID n=10	0081 600mg BID n=11
Cmax (µM)	23 ± 13 22 (1.9 – 46)	19 ± 12 15 (5 – 45)	26 ± 11 23 (6 – 42)
Css (µM)	16 ± 11 13 (0.6 – 36)	14 ± 10 10 (4 – 34)	17 ± 7 18 (3 – 28)
Cmin (µM)	11 ± 9 7.5 (0.1 – 26)	9.4 ± 7.7 5.5 (2.3 – 25)	8.1 ± 5.7 7.2 (0.0 – 19)

*Format of cells: mean ± SD, median, (range)

Table 3

Parameter	Delavirdine geometric means ratio (90% CI) (400 mg TID with SQV vs. 400 mg TID without SQV)
Cmax	0.84 (0.47, 1.53)
Cmin	1.19 (0.46, 3.11)
AUC	0.95 (0.48, 1.90)

Table 4

Conclusion:

Coadministration of saquinavir soft gel capsule with delavirdine in HIV-1 infected patients did not change the steady-state pharmacokinetics of delavirdine. However, delavirdine significantly increased saquinavir plasma concentrations. The applicant should include these results in the updated label.

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Clinical Pharmacology 1b

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