CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-779 / S-042
20-778 / S-022
21-503 / S-001

Trade Name: Viracept

Generic Name: (nelfinavir mesylate)

Sponsor: Pfizer Inc.

Approval Date: March 19, 2004

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20-779 / S-042
20-778 / S-022
21-503 / S-001

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-779/SE5-042 (250 mg tablets)
NDA 20-778/SE5-022 (oral powder)
NDA 21-503/SE5-001 (625 mg tablets)

Pfizer Inc.
Attn: Phyllis M. Christesen, Senior Director/Team Leader
US Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Christesen:

Please refer to your supplemental new drug applications dated June 19, 2003, received June 20, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viracept® (nelfinavir mesylate) 250 mg tablets, oral powder, and 625 mg tablets.

We acknowledge receipt of your submissions dated:

August 1, 2003	October 30, 2003	March 10, 2004
August 21, 2003	November 5, 2003	March 12, 2004
September 2, 2003	December 19, 2003	March 16, 2004
September 25, 2003	February 16, 2004	
October 22, 2003	February 20, 2004	
October 23, 2003	March 5, 2004	

In addition we acknowledge your submissions emailed to us on March 16, and 17, and 18, 2004.

These supplemental new drug applications provide for the use of Viracept® (nelfinavir mesylate) 250 mg tablets and oral powder in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients from two to thirteen years of age.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert, dated March 18, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission

should be designated **"FPL for approved supplement NDA 20-779/S-042, NDA 20-778/S-022, 21-503/S-001".** Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jeff O'Neill, Regulatory Project Manager, at (301) 827 2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure Approved Draft Labeling (product package insert and patient package insert)

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

/s/

Debra Birnkrant
3/19/04 02:22:45 PM
NDA 20-779, 21-503, 20-778

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-779 / S-042
20-778 / S-022
21-503 / S-001

LABELING

69-6003-00-7.1

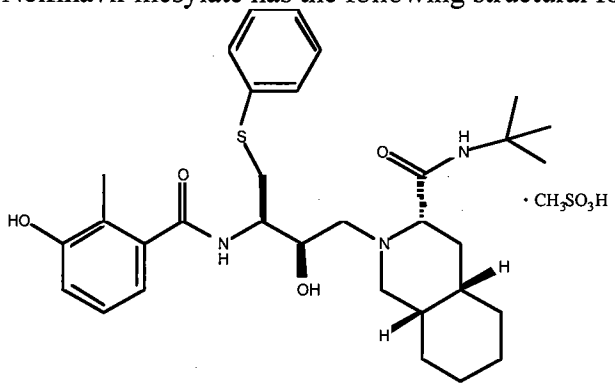
AGOURON PHARMACEUTICALS, INC.
La Jolla, CA 92037, USA

VIRACEPT®

(nelfinavir mesylate)
TABLETS and ORAL POWDER

DESCRIPTION

VIRACEPT® (nelfinavir mesylate) is an inhibitor of the human immunodeficiency virus (HIV) protease. VIRACEPT Tablets are available for oral administration as a light blue, capsule-shaped tablet with a clear film coating in 250 mg strength (as nelfinavir free base) and as a white oval tablet with a clear film coating in 625 mg strength (as nelfinavir free base). Each tablet contains the following common inactive ingredients: calcium silicate, crospovidone, magnesium stearate, hypromellose, and triacetin. In addition, the 250 mg tablet contains FD&C blue #2 powder and the 625 mg tablet contains colloidal silicon dioxide. VIRACEPT Oral Powder is available for oral administration in a 50 mg/g strength (as nelfinavir free base) in bottles. The oral powder also contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hypromellose, aspartame, sucrose palmitate, and natural and artificial flavor. The chemical name for nelfinavir mesylate is [3*S*-[2(2*S**, 3*S**), 3α,4aβ,8aβ]]-*N*-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinoline carboxamide mono-methanesulfonate (salt) and the molecular weight is 663.90 (567.79 as the free base). Nelfinavir mesylate has the following structural formula:



Nelfinavir mesylate is a white to off-white amorphous powder, slightly soluble in water at pH ≤4 and freely soluble in methanol, ethanol, 2-propanol and propylene glycol.

MICROBIOLOGY

Mechanism of Action: Nelfinavir is an inhibitor of the HIV-1 protease. Inhibition of the viral protease prevents cleavage of the *gag* and *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Antiviral Activity In Vitro: The antiviral activity of nelfinavir *in vitro* has been demonstrated in both acute and/or chronic HIV infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against several laboratory strains and clinical isolates of HIV-1 and the HIV-2 strain ROD. The EC_{95} (95% effective concentration) of

nelfinavir ranged from 7 to 196 nM. Drug combination studies with protease inhibitors showed nelfinavir had antagonistic interactions with indinavir, additive interactions with ritonavir or saquinavir and synergistic interactions with amprenavir and lopinavir. Minimal to no cellular cytotoxicity was observed with any of these protease inhibitors alone or in combination with nelfinavir. In combination with reverse transcriptase inhibitors, nelfinavir demonstrated additive (didanosine or stavudine) to synergistic (abacavir, delavirdine, efavirenz, lamivudine, nevirapine, tenofovir, zalcitabine or zidovudine) antiviral activity *in vitro* without enhanced cytotoxicity.

Drug Resistance: HIV-1 isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. HIV isolates from selected patients treated with nelfinavir alone or in combination with reverse transcriptase inhibitors were monitored for phenotypic (n=19) and genotypic (n=195, 157 of which were evaluable) changes in clinical trials over a period of 2 to 82 weeks. One or more viral protease mutations at amino acid positions 30, 35, 36, 46, 71, 77 and 88 were detected in the HIV-1 of >10% of patients with evaluable isolates. The overall incidence of the D30N mutation in the viral protease of evaluable isolates (n=157) from patients receiving nelfinavir monotherapy or nelfinavir in combination with zidovudine and lamivudine or stavudine was 54.8%. The overall incidence of other mutations associated with primary protease inhibitor resistance was 9.6% for the L90M substitution whereas substitutions at 48, 82, or 84 were not observed. Of the 19 clinical isolates for which both phenotypic and genotypic analyses were performed, 9 showed reduced susceptibility (5- to 93-fold) to nelfinavir *in vitro*. All 9 patient isolates possessed one or more mutations in the viral protease gene. Amino acid position 30 appeared to be the most frequent mutation site.

Cross-resistance: *Non-clinical Studies-* Patient-derived recombinant HIV isolates containing the D30N mutation (n=4) and demonstrating high-level (>10-fold) NFV-resistance remained susceptible (<2.5-fold resistance) to amprenavir, indinavir, lopinavir, and saquinavir, *in vitro*. Patient-derived recombinant HIV isolates containing the L90M mutation (n=8) demonstrated moderate to high-level resistance to NFV and had varying levels of susceptibility to amprenavir, indinavir, lopinavir, and saquinavir, *in vitro*. Most patient-derived recombinant isolates with phenotypic and genotypic evidence of reduced susceptibility (>2.5-fold) to amprenavir, indinavir, lopinavir, and/or saquinavir demonstrated high-level cross-resistance to nelfinavir, *in vitro*. Mutations associated with resistance to other PIs (e.g. G48V, V82A/F/T, I84V, L90M) appeared to confer high-level cross-resistance to NFV. Following ritonavir therapy 6 of 7 clinical isolates with decreased ritonavir susceptibility (8- to 113-fold) *in vitro* compared to baseline also exhibited decreased susceptibility to nelfinavir *in vitro* (5- to 40-fold). Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because different enzyme targets are involved. Clinical isolates (n=5) with decreased susceptibility to lamivudine, nevirapine or zidovudine remain fully susceptible to nelfinavir *in vitro*.

Clinical Studies- There have been no controlled or comparative studies evaluating the virologic response to subsequent protease inhibitor-containing regimens in patients who have demonstrated loss of virologic response to a nelfinavir-containing regimen. However, virologic response was evaluated in a single-arm prospective study of 26 patients with extensive prior antiretroviral experience with reverse transcriptase inhibitors (mean 2.9) who had received VIRACEPT for a mean duration of 59.7 weeks and were switched to a ritonavir (400 mg BID)/saquinavir hard-gel (400 mg BID) containing regimen after a prolonged period of VIRACEPT failure (median 48 weeks). Sequence analysis of HIV-1 isolates prior to switch demonstrated a D30N or an L90M substitution in 18 and 6 patients, respectively. Subjects remained on therapy for a mean of 48 weeks (range 40 to 56 weeks) where 17 of 26 (65%) subjects and 13 of 26 (50%) subjects were treatment responders with HIV RNA below the assay limit of detection (<500 HIV RNA copies/mL, Chiron bDNA) at 24 and 48 weeks, respectively.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetic properties of nelfinavir were evaluated in healthy volunteers and HIV-infected patients; no substantial differences were observed between the two groups.

Absorption: Pharmacokinetic parameters of nelfinavir (area under the plasma concentration-time curve during a 24-hour period at steady-state [AUC_{24}], peak plasma concentrations [C_{max}], morning and evening trough concentrations [C_{trough}]) from a pharmacokinetic study in HIV-positive patients after multiple dosing with 1250 mg (five 250 mg tablets) twice daily (BID) for 28 days (10 patients) and 750 mg (three 250 mg tablets) three times daily (TID) for 28 days (11 patients) are summarized in Table 1.

Table 1
Summary of a Pharmacokinetic Study in HIV-positive Patients with Multiple Dosing of 1250 mg BID for 28 days and 750 mg TID for 28 days

Regimen	AUC_{24} mg.h/L	C_{max} mg/L	C_{trough} Morning mg/L	C_{trough} AFTERNOON OR EVENING mg/L
1250 mg BID	52.8 ± 15.7	4.0 ± 0.8	2.2 ± 1.3	0.7 ± 0.4
750 mg TID	43.6 ± 17.8	3.0 ± 1.6	1.4 ± 0.6	1.0 ± 0.5

data are mean ± SD

The difference between morning and afternoon or evening trough concentrations for the TID and BID regimens was also observed in healthy volunteers who were dosed at precisely 8- or 12-hour intervals.

In healthy volunteers receiving a single 1250 mg dose, the 625 mg tablet was not bioequivalent to the 250 mg tablet formulation. Under fasted conditions (n=27), the AUC and C_{max} were 34% and 24% higher, respectively, for the 625 mg tablets. In a relative bioavailability assessment under fed conditions (n=28), the AUC was 24% higher for the 625 mg tablet; the C_{max} was comparable for both formulations. (See ADVERSE REACTIONS).

IN HEALTHY VOLUNTEERS RECEIVING A SINGLE 750 MG DOSE UNDER FED CONDITIONS, NELFINAVIR CONCENTRATIONS WERE SIMILAR FOLLOWING ADMINISTRATION OF THE 250 MG TABLET AND ORAL POWDER.

Effect of Food on Oral Absorption: Food increases nelfinavir exposure and decreases nelfinavir pharmacokinetic variability relative to the fasted state. Healthy volunteers received a single dose of 1250 mg of VIRACEPT 250 mg tablets (5 tablets) under fasted or fed conditions (three different meals). Results from the study are summarized in Table 2.

Table 2
Changes in AUC, C_{max} and T_{max} for Nelfinavir in Fed State Relative to Fasted State Following 1250 mg VIRACEPT (5 x 250 mg tablets)

Number of Kcal	% Fat	Number of subjects	AUC fold increase	C_{max} fold increase	Increase in T_{max} (hr)
125	20	n=21	2.2	2.0	1.00
500	20	n=22	3.1	2.3	2.00
1000	50	n=23	5.2	3.3	2.00

A food effect study has not been conducted with the 625 mg tablet. However, based on a cross-study comparison (n=26 fed vs. n=26 fasted) following single dose administration of nelfinavir

1250 mg, the magnitude of the food effect for the 625 mg nelfinavir tablet appears comparable to that of the 250 mg tablets. VIRACEPT should be taken with a meal.

Distribution: The apparent volume of distribution following oral administration of nelfinavir was 2-7 L/kg. Nelfinavir in serum is extensively protein-bound (>98%).

Metabolism: Unchanged nelfinavir comprised 82-86% of the total plasma radioactivity after a single oral 750 mg dose of ^{14}C-nelfinavir. *In vitro*, multiple cytochrome P-450 enzymes including CYP3A and CYP2C19 are responsible for metabolism of nelfinavir. One major and several minor oxidative metabolites were found in plasma. The major oxidative metabolite has *in vitro* antiviral activity comparable to the parent drug.

Elimination: The terminal half-life in plasma was typically 3.5 to 5 hours. The majority (87%) of an oral 750 mg dose containing ^{14}C-nelfinavir was recovered in the feces; fecal radioactivity consisted of numerous oxidative metabolites (78%) and unchanged nelfinavir (22%). Only 1-2% of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

Special Populations

Hepatic Insufficiency: The multi-dose pharmacokinetics of nelfinavir have not been studied in HIV-positive patients with hepatic insufficiency.

Renal Insufficiency: The pharmacokinetics of nelfinavir have not been studied in patients with renal insufficiency; however, less than 2% of nelfinavir is excreted in the urine, so the impact of renal impairment on nelfinavir elimination should be minimal.

Gender and Race: No significant pharmacokinetic differences have been detected between males and females. Pharmacokinetic differences due to race have not been evaluated.

Pediatrics: The pharmacokinetics of nelfinavir have been investigated in 5 studies in pediatric patients from birth to 13 years of age either receiving VIRACEPT three times or twice daily. The dosing regimens and associated AUC_{24} values are summarized in Table 3.

Table 3
Summary of Steady-state AUC_{24} of Nelfinavir in Pediatric Studies

Protocol No.	Dosing Regimen[1]	N[2]	Age (years)	AUC_{24} (mg.hr/L) Arithmetic mean ± SD
AG1343-524	20 (19-28) mg/kg TID	14	2-13 years	56.1 ± 29.8
PACTG 725	55 (48-60) mg/kg BID	6	3 –11 years	101.8 ± 56.1
PENTA 7	40 (34-43) mg/kg TID	4	2-9 months	33.8 ± 8.9
PENTA 7	75 (55-83) mg/kg BID	12	2-9 months	37.2 ± 19.2
PACTG 353	40 (14 –56) mg/kg BID	10	6 weeks	44.1±27.4
			1 week	45.8 ± 32.1

[1] Protocol specified dose (actual dose range)
[2] N: number of subjects with evaluable pharmacokinetic results
C_{trough} values are not presented in the table because they are not available for all studies

Pharmacokinetic data are also available for 86 patients (age 2 to 12 years) who received VIRACEPT 25-35 mg/kg TID in Study AG1343-556. The pharmacokinetic data from Study AG1343-556 were more variable than data from other studies conducted in the pediatric population; the 95% confidence interval for AUC_{24} was 9 to 121 mg.hr/L.

Overall, use of VIRACEPT in the pediatric population is associated with highly variable drug exposure. The high variability may be due to inconsistent food intake in pediatric patients. (see PRECAUTIONS Pediatric USE; DOSAGE AND ADMINISTRATION).

Geriatric Patients: The pharmacokinetics of nelfinavir have not been studied in patients over 65 years of age.

Drug Interactions (also see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions)

CYP3A and CYP2C19 appear to be the predominant enzymes that metabolize nelfinavir in humans. The potential ability of nelfinavir to inhibit the major human cytochrome P450 enzymes (CYP3A, CYP2C19, CYP2D6, CYP2C9, CYP1A2 and CYP2E1) has been investigated *in vitro*. Only CYP3A was inhibited at concentrations in the therapeutic range. Specific drug interaction studies were

performed with nelfinavir and a number of drugs. Table 4 summarizes the effects of nelfinavir on the geometric mean AUC, C_{max} and C_{min} of coadministered drugs. Table 5 shows the effects of coadministered drugs on the geometric mean AUC, C_{max} and C_{min} of nelfinavir.

Table 4: Drug Interactions:
Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of VIRACEPT

Coadministered Drug	Nelfinavir Dose	N	% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
			AUC	C_{max}	C_{min}
HIV-Protease Inhibitors					
Indinavir 800 mg Single Dose	750 mg q8h x 7 days	6	↑51% (↑29-↑77%)	↓10% (↓28-↑13%)	NA
Ritonavir 500 mg Single Dose	750 mg q8h x 5 doses	10	↔	↔	NA
Saquinavir 1200 mg Single Dose [2]	750 mg tid x 4 days	14	↑392% (↑291-↑521%)	↑179% (↑117-↑259%)	NA
Amprenavir 800 mg tid x 14 days	750 mg tid x 14 days	6	↔	↓14% (↓38-↑20%)	↑189% (↑52-↑448%)
Nucleoside Reverse Transcriptase Inhibitors					
Lamivudine 150 mg Single Dose	750 mg q8h x 7-10 days	11	↑10% (↑2-↑18%)	↑31% (↑9-↑56%)	NA
Stavudine 30-40 mg bid x 56 days	750 mg tid x 56 days	8	See footnote [3]		
Zidovudine 200 mg Single Dose	750 mg q8h x 7-10 days	11	↓35% (↓29-↓40%)	↓31% (↓13-↓46%)	NA
Non-Nucleoside Reverse Transcriptase Inhibitors					
Efavirenz 600 mg qd x 7 days	750 mg q8h x 7 days	10	↓12% (↓31-↑12%)	↓12% (↓29-↑8%)	↓22% (↓54-↑32%)
Nevirapine 200 mg qd x 14 days [3] Followed by 200 mg bid x 14 days	750 mg tid x 36 days	23	See footnote [3]		
Delavirdine 400 mg q8h x 14 days	750 mg q8h x 7 days	7	↓31% (↓57-↑10%)	↓27% (↓49-↑4%)	↓33% (↓70-↑49%)
Anti-infective Agents					
Rifabutin 150 mg qd x 8 days [4]	750 mg q8h x 7-8 days [5]	12	↑83% (↑72-↑96%)	↑19% (↑11-↑28%)	↑177% (↑144-↑215%)
Rifabutin 300 mg qd x 8 days	750 mg q8h x 7-8 days	10	↑207% (↑161-↑263%)	↑146% (↑118-↑178%)	↑305% (↑245-↑375%)
Azithromycin 1200 mg Single Dose	750 mg tid x 11 days	12	↑112% (↑80-↑150%)	↑136% (↑77-↑215%)	NA

HMG-CoA Reductase Inhibitors					
Atorvastatin 10 mg qd x 28 days	1250 mg bid x 14 days	15	↑74% (↑41-↑116%)	↑122% (↑68-↑193%)	↑39% (↓21-↑145%)
Simvastatin 20 mg qd x 28 days	1250 mg bid x 14 days	16	↑505% (↑393-↑643%)	↑517% (↑367-↑715%)	ND
Other Agents					
Ethinyl estradiol 35 µg qd x 15 days	750 mg q8h x 7 days	12	↓47% (↓42-↓52%)	↓28% (↓16-↓37%)	↓62% (↓57-↓67%)
Norethindrone 0.4 mg qd x 15 days	750 mg q8h x 7 days	12	↓18% (↓13-↓23%)	↔	↓46% (↓38-↓53%)
Methadone 80 mg +/- 21 mg qd [6] > 1 month	1250 mg bid x 8 days	13	↓47% (↓42-↓51%)	↓46% (↓42-↓49%)	↓53% (↓49-↓57%)
Phenytoin 300 mg qd x 14 days [7]	1250 mg bid x 7 days	12	↓29% (↓17-↓39%)	↓21% (↓12-↓29%)	↓39% (↓27-↓49%)

NA: Not relevant for single-dose treatment; ND: Cannot be determined

[1] ↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change (geometric mean exposure increased or decreased < 10%)

[2] Using the soft-gelatin capsule formulation of saquinavir 1200 mg

[3] Based on non-definitive cross-study comparison, drug plasma concentrations appeared to be unaffected by coadministration

[4] Rifabutin 150 mg qd changes are relative to Rifabutin 300 mg qd x 8 days without coadministration with nelfinavir

[5] Comparable changes in rifabutin concentrations were observed with VIRACEPT 1250 mg q12h x 7 days

[6] Changes are reported for total plasma methadone; changes for the individual R-enantiomer and S-enantiomer were similar

[7] Phenytoin exposure measures are reported for total phenytoin exposure. The effect of nelfinavir on unbound phenytoin was similar

Table 5: Drug Interactions:
Changes in Pharmacokinetic Parameters for Nelfinavir in the Presence of the Coadministered Drug

Coadministered Drug	Nelfinavir Dose	N	% Change of Nelfinavir Pharmacokinetic Parameters[1] (90% CI)		
			AUC	C_{max}	C_{min}
HIV-Protease Inhibitors					
Indinavir 800 mg q8h x 7 days	750 mg Single Dose	6	↑83% (↑42-↑137%)	↑31% (↑16-↑48%)	NA
Ritonavir 500 mg q12h x 3 doses	750 mg Single Dose	10	↑152% (↑96-↑224%)	↑44% (↑28-↑63%)	NA
Saquinavir 1200 mg tid x 4 days [2]	750 mg Single Dose	14	↑18% (↑7-↑30%)	↔	NA
Amprenavir 800 mg tid x 14 days	750 mg tid x 14 days	6	See footnote [3]		
Nucleoside Reverse Transcriptase Inhibitors					
Didanosine 200 mg Single Dose	750 mg Single Dose	9	↔	↔	NA
Zidovudine 200 mg + Lamivudine 150 mg Single Dose	750 mg q8h x 7-10 days	11	↔	↔	↔
Non-Nucleoside Reverse Transcriptase Inhibitors					
Efavirenz 600 mg qd x 7 days	750 mg q8h x 7 days	7	↑20% (↑8-↑34%)	↑21% (↑10-↑33%)	↔
Nevirapine 200 mg qd x 14 days Followed by 200 mg bid x 14 days	750 mg tid x 36 days	23	↔	↔	↓32% (↓50-↑5%)
Delavirdine 400 mg q8h x 7 days	750 mg q8h x 14 days	12	↑107% (↑83-↑135%)	↑88% (↑66-↑113%)	↑136% (↑103-↑175%)
Anti-infective Agents					
Ketoconazole 400 mg qd x 7 days	500 mg q8h x 5-6 days	12	↑35% (↑24-↑46%)	↑25% (↑11-↑40%)	↑14% (↓23-↑69%)
Rifabutin 150 mg qd x 8 days	750 mg q8h x 7-8 days	11	↓23% (↓14-↓31%)	↓18% (↓8-↓27%)	↓25% (↓8-↓39%)
	1250 mg q12h x 7-8 days	11	↔	↔	↓15% (↓43-↑27%)
Rifabutin 300 mg qd x 8 days	750 mg q8h x 7-8 days	10	↓32% (↓15-↓46%)	↓24% (↓10-↓36%)	↓53% (↓15-↓73%)
Rifampin 600 mg qd x 7 days	750 mg q8h x 5-6 days	12	↓83% (↓79-↓86%)	↓76% (↓69-↓82%)	↓92% (↓86-↓95%)
Azithromycin 1200 mg Single Dose	750 mg tid x 9 days	12	↓15% (↓7-↓22%)	↓10% (↓19-↑1%)	↓29% (↓19-↓38%)

HMG-CoA Reductase Inhibitors					
Atorvastatin 10 mg qd x 28 days	1250 mg bid x 14 days	15	See footnote [3]		
Simvastatin 20 mg qd x 28 days	1250 mg bid x 14 days	16	See footnote [3]		
Other Agents					
Methadone 80 mg + / - 21 mg qd > 1 month	1250 mg bid x 8 days	13	See footnote [3]		
Phenytoin 300 mg qd x 7 days	1250 mg bid x 14 days	15	↔	↔	↓18% (↓45-↑23%)

NA: Not relevant for single-dose treatment

[1] ↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change (geometric mean exposure increased or decreased < 10%)

[2] Using the soft-gelatin capsule formulation of saquinavir 1200 mg

[3] Based on non-definitive cross-study comparison, nelfinavir plasma concentrations appeared to be unaffected by coadministration

For information regarding clinical recommendations see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions.

INDICATIONS AND USAGE

VIRACEPT in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Description of Studies

In the clinical studies described below, efficacy was evaluated by the percent of patients with plasma HIV RNA < 400 copies/mL (Studies 511 and 542) or < 500 copies/mL (Study ACTG 364), using the Roche RT-PCR (Amplicor) HIV-1 Monitor or < 50 copies/mL, using the Roche HIV-1 Ultrasensitive assay (Study Avanti 3). In the analysis presented in each figure, patients who terminated the study early for any reason, switched therapy due to inadequate efficacy or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 400 copies/mL, above 500 copies/mL, or above 50 copies/mL at subsequent time points, depending on the assay that was used.

a. Studies in Antiretroviral Treatment Naïve Patients

Study 511: VIRACEPT + zidovudine + lamivudine versus zidovudine + lamivudine

Study 511 was a double-blind, randomized, placebo controlled trial comparing treatment with zidovudine (ZDV; 200 mg TID) and lamivudine (3TC; 150 mg BID) plus 2 doses of VIRACEPT (750 mg and 500 mg TID) to zidovudine (200 mg TID) and lamivudine (150 mg BID) alone in 297 antiretroviral naive HIV-1 infected patients (median age 35 years [range 21 to 63], 89% male and 78% Caucasian). Mean baseline CD4 cell count was 288 cells/mm^3 and mean baseline plasma HIV RNA was 5.21 log_{10} copies/mL (160,394 copies/mL). The percent of patients with plasma HIV RNA < 400 copies/mL and mean changes in CD4 cell count are summarized in Figures 1 and 2, respectively.

Figure 1

Study 511: Percentage of Patients With HIV RNA Below 400 Copies/mL

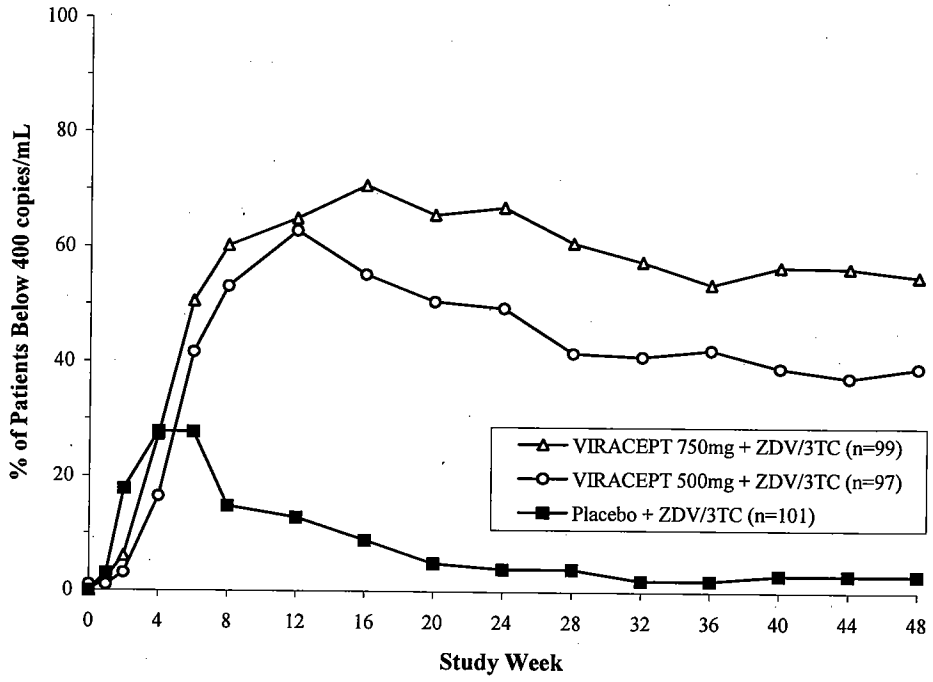
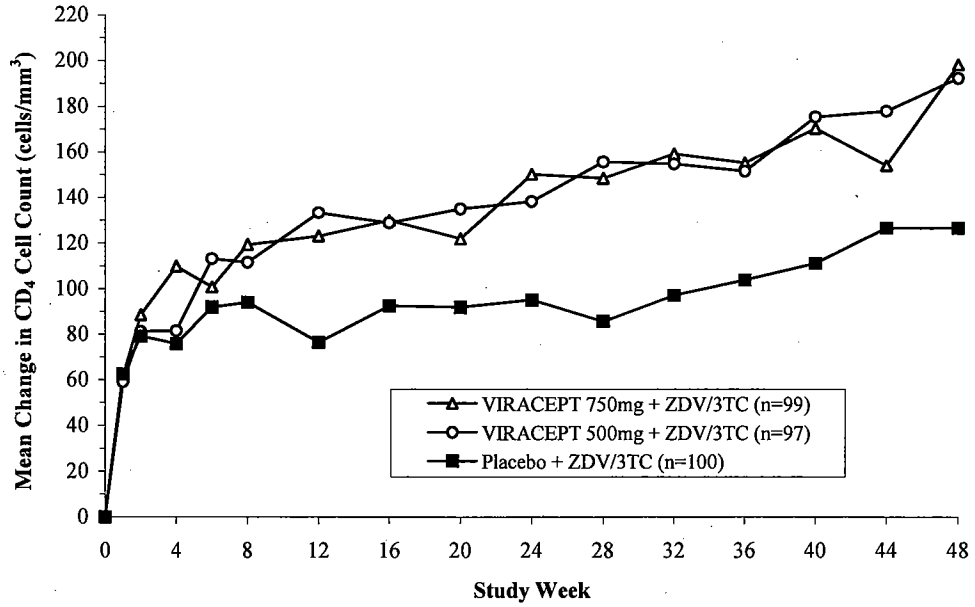


Figure 2

Study 511: Mean Change From Baseline in CD_4 Cell Counts



Study 542: VIRACEPT BID + stavudine + lamivudine compared to VIRACEPT TID + stavudine + lamivudine

Study 542 is an ongoing, randomized, open-label trial comparing the HIV RNA suppression achieved by VIRACEPT 1250 mg BID versus VIRACEPT 750 mg TID in patients also receiving stavudine (d4T; 30-40 mg BID) and lamivudine (3TC; 150 mg BID). Patients had a median age of 36 years (range 18 to 83), were 84% male, and were 91% Caucasian. Patients had received less than 6 months of therapy with nucleoside transcriptase inhibitors and were naïve to protease inhibitors. Mean baseline CD4 cell count was 296 cells/mm^3 and mean baseline plasma HIV RNA was 5.0 $\log_{10}$ copies/mL (100,706 copies/mL).

Results showed that there was no significant difference in mean CD4 cell count among treatment groups; the mean increases from baseline for the BID and TID arms were 150 cells/mm^3 at 24 weeks and approximately 200 cells/mm^3 at 48 weeks.

The percent of patients with HIV RNA < 400 copies/mL is summarized in Figure 3. The outcomes of patients through 48 weeks of treatment are summarized in Table 6.

Figure 3

Study 542: Percentage of Patients With HIV RNA Below 400 Copies/mL

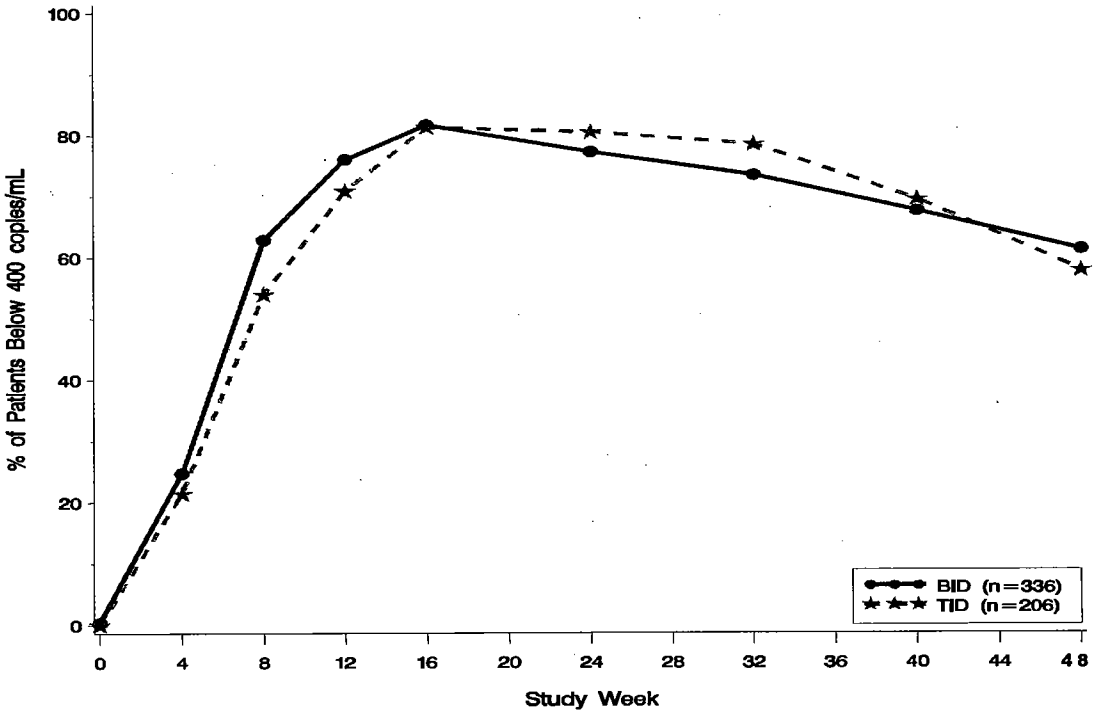


Table 6
Outcomes of Randomized Treatment Through 48 Weeks

Outcome	VIRACEPT 1250 mg BID Regimen	VIRACEPT 750 mg TID Regimen
Number of patients evaluable*	323	192
HIV RNA < 400 copies/mL	198 (61%)	111 (58%)
HIV RNA ≥ 400 copies/mL	46 (14%)	22 (11%)
Discontinued due to VIRACEPT toxicity**	9 (3%)	2 (1%)
Discontinued due to other antiretroviral agents' toxicity**	3 (1%)	3 (2%)
Others***	67 (21%)	54 (28%)

*Twelve patients in the BID arm and fourteen patients in the TID arm have not yet reached 48 weeks of therapy.
**These rates only reflect dose-limiting toxicities that were counted as the initial reason for treatment failure in the analysis (see ADVERSE REACTIONS for a description of the safety profile of these regimens).
***Consent withdrawn, lost to follow-up, intercurrent illness, noncompliance or missing data; all assumed as failures.

STUDY AVANTI 3: VIRACEPT TID + ZIDOVUDINE + LAMIVUDINE COMPARED TO ZIDOVUDINE + LAMIVUDINE

Study Avanti 3 was a placebo-controlled, randomized, double-blind study designed to evaluate the safety and efficacy of VIRACEPT (750 mg TID) in combination with zidovudine (ZDV; 300 mg BID) and lamivudine (3TC; 150 mg BID) (n=53) versus placebo in combination with ZDV and 3TC (n=52) administered to antiretroviral-naive patients with HIV infection and a CD4 cell count between 150 and 500 cells/μL. Patients had a mean age of 35 (range 22-59), were 89% male, and 88% Caucasian. Mean baseline CD4 cell count was 304 cells/mm^3 and mean baseline plasma HIV RNA was 4.8 $\log_{10}$ copies/mL (57,887 copies/mL). The percent of patients with plasma HIV RNA < 50 copies/mL at 52 weeks was 54% for the VIRACEPT + ZDV + 3TC treatment group and 13% for the ZDV + 3TC treatment group.

b. Studies in Antiretroviral Treatment Experienced Patients

STUDY ACTG 364: VIRACEPT TID + 2NRTIS COMPARED TO EFAVIRENZ + 2NRTIS COMPARED TO VIRACEPT + EFAVIRENZ + 2NRTIS

Study ACTG 364 was a randomized, double-blind study that evaluated the combination of VIRACEPT 750 mg TID and/or efavirenz 600 mg QD with 2 NRTIs (either didanosine [ddI] + d4T, ddI + 3TC, or d4T + 3TC) in patients with prolonged prior nucleoside exposure who had completed 2 previous ACTG studies. Patients had a mean age of 41 years (range 18 to 75), were 88% male, and were 74% Caucasian. Mean baseline CD4 cell count was 389 cells/mm^3 and mean baseline plasma HIV RNA was 3.9 $\log_{10}$ copies/mL (7,954 copies/mL).

The percent of patients with plasma HIV RNA < 500 copies/mL at 48 weeks was 42%, 62%, and 72% for the VIRACEPT (n=66), EFV (n=65), and VIRACEPT + EFV (n=64) treatment groups, respectively. The 4-drug combination of VIRACEPT + EFV + 2 NRTIs was more effective in suppressing plasma HIV RNA in these patients than either 3-drug regimen.

CONTRAINDICATIONS

VIRACEPT is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Coadministration of VIRACEPT is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 7.

Table 7
Drugs That Are Contraindicated With VIRACEPT

Drug Class	Drugs Within Class That Are Contraindicated With VIRACEPT
Antiarrhythmics	Amiodarone, Quinidine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
Neuroleptic	Pimozide
Sedative/Hypnotics	Midazolam, Triazolam

WARNINGS

ALERT: Find out about medicines that should not be taken with VIRACEPT. This statement is included on the product's bottle label.

Drug Interactions (also see PRECAUTIONS)

Nelfinavir is an inhibitor of the CYP3A enzyme. Coadministration of VIRACEPT and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects. Caution should be exercised when inhibitors of CYP3A, including VIRACEPT, are coadministered with drugs that are metabolized by CYP3A and that prolong the QT interval. (See ADVERSE REACTIONS; Post-Marketing Experience). Nelfinavir is metabolized by CYP3A and CYP2C19. Coadministration of VIRACEPT and drugs that induce CYP3A or CYP2C19 may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Coadministration of VIRACEPT and drugs that inhibit CYP3A or CYP2C19 may increase nelfinavir plasma concentrations. (Also see **PRECAUTIONS: Table 8: Drugs That Should Not Be Coadministered With VIRACEPT - Table 9: Established and Other Potentially Significant Drug Interactions With VIRACEPT.**)

Concomitant use of VIRACEPT with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including VIRACEPT, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A pathway (e.g., atorvastatin). (Also see **Tables 4 and 5: Drug Interactions**). The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including VIRACEPT, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving protease inhibitors, including VIRACEPT. Coadministration of a protease inhibitor with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. (See PRECAUTIONS, Drug Interactions and Information for Patients, and the complete prescribing information for sildenafil.)

Concomitant use of St. John's wort (hypericum perforatum) or St. John's wort containing products and VIRACEPT is not recommended. Coadministration of St. John's wort with protease inhibitors, including VIRACEPT, is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of VIRACEPT and lead to loss of virologic response and possible resistance to VIRACEPT or to the class of protease inhibitors.

Patients with Phenylketonuria

Patients with Phenylketonuria: VIRACEPT Oral Powder contains 11.2 mg phenylalanine per gram of powder.

Diabetes mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

General

Nelfinavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with hepatic impairment.

Resistance/Cross Resistance

HIV cross-resistance between protease inhibitors has been observed. (See MICROBIOLOGY.)

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information For Patients

A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with VIRACEPT**. A Patient Package Insert (PPI) for VIRACEPT is available for patient information.

For optimal absorption, patients should be advised to take VIRACEPT with food (see CLINICAL PHARMACOLOGY: Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Patients should be informed that VIRACEPT is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections.

Patients should be told that there is currently no data demonstrating that VIRACEPT therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should be advised to take VIRACEPT and other concomitant antiretroviral therapy every day as prescribed. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of VIRACEPT is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should be informed that VIRACEPT Tablets are film-coated and that this film-coating is intended to make the tablets easier to swallow.

The most frequent adverse event associated with VIRACEPT is diarrhea, which can usually be controlled with non-prescription drugs, such as loperamide, which slow gastrointestinal motility.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

VIRACEPT may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients receiving oral contraceptives should be instructed that alternate or additional contraceptive measures should be used during therapy with VIRACEPT.

Patients receiving sildenafil and nelfinavir should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and prolonged penile erection, and should promptly report any symptoms to their doctor.

Drug Interactions (Also see CONTRAINDICATIONS, WARNINGS, CLINICAL PHARMACOLOGY: Drug Interactions)

Nelfinavir is an inhibitor of CYP3A. Coadministration of VIRACEPT and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects. (See Tables 8 and 9). Nelfinavir is metabolized by CYP3A and CYP2C19. Coadministration of VIRACEPT and drugs that induce CYP3A or CYP2C19, such as rifampin, may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Coadministration of VIRACEPT and drugs that inhibit CYP3A or CYP2C19 may increase nelfinavir plasma concentrations.

Drug interaction studies reveal no clinically significant drug interactions between nelfinavir and didanosine, lamivudine, stavudine, zidovudine, efavirenz, nevirapine, or ketoconazole and no dose adjustments are needed. In the case of didanosine, it is recommended that didanosine be administered on an empty stomach; therefore, nelfinavir should be administered with food one hour after or more than 2 hours before didanosine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between VIRACEPT and dapsone, trimethoprim/sulfamethoxazole, or itraconazole.

Table 8
Drugs That Should Not Be Coadministered With VIRACEPT

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: amiodarone, quinidine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to VIRACEPT or other coadministered antiretroviral agents.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to VIRACEPT or other coadministered antiretroviral agents.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 9
Established and Other Potentially Significant Drug Interactions:
Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies
(see CLINICAL PHARMACOLOGY, for Magnitude of Interaction, Tables 4 and 5)

Concomitant Drug Class: ***Drug Name***	***Effect on Concentration***	**Clinical Comment**
HIV-Antiviral Agents		
Protease Inhibitors: indinavir	↑ nelfinavir ↑ indinavir	Appropriate doses for these combinations, with respect to safety and efficacy, have not been established.
ritonavir	↑ nelfinavir	
saquinavir	↑ saquinavir	
Non-nucleoside Reverse Transcriptase Inhibitors: delavirdine	↑ nelfinavir ↓ delavirdine	Appropriate doses for these combinations, with respect to safety and efficacy, have not been established.
nevirapine	↓ nelfinavir (C_{min})	
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after VIRACEPT (given with food).
Other Agents		
Anti-Convulsants: carbamazepine phenobarbital	↓ nelfinavir	May decrease nelfinavir plasma concentrations. VIRACEPT may not be effective due to decreased nelfinavir plasma concentrations in patients taking these agents concomitantly.
Anti-Convulsant: phenytoin	↓ phenytoin	Phenytoin plasma/serum concentrations should be monitored; phenytoin dose may require adjustment to compensate for altered phenytoin concentration.

Anti-Mycobacterial: rifabutin	↑ rifabutin ↓ nelfinavir (750 mg TID) ↔ nelfinavir (1250 mg BID)	It is recommended that the dose of rifabutin be reduced to one-half the usual dose when administered with VIRACEPT; 1250 mg BID is the preferred dose of VIRACEPT when coadministered with rifabutin.
Erectile Dysfunction Agent: sildenafil	↑ sildenafil	Sildenafil should not exceed a maximum single dose of 25 mg in a 48 hour period.
HMG-CoA Reductase Inhibitor: atorvastatin	↑ atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with VIRACEPT.
Immuno-suppressants: cyclosporine tacrolimus sirolimus	↑ immuno-suppressants	Plasma concentrations may be increased by VIRACEPT.
Narcotic Analgesic: methadone	↓ methadone	Dosage of methadone may need to be increased when coadministered with VIRACEPT.
Oral Contra-ceptive: ethinyl estradiol	↓ ethinyl estradiol	Alternative or additional contraceptive measures should be used when oral contraceptives and VIRACEPT are coadministered.
Macrolide Antibiotic: azithromycin	↑ azithromycin	Dose adjustment of azithromycin is not recommended, but close monitoring for known side effects such as liver enzyme abnormalities and hearing impairment is warranted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats have been conducted with nelfinavir at doses of 0, 100, 300, and 1000 mg/kg/day via oral gavage. Thyroid follicular cell adenomas and carcinomas were increased in male rats at 300 mg/kg/day and higher and in female rats at 1000 mg/kg/day. The systemic exposures (C_{max}) at 300 and 1000 mg/kg/day were 1- to 3-fold, respectively, of those measured in humans at the recommended therapeutic dose (750 mg TID or 1250 mg BID). The mechanism of nelfinavir-induced tumorogenesis in rats is unknown. However, nelfinavir showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* genetic toxicology assays. These studies included bacterial mutation assays in *S. typhimurium* and *E. coli,* a mouse lymphoma tyrosine kinase assay, a chromosomal aberration assay in human lymphocytes, and an *in vivo* mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of nelfinavir, the relevance to humans of neoplasms in nelfinavir-treated rats is not known.

Nelfinavir produced no effects on either male or female mating and fertility or embryo survival in rats at systemic exposures comparable to the human therapeutic exposure.

Pregnancy - Pregnancy Category B

There were no effects on fetal development or maternal toxicity when nelfinavir was administered to pregnant rats at systemic exposures (AUC) comparable to human exposure. Administration of nelfinavir to pregnant rabbits resulted in no fetal development effects up to a dose at which a slight decrease in maternal body weight was observed; however, even at the highest dose evaluated, systemic exposure in rabbits was significantly lower than human exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir. However, there are no adequate and well-controlled studies in pregnant women taking VIRACEPT. Because animal reproduction studies are not always predictive of human response, VIRACEPT should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: (APR): To monitor maternal-fetal outcomes of pregnant women exposed to VIRACEPT and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats have demonstrated that nelfinavir is excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIRACEPT.**

Pediatric Use

The safety and effectiveness of VIRACEPT have been established in patients from 2 to 13 years of age. The use of VIRACEPT in these age groups is supported by evidence from adequate and well-controlled studies of VIRACEPT in adults and pharmacokinetic studies and studies supporting activity in pediatric patients. In patients less than 2 years of age, VIRACEPT was found to be safe at the doses studied but a reliably effective dose could not be established (see CLINICAL PHARMACOLOGY:

Special Populations, ADVERSE REACTIONS: Pediatric Population, and DOSAGE AND ADMINISTRATION: Pediatric Patients).

The following issues should be considered when initiating VIRACEPT in pediatric patients:

- In pediatric patients ≥ 2 years of age receiving VIRACEPT as part of triple combination antiretroviral therapy in randomized studies, the proportion of patients achieving an HIV RNA level <400 copies/mL through 48 weeks ranged from 26% to 42%.

- Response rates in children <2 years of age appeared to be poorer than those in patients ≥ 2 years of age in some studies.

- Highly variable drug exposure remains a significant problem in the use of VIRACEPT in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing. Pharmacokinetic results from the pediatric studies are reported in Table 3 (see Clinical Pharmacology, Special Populations).

Study 556 was a randomized, double-blind, placebo-controlled trial with VIRACEPT or placebo coadministered with ZDV and ddI in 141 HIV-positive children who had received minimal antiretroviral therapy. The mean age of the children was 3.9 years. 94 (67%) children were between 2 - 12 years, and 47 (33%) were < 2 years of age. The mean baseline HIV RNA value was 5.0 log for all patients and the mean CD4 cell count was 886 cells/mm^3 for all patients. The efficacy of VIRACEPT measured by HIV RNA <400 at 48 weeks in children ≥ 2 years of age was 26% compared to 2% of placebo patients (p= 0.0008). In the children < 2 years of age, only 1 of 27 and 2 out of 20 maintained an undetectable HIV RNA level at 48 weeks for placebo and VIRACEPT patients respectively.

PACTG 377 was an open-label study that randomized 181 HIV treatment-experienced pediatric patients to receive: d4T+NVP+RTV, d4T+3TC+NFV, d4T+NVP+NFV, or d4T+3TC+NVP+NFV with NFV given on a TID schedule. The median age was 5.9 years and 46% were male. At baseline the median HIV RNA was 4.4 log and median CD4 cell count was 690 cells/mm^3. Substudy PACTG 725 evaluated d4T+3TC+NFV with NFV given on a BID schedule. The proportion of patients with detectable viral load at baseline achieving HIV RNA <400 copies/mL at 48 weeks was: 41% for d4T+NVP+RTV, 42% for d4T+3TC+NFV, 30% for d4T+NVP+NFV, and 52% for d4T+3TC+NVP+NFV. No significant clinical differences were identified between patients receiving VIRACEPT in BID or TID schedules.

VIRACEPT has been evaluated in 2 studies of young infants. The PENTA 7 study was an open-label study to evaluate the toxicity, tolerability, pharmacokinetics, and activity of NFV+d4T+ddI in 20 HIV-infected infants less than 12 weeks of age. PACTG 353 evaluated the pharmacokinetics and safety of VIRACEPT in infants born to HIV-infected women receiving NFV as part of combination therapy during pregnancy.

Geriatric Use

Clinical studies of VIRACEPT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

The safety of VIRACEPT was studied in over 5000 patients who received drug either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving VIRACEPT was diarrhea, which was generally of mild to moderate intensity. The frequency of nelfinavir-associated diarrhea may be increased in patients receiving the 625 mg tablet because of the increased bioavailability of this formulation.

Drug-related clinical adverse experiences of moderate or severe intensity in ≥ 2% of patients treated with VIRACEPT coadministered with d4T and 3TC (Study 542) for up to 48 weeks or with ZDV plus 3TC (Study 511) for up to 24 weeks are presented in Table 10.

Table 10
Percentage of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Patients

	Study 511 24 weeks			**Study 542 48 weeks**	
Adverse Events	Placebo + ZDV/3TC (n=101)	500 mg TID VIRACEPT + ZDV/3TC (n=97)	750 mg TID VIRACEPT + ZDV/3TC (n=100)	1250 mg BID VIRACEPT + d4T/3TC (n=344)	750 mg TID VIRACEPT + d4T/3TC (n=210)
Digestive System					
Diarrhea	3%	14%	20%	20%	15%
Nausea	4%	3%	7%	3%	3%
Flatulence	0	5%	2%	1%	1%
Skin/Appendages					
Rash	1%	1%	3%	2%	1%

[1] Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions

Adverse events occurring in less than 2% of patients receiving VIRACEPT in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.

Body as a Whole: abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain, and redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Digestive System: anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.

Hemic/Lymphatic System: anemia, leukopenia and thrombocytopenia.

Metabolic/Nutritional System: increases in alkaline phosphatase, amylase, creatine phosphokinase, lactic dehydrogenase, SGOT, SGPT and gamma glutamyl transpeptidase; hyperlipemia, hyperuricemia, hyperglycemia, hypoglycemia, dehydration, and liver function tests abnormal.
Musculoskeletal System: arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.
Nervous System: anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paresthesia, seizures, sleep disorder, somnolence and suicide ideation.
Respiratory System: dyspnea, pharyngitis, rhinitis, and sinusitis.
Skin/Appendages: dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria.
Special Senses: acute iritis and eye disorder.
Urogenital System: kidney calculus, sexual dysfunction and urine abnormality.

Post-Marketing Experience

The following additional adverse experiences have been reported from postmarketing surveillance as at least possibly related or of unknown relationship to VIRACEPT:
Body as a Whole: hypersensitivity reactions (including bronchospasm, moderate to severe rash, fever and edema)
Cardiovascular System: QTc prolongation, torsades de pointes
Digestive System: jaundice
Metabolic/Nutritional System: bilirubinemia, metabolic acidosis

Laboratory Abnormalities

The percentage of patients with marked laboratory abnormalities in Studies 542 and 511 are presented in Table 11. Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline.

Table 11
Percentage of Patients by Treatment Group With Marked Laboratory Abnormalities [1] in > 2% of Patients

	Study 511			Study 542	
	Placebo + ZDV/3TC (n=101)	500 mg TID VIRACEPT + ZDV/3TC (n=97)	750 mg TID VIRACEPT + ZDV/3TC (n=100)	1250 mg BID VIRACEPT + d4T/3TC (n=344)	750 mg TID VIRACEPT + d4T/3TC (n=210)
Hematology					
Hemoglobin	6%	3%	2%	0	0
Neutrophils	4%	3%	5%	2%	1%
Lymphocytes	1%	6%	1%	1%	0
Chemistry					
ALT (SGPT)	6%	1%	1%	2%	1%
AST (SGOT)	4%	1%	0	2%	1%
Creatine Kinase	7%	2%	2%	NA	NA

[1] Marked laboratory abnormalities are defined as a shift from Grade 0 at baseline to at least Grade 3 or from Grade 1 to Grade 4

Pediatric Population

VIRACEPT has been studied in approximately 400 pediatric patients in clinical trials from birth to 13 years of age. The adverse event profile seen during pediatric clinical trials was similar to that for adults.

The most commonly reported drug-related, treatment-emergent adverse events reported in the pediatric studies included: diarrhea, leukopenia/neutropenia, rash, anorexia, and abdominal pain. Diarrhea, regardless of assigned relationship to study drug, was reported in 39% to 47% of pediatric patients receiving VIRACEPT in 2 of the larger treatment trials. Leukopenia/neutropenia was the laboratory abnormality most commonly reported as a significant event across the pediatric studies.

OVERDOSAGE

Human experience of acute overdose with VIRACEPT is limited. There is no specific antidote for overdose with VIRACEPT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since nelfinavir is highly protein bound, dialysis is unlikely to significantly remove drug from blood.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose is 1250 mg (five 250 mg tablets or two 625 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily. VIRACEPT should be taken with a meal. Patients unable to swallow the 250 or 625 mg tablets may dissolve the tablets in a small amount of water. Once

dissolved, patients should mix the cloudy liquid well, and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure the entire dose is consumed.

Pediatric Patients (2-13 years): In children 2 years of age and older, the recommended oral dose of VIRACEPT oral powder or 250 mg tablets is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily. All doses should be taken **with a meal.** Doses higher than the adult maximum dose of 2500 mg per day have not been studied in children. For children unable to take tablets, VIRACEPT Oral Powder may be administered. The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk or dietary supplements; once mixed, the entire contents must be consumed in order to obtain the full dose. If the mixture is not consumed immediately, it must be stored under refrigeration, but storage must not exceed 6 hours. Acidic food or juice (e.g., orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT, because the combination may result in a bitter taste. VIRACEPT Oral Powder should not be reconstituted with water in its original container.

The healthcare provider should assess appropriate formulation and dosage for each patient. Crushed 250 mg tablets can be used in lieu of powder. Tables 12 and 13 provide dosing guidelines for VIRACEPT tablets and powder based on age and body weight.

Table 12
Dosing Table for Children ≥ 2 years of age (tablets)

Body Weight		**Twice Daily (BID) 45 - 55 mg/kg ≥2 years**	**Three Times Daily (TID) 25 - 35 mg/kg ≥2 years**
		# of tablets (250 mg)	# of tablets (250 mg)
Kg.	**Lbs.**		
10 - 12	**22 –26.4**	2	1
13 - 18	**28.6 – 39.6**	3	2
19 - 20	**41.8 - 44**	4	2
≥21	**≥46.2**	4-5[1]	3[2]

[1] For BID dosing, the maximum dose per day is 5 tablets BID
[2] For TID dosing, the maximum dose per day is 3 tablets TID

Table 13
Dosing Table for children ≥2 years of age (powder)

Body Weight		**Twice Daily (BID) 45-55 mg/kg**		**Three Times Daily (TID) 25-35 mg/kg**	
Kg.	Lbs.	Scoops of Powder (50 mg/1 g)	Teaspoons [1] of Powder	Scoops of Powder (50 mg/1 g)	Teaspoons [1] of Powder
9.0 to < 10.5	20 to < 23	10	2 1/2	6	1 1/2
10.5 to < 12	23 to < 26.5	11	2 3/4	7	1 3/4
12 to < 14	26.5 to < 31	13	3 1/4	8	2
14 to < 16	31 to < 35	15	3 3/4	9	2 1/4
16 to < 18	35 to < 39.5	Not recommended [2]	Not recommended [2]	10	2 1/2
18 to < 23	39.5 to < 50.5	Not recommended [2]	Not recommended [2]	12	3
≥ 23	≥ 50.5	Not recommended [2]	Not recommended [2]	15	3 3/4

1 If a teaspoon is used to measure VIRACEPT oral powder, 1 level teaspoon contains 200 mg of VIRACEPT (4 level scoops equals 1 level teaspoon)

2 Use VIRACEPT 250 mg tablet

HOW SUPPLIED

VIRACEPT (nelfinavir mesylate) 250 mg: Light blue, capsule-shaped tablets with a clear film coating engraved with "VIRACEPT" on one side and "250 mg" on the other.

Bottles of 300, 250 mg tablets.....NDC 63010-010-30

VIRACEPT (nelfinavir mesylate) 625 mg: White oval tablet with a clear film coating engraved with "V" on one side and "625" on the other.

Bottles of 120, 625 mg tablets.....NDC 63010-027-70

VIRACEPT (nelfinavir mesylate) Oral Powder is available as a 50 mg/g off-white powder containing 50 mg (as nelfinavir free base) in each level scoopful (1 gram).

Multiple use bottles of 144 grams of powder with scoop .....NDC 63010-011-90

VIRACEPT TABLETS AND ORAL POWDER SHOULD BE STORED AT 15° TO 30°C (59° TO 86°F).

Keep container tightly closed. Dispense in original container.

RX only

VIRACEPT and Agouron are registered trademarks of Agouron Pharmaceuticals, Inc.

23-6004-00-5.1
Agouron Pharmaceuticals, Inc.
VIRACEPT®
Patient Prescribing Information

[logo]

VIRACEPT® (nelfinavir mesylate) TABLETS and ORAL POWDER

ALERT: Find out about medicines that should NOT be taken with VIRACEPT. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH VIRACEPT".

Patient Information

VIRACEPT® (VI-ra-cept)
Generic Name: nelfinavir (nel-FIN-na-veer) mesylate

Please read this information carefully before taking VIRACEPT. Also, please read this leaflet each time you renew the prescription, in case anything has changed. This is a summary and not a replacement for a careful discussion with your healthcare provider. You and your healthcare provider should discuss VIRACEPT when you start taking this medication and at regular checkups. You should remain under a healthcare provider's care when taking VIRACEPT and should not change or stop treatment without first talking with your healthcare provider.

What is VIRACEPT and how does it work?

VIRACEPT is a type of medicine called an HIV (human immunodeficiency virus) protease (PRO-tee-ase) inhibitor. VIRACEPT is always used in combination with other antiretroviral drugs in the treatment of people with HIV infection. VIRACEPT is for adults and for children 2 years of age and older.

Infection with HIV leads to the destruction of CD4 (T) cells, which are important to the immune system. After a large number of CD4 (T) cells have been destroyed, the infected person develops acquired immune deficiency syndrome (AIDS).

VIRACEPT works by blocking HIV protease (a protein-cutting enzyme), which is required for HIV to multiply. VIRACEPT has been shown to significantly reduce the amount of HIV in the blood. Although VIRACEPT is not a cure for HIV or AIDS, VIRACEPT can help reduce your risk for death and illness associated with HIV. Patients who took VIRACEPT also had significant increases in the number of CD4 (T) cells.

Does VIRACEPT cure HIV or AIDS?

VIRACEPT is not a cure for HIV infection or AIDS. People taking VIRACEPT may still develop opportunistic infections or other conditions associated with HIV infection. Some of these conditions are pneumonia, herpes virus infections, *Mycobacterium avium* complex (MAC) infections, and Kaposi's sarcoma.

Does VIRACEPT reduce the risk of passing HIV to others?

VIRACEPT does not reduce the risk of transmitting HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

How should I take VIRACEPT?

- You should stay under a healthcare provider's care when taking VIRACEPT. Do not change your treatment or stop treatment without first talking with your healthcare provider.

- You must take VIRACEPT every day exactly as your healthcare provider prescribed it. Follow the directions from your healthcare provider, exactly as written on the label.

- Dosing in adults (including children 14 years of age and older): The recommended adult dose of VIRACEPT is 1250 mg (five 250 mg tablets or two 625 mg tablets) taken two times a day or 750 mg (three 250 mg tablets) taken three times a day. **Each dose should always be taken with a meal** to help achieve higher VIRACEPT levels. VIRACEPT Tablets are film-coated to help make the tablets easier to swallow.

- Dosing in children 2 years of age and older: The VIRACEPT dose in children depends on their weight. The recommended oral dose of VIRACEPT oral powder or 250 mg tablets is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily. All doses should be taken **with a meal.** Children who cannot swallow tablets may take VIRACEPT Oral Powder or crushed tablets.

- If you or your child is unable to swallow the tablets, dissolve the tablets in a small amount of water. Once dissolved, mix the cloudy liquid well, and consume immediately. The glass should be rinsed with water and the rinse swallowed to ensure the entire dose is consumed.

- **Do not change your dose or stop taking VIRACEPT without first consulting with your healthcare provider.**

- When your VIRACEPT supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to antiretroviral medications, including VIRACEPT, but there are other antiretroviral treatment options. Talk to your healthcare provider about how to optimize your long-term treatment.

- Be sure to set up a schedule and follow it carefully.

- Only take medicine that has been prescribed specifically for you. Do not give VIRACEPT to others or take medicine prescribed for someone else.

How should VIRACEPT Oral Powder be prepared?

- The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk, dietary supplements, or dairy foods such as pudding or ice cream. Once mixed, the entire amount must be taken to obtain the full dose. If the mixture is not consumed immediately, it must be stored under refrigeration, but storage must not exceed 6 hours. Do **not** heat the mixed dose once it has been prepared.

- Do **not** mix the powder with any acidic food or juice, such as orange or grapefruit juice, apple juice, or apple sauce, because this may create a bitter taste.

- Do **not** add water to bottles of oral powder.

- VIRACEPT powder is supplied with a scoop for measuring. For help in determining the exact dose of powder for your child, please ask your doctor, nurse, pharmacist, or other healthcare provider.

What should I do if I miss a dose?

If you forget to take a dose of VIRACEPT, take it as soon as possible. However, if you skip the dose entirely, do not double the next dose. If you forget a lot of doses, talk to your healthcare provider about how you should continue taking your medicine.

What happens if I take too much VIRACEPT?

If you suspect that you took more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately.

Who should not take VIRACEPT?

Together with your healthcare provider, you need to decide whether VIRACEPT is appropriate for you.

- **Do not take VIRACEPT if you are taking certain medicines.** These could cause serious side effects that could cause death. Before you take VIRACEPT, you must tell your healthcare provider about all medicines you are taking or are planning to take. These include prescription and non-prescription medicines and herbal supplements.

For more information about medicines you should not take with VIRACEPT, please read the section titled "**MEDICINES YOU SHOULD NOT TAKE WITH VIRACEPT**."

- **Do not take VIRACEPT if you have an allergy to VIRACEPT.** Also tell your healthcare provider if you have any known allergies to other medicines, foods, preservatives, or dyes.

- **Tell your healthcare provider if you are pregnant or plan to become pregnant.** The effects of VIRACEPT on pregnant women or their unborn babies are not known.

- If you are breast-feeding, it is very important that you speak with your healthcare provider about the best way to feed your baby. If your baby does not already have HIV, there is a chance that it can be transmitted through breast-feeding. **The Centers for Disease Control and Prevention recommends that women with HIV do not breast-feed.**

- **Talk with your healthcare provider if you have liver or kidney disease.** VIRACEPT has not been extensively studied in people with liver or kidney disease.

- **Certain medical problems may affect the use of VIRACEPT.** Be sure to tell your healthcare provider of any other medical problems you may have.

Can VIRACEPT be taken with other medications?

VIRACEPT may interact with other drugs, including those you take without a prescription. You must tell your healthcare provider about all medicines you are taking or planning to take before you take VIRACEPT. It is a good idea to keep a complete list of all the medicines that you take, including non-prescription medicines, herbal remedies and supplements and street drugs. Update this list when medicines are added or stopped. Give copies of this list to all of your healthcare providers **every** time you visit or fill a prescription.

MEDICINES YOU SHOULD NOT TAKE WITH VIRACEPT:
Do not take the following drugs because they can cause serious problems or death if taken with VIRACEPT:

- Cordarone® (amiodarone) (for irregular heartbeat)
- Orap® (pimozide) (for seizures)
- Quinidine® (for irregular heartbeat), also known as Quinaglute®, Cardioquin®, Quinidex®, and others
- D.H.E. 45® Injection, Ergomar®, Migranal® ,Wigraine® and Cafergot® (for migraine headaches) and Methergine® (for bleeding after childbirth)
- Halcion® (triazolam) (for sleep problem)
- Versed® (midazolam) (sedative hypnotic)

Do not take the following medicines when you take VIRACEPT. They may reduce the levels of VIRACEPT in the blood and make it less effective. Talk with your healthcare provider if you are currently taking these medicines because other medicines may have to be given to take their place:

- Rifampin® (also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®) (for tuberculosis)
- Phenobarbital (for seizures)
- Tegretol® (carbamazepine) (for seizures)

Do not take VIRACEPT with St. John's wort (hypericum perforatum), an herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your healthcare provider if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease VIRACEPT levels and lead to increased viral load and possible resistance to VIRACEPT.

Do not take VIRACEPT with cholesterol-lowering medicines Mevacor® (lovastatin) or Zocor® (simvastatin) because of possible serious reactions. There is also an increased risk of drug interactions between VIRACEPT and Lipitor® (atorvastatin) and Lescol® (fluvastatin); talk to your healthcare provider before you take any of these cholesterol-reducing medicines with VIRACEPT.

Talk to your healthcare provider before you start taking any new prescription or non-prescription medicines or herbal supplements with VIRACEPT.

Medicines that require dose adjustments:

It is possible that your healthcare provider may need to increase or decrease the dose of other medicines when you are also taking VIRACEPT.

BEFORE YOU TAKE VIAGRA® (SILDENAFIL) WITH VIRACEPT, TALK TO YOUR HEALTHCARE PROVIDER ABOUT POSSIBLE DRUG INTERACTIONS AND SIDE EFFECTS. IF YOU TAKE VIAGRA AND VIRACEPT TOGETHER, YOU MAY BE AT INCREASED RISK OF SIDE EFFECTS OF VIAGRA SUCH AS LOW BLOOD PRESSURE, VISUAL CHANGES, AND PENILE ERECTION LASTING MORE THAN 4 HOURS. IF AN ERECTION LASTS LONGER THAN 4 HOURS, YOU

SHOULD SEEK IMMEDIATE MEDICAL ASSISTANCE TO AVOID PERMANENT DAMAGE TO YOUR PENIS. YOUR HEALTHCARE PROVIDER CAN EXPLAIN THESE SYMPTOMS TO YOU.

- **If you are taking both didanosine (Videx®) and VIRACEPT:**
  YOU SHOULD TAKE VIRACEPT WITH FOOD ONE HOUR AFTER OR MORE THAN TWO HOURS BEFORE YOU TAKE VIDEX BUFFERED TABLETS.

- IF YOU ARE TAKING ORAL CONTRACEPTIVES ("THE PILL") TO PREVENT PREGNANCY, YOU SHOULD USE AN ADDITIONAL OR DIFFERENT TYPE OF CONTRACEPTION SINCE VIRACEPT MAY REDUCE THE EFFECTIVENESS OF ORAL CONTRACEPTIVES.

- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** RESCRIPTOR® (delavirdine) may increase the amount of VIRACEPT in your blood and VIRACEPT may lower the amount of RESCRIPTOR in your blood.

- **Protease Inhibitors (PIs):** VIRACEPT may increase the amount of Crixivan® (indinavir), Norvir® (ritonavir), and Invirase® or Fortovase® (saquinavir) in your blood. As a result, your healthcare provider may choose to lower the dose of VIRACEPT or one of these other medicines or monitor certain lab tests if VIRACEPT is taken in combination with one or more of these other medicines.

- If you are taking Mycobutin® (rifabutin), your healthcare provider may lower the dose of Mycobutin.

- If you are taking Dilantin® (phenytoin), your healthcare provider will need to monitor the levels of phenytoin in your blood and may need to adjust the dose of phenytoin.

- **Other Special considerations**

  VIRACEPT Oral Powder contains aspartame, a low-calorie sweetener, and therefore should not be taken by children with phenylketonuria (PKU).

What are the possible side effects of VIRACEPT?

- This list of side effects is not complete. If you have questions about side effects, ask your healthcare provider, nurse, or pharmacist. You should report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects. Most of the side effects experienced with VIRACEPT have been mild to moderate.

- Diarrhea is the most common side effect in people taking VIRACEPT, and most adult patients had at least mild diarrhea at some point during treatment. In clinical studies, about 15-20% of patients receiving VIRACEPT 750 mg (three 250 mg tablets) three times daily or 1250 mg (five 250 mg tablets or two 625 mg tablets) two times daily had four or more loose stools a day. Diarrhea may be more common in patients receiving the 625 mg formulation. In most cases, VIRACEPT-associated diarrhea can be controlled using antidiarrheal medicines, such as Imodium® A-D (loperamide).

- Other side effects that occurred in 3-7% of patients receiving VIRACEPT include nausea, gas, and rash.

- The side effects observed in children and adults receiving VIRACEPT are similar. Diarrhea was also the most common side effect seen in children. Some children experienced low white blood cells (leukopenia/neutropenia), which improved without stopping VIRACEPT in most cases.

- Diabetes and high blood sugar (hyperglycemia) occur in patients taking protease inhibitors such as VIRACEPT. Some patients had diabetes before starting protease inhibitors, others did not. Some patients needed changes in their diabetes medicine. Others needed new diabetes medicine after starting their VIRACEPT medicine.

- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

- Some patients with hemophilia have increased bleeding with protease inhibitors.

- There were other side effects, some of them serious, noted in clinical studies that occurred in less than 2% of patients receiving VIRACEPT. However, these side effects may have been due to other drugs that patients were taking or to the illness itself. Except for diarrhea, there were not many differences in side effects in patients who took VIRACEPT along with other drugs compared with those who took only the other drugs.

- Before you start using any medicine, talk with your healthcare provider about what to expect and discuss ways to reduce the side effects you may have.

How should VIRACEPT be stored?

- Keep VIRACEPT and all other medicines out of the reach of children.

- Keep bottle closed and store at room temperature (between 59°F and 86°F) away from sources of moisture such as a sink or other damp place. Heat and moisture may reduce the effectiveness of VIRACEPT.

- Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

- Store in original container.

General advice about prescription medicines

Discuss all questions about your health with your healthcare provider. If you have questions about VIRACEPT or any other medication you are taking, ask your doctor, nurse, pharmacist, or other healthcare provider. You can also call 1.888.VIRACEPT (1.888.847.2237) toll free.

[icon/logo] **Agouron®**
Pharmaceuticals Inc.
La Jolla, California, 92037, USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-779 / S-042
20-778 / S-022
21-503 / S-001

MEDICAL REVIEW

Clinical Review

NDA 20-778, SE5-022
NDA 20-779, SE5-042
NDA 21- 503, SE5-001

Date submitted: June 19, 2003

Amendments submitted:

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Applicant:

Agouron Pharmaceuticals, Inc.
A Pfizer Company
10777 Science Center Drive
San Diego, CA 92121

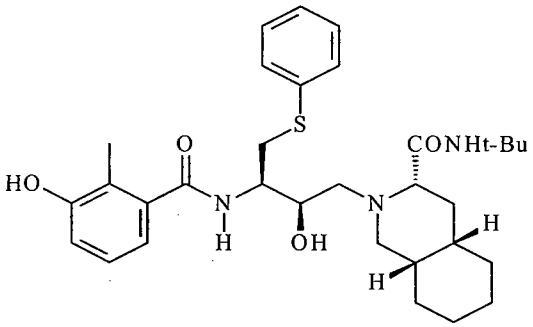
Drug name: Nelfinavir mesylate (Viracept®)

Formulation:

250 and 625 mg tablets
Oral powder 50 mg/g

Indication: Treatment of HIV infection in combination with other antiretroviral drugs

Chemical structure:



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Clinical Review for NDA 20-778, SE5-022, NDA 20-779, SE5-042, NDA 21-503, SE5-001

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This efficacy supplement to NDA 20-778 (and also NDAs 20-779 and 21-503) containing pharmacokinetic (PK), safety, and activity data regarding the use of nelfinavir mesylate (Viracept, NFV) in HIV-infected pediatric patients should be approved. NFV was previously granted approval for use as part of combination antiretroviral treatment in adults and in pediatric patients 2 years of age and older. The dose originally approved in pediatric patients was 20-30 mg/kg TID but there have been clinical concerns that this dose resulted in frequent virologic failure. The current supplement presented additional data confirming that doses of 25-35 mg/kg TID or 45-55 mg/kg BID provided NFV exposure associated with clinical evidence of activity over 48 weeks of dosing in patients 2 to 13 years of age. In this age group, HIV RNA levels decreased over time and CD4 cell counts increased in all groups receiving NFV in combination with other drugs. In the only randomized, placebo-controlled, pediatric study (Study 556), a significantly greater proportion of patients receiving NFV achieved virologic response over 48 weeks than those receiving placebo (21% vs. 3%). For patients less than 2 years of age, a reliably effective dose of NFV could not be determined due to marked variability in drug exposure and efficacy results poorer than those documented in older children.

The studied doses of NFV produced an acceptable tolerability and safety profile across the pediatric age range. While adverse events were common in the study populations, relatively few were considered drug-related (diarrhea being the exception), relatively few were severe in intensity or required discontinuation of study drug, and many were attributable to common childhood illnesses or conditions. As was seen in the adult treatment trials, the most common adverse event associated with NFV was diarrhea, reported in up to 39-47% of pediatric patients. Neutropenia/leukopenia was the most commonly observed significant laboratory abnormality, occurring as a Grade 3 or 4 abnormality in 14-16% in some of the submitted studies. Lesser degrees of neutropenia occurred in up to 70% of patients < 3 months of age who received NFV in the submitted studies. Laboratory abnormalities rarely led to discontinuation of NFV.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There were no recommendations for additional Phase 4 studies or risk management steps based on review of this supplement.

The review team considered the variability in NFV exposure the greatest barrier to achieving efficacy in pediatric patients. Inadequate drug exposure may lead to failure of virologic suppression of HIV and emergence of resistance. The product label was revised to contain statements emphasizing this variablility in NFV exposure observed in the pediatric studies and the difficulties encountered maintaining adherence and adequate food intake in the pediatric population.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

NFV is an oral protease inhibitor approved in both tablet and powder formulations for the treatment of HIV infection in patients 2 years of age or older. This supplement presented additional clinical and PK data on the use of NFV as part of combination drug regimens for the treatment of HIV infection in pediatric patients. Five studies were submitted for review. These included: Study 524 (enrolling ages < 3 months to 13 years, N=65), Study 556 (ages 3 months to 12 years, N=141), PACTG 377 (ages 4 months to 17 years, N=181) with its PK substudy PACTG 725 (ages 3 to 11 years, N=12), PENTA-7 (age < 3 months, N=20), and PACTG 353 (neonates, N=31). These studies covered the pediatric age range from birth to 13 years of age using a variety of different NFV doses and schedules (for details of study design and dose schedules see Section VI, C, Detailed Review of Trials by Indication and Appendix B of the Clinical Review). Studies 524 and 556 were conducted by Agouron. PACTG 377/725 and PACTG 353 were conducted by the Pediatric AIDS Clinical Trials Group, Division of AIDS, NIH, and PENTA-7 was conducted by the Paediatric European Network for the Treatment of AIDS, all in collaboration with Agouron.

B. Efficacy

Collectively, the four pediatric treatment studies provide evidence of NFV's activity as part of a combination antiretroviral regimen for pediatric patients. All of the studies document that pediatric patients receiving NFV achieved significant mean decreases in HIV RNA levels over time and most also achieved increases in CD4 cell counts or percentages. These surrogate endpoints have been shown to predict improved clinical outcome in other antiretroviral drug studies. However, because of the differences in study design, doses and regimens studied, and age groups studied it was difficult to identify an effective dose in all age groups.

Only one of the studies, Study 556, provided efficacy results from a randomized, blinded study that allowed analysis of the contribution of NFV to the success or failure of a multi-drug regimen. This study compared NFV (TID) + ZDV + ddI to placebo + ZDV + ddI in patients with minimal prior treatment over a 48 week study period. In this study, the NFV-containing regimen clearly performed better than the placebo regimen with a greater proportion of patients achieving and maintaining HIV RNA < 400 copies/mL (21% compared to 3%, p=0.0002) and the NFV patients achieving a longer median time to loss of virologic response (122 days compared to 0, p=0.0026). PACTG 377, evaluated 4 different 3- and 4-drug combinations of antiretroviral agents in a randomized, open-label study design and the substudy PACTG 725 allowed comparison of similar BID and TID NFV regimens. None of the regimens provide a direct comparison of TID NFV to another PI or NNRTI, however, the NFV-containing arms of the study achieved undetectable HIV RNA levels in 30% to 52% of patients. In the small substudy PACTG 725 evaluating the BID NFV regimen, 55% of patients achieved HIV RNA < 400 copies/mL at 48 weeks.

While the benefit of NFV was demonstrated with these studies, the magnitude of the virologic response rate at 48 weeks in pediatric patients was generally less than expected, particularly that observed in Study 556. Efficacy in treatment-naïve adults receiving NFV in a 3-drug regimen has been demonstrated to be about 60% after 48 weeks. Response rates for patients less than 2 years of age appeared to be significantly worse than those in patients 2 years of age and older in Study 556 and reached only 37% in infants < 3 months in PENTA-7, the study administering the highest doses of NFV. Consequently, associations between the doses studied and a reasonable level of effectiveness could not be concluded for all age groups. Although the applicant proposed dose recommendations for pediatric patients from

The review team identified several factors that may explain the low response rates observed in the pediatric trials submitted. Some of the studies (Study 556, PENTA-7) failed to achieve the adult target NFV exposure. Study 556 produced PK data that were the most variable of any of the studies submitted. This variability in the PK in this population may have accounted for the low proportion of patients who achieved durable virologic response in this study and it limited the interpretability of the PK data. Also, patients enrolled in some pediatric studies had median HIV RNA levels at baseline (5.0 to 5.5 log) that were higher than those generally seen in adult studies. Finally, these studies were designed and initiated between 1997-99 at a time when treatment-experienced pediatric patients did not always receive an optimized, resistance-minimizing background regimen of antiretroviral drugs in addition to the study drug.

C. Safety

The safety database for assessment of NFV in patients across the pediatric age range from birth to 13 years of age was adequate. A total of 302 patients received NFV in the 4 pediatric treatment trials (Studies 524, 556, PACTG 377/725, and PENTA-7) for up to 96 weeks. The primary safety review was conducted over 48 weeks of study drug dosing in these studies. Another 31 HIV-exposed neonates were evaluated for safety after 3rd trimester prenatal exposure and 6 weeks of infant dosing. Across the pediatric studies, the safety profile of NFV was generally similar to that previously described in adults and in the small number of children presented in the original NDA. Although minor differences were noted in individual studies, no major differences in the safety profile for NFV could be identified in different pediatric age groups. Serious adverse events were rarely considered related to NFV and no deaths were attributed to the drug.

As in adults, the most commonly reported side effect was diarrhea. Because of differences in study reporting it was difficult to determine the frequency of diarrhea attributable to NFV. In Study 556 in which it was combined with ddI, another drug known to be associated with diarrhea, 39% to 43% of patients in the NFV and placebo arms, respectively, reported some degree of diarrhea. Moderate to severe diarrhea was reported in 6-11% of patients enrolled in Studies 524 and 556 and "gastrointestinal events" of moderate to severe intensity were reported in 18-27% of the patients receiving a NFV-containing regimen in PACTG 377/725. In studies of NFV in adults, higher rates of diarrhea have been correlated with higher drug exposures. Because of the marked variability of drug exposure found in the pediatric studies, no exposure-response relationship for diarrhea could be identified in children.

Neutropenia/leukopenia occurred more frequently in the pediatric studies than was observed in the adult clinical trials. Study 556 was the only study not reporting Grade 3 or 4 neutropenia in patients receiving NFV. Neutropenia was defined and reported differently across the studies, with some reporting "neutropenia" as an AE while in others it was included in the laboratory data analysis. In PACTG 353 and PENTA-7, some degree of neutropenia was reported in 40-70% of infants enrolled using very conservative cut-off values for all grades of neutropenia in infants < 3 months of age. Neutropenia was also reported in studies enrolling older children, with Grade 3 or 4 abnormalities reported in 14-16% of patients in Studies 524 and PACTG 377. Again, no exposure-response relationship could be identified for neutropenia.

Because all studies administered NFV as part of combination antiretroviral therapy, it was difficult to determine the exact contribution of NFV to any clinical or laboratory toxicity. Many of the approved antiretroviral drugs have overlapping toxicity profiles so it is possible that drugs such as ddI may have

contributed to diarrhea in some studies or that ZDV may have contributed to neutropenia in some.

D. Dosing

The applicant proposed NFV dose recommendations of 25-35 mg/kg TID or [redacted] or patients from 2 to 13 years of age and dose recommendations of [redacted] Additionally, a dose of [redacted] as proposed for neonates. The review team agreed with the applicant's proposed dose of 25-35 mg/kg TID for children 2 years of age or older but recommended a lower dose of 45-55 mg/kg BID in this age group. We also agreed that dose recommendations in pediatric patients applied to both the oral powder and 250 mg tablet formulations. As noted above, the review team could not confirm reliably effective dose recommendations for children < 2 years.

The PK profile of NFV has been characterized in adults receiving both TID and BID dosing schedules. The adult approved doses have been correlated with clinical efficacy in large treatment trials. The goal of the pediatric PK studies was to achieve the same NFV exposure, as measured by AUC_{24}, that was associated with efficacy in adults (AUC_{24} of 44 to 53 mg*h/L for TID and BID regimens, respectively). The most important PK characteristic of NFV is the remarkable variability of exposure. This variability appears to be greater in children than in adults. Variability in drug exposure appears to be due to the marked drug-food effect observed with NFV. The effect of food on NFV exposure varies depending on meal content with higher calorie/higher fat meals increasing exposure more than low calorie/low fat meals. Consequently, it is recommended that all doses of NFV be taken with a meal.

In patients 2 to 13 years of age, the weight of clinical and PK evidence from 3 treatment studies (Studies 524, 556 and PACTG 377) supported the proposed dose of 25-35 mg/kg TID, a slight change from the originally approved dose in this age group. In PACTG 725 evaluating the BID regimen of NFV, the mean NFV exposure exceeded the target adult exposure although there was still significant variability. However, the dose studied was reasonably well-tolerated and proved to be effective in this small group. It was not considered appropirate to recommend a dose higher than the studied dose and we recommended making the study dose the upper limit of a dose range to allow for some flexibility. Studies in patients < 2 years of age either failed to achieve both the target NFV exposure and adequate response rates (PENTA-7) or achieved the target exposure in a very narrow age group (PACTG 353). These studies included very young patient populations in whom the requirement for taking NFV with a meal may be the most difficult to accomplish and the drug-food effect may have a significant impact.

E. Special Populations

This submission completes the applicant's presentation of their pediatric development program for NFV. Agouron/Pfizer was granted pediatric exclusivity in September, 2003, as a result of submitting these studies. Because the numbers of patients in individual studies or treatment arms were relatively small, a subgroup analysis of treatment differences between sexes or among racial/ethnic backgrounds could not be performed. A full evaluation of the pediatric development program for NFV including detailed descriptions of the pediatric clinical studies is contained in this review.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug name: Nelfinavir mesylate (Viracept)

Drug class: HIV protease inhibitor, antiretroviral

Indication: Treatment of HIV infection in combination with other antiretroviral drugs

Dose: 750 mg PO TID or 1250 mg BID for adults
[redacted] for pediatric patients > 2 years of age

B. State of Armamentarium for Indication(s)

There are currently 22 drugs approved for use in the treatment of HIV infection in adult patients. Pediatric dosing recommendations are presented in the product labels of 12 of these drugs and pediatric dosing is not recommended in another 2 product labels because of dose constraints (the 2 fixed-dose combination products, Combivir and Trizivir). HIV protease inhibitors (PIs) have become the mainstay of highly active antiretroviral therapy when given in combination with nucleoside reverse transcriptase inhibitors (NRTIs). Combinations of 3 or 4 antiretroviral drugs are now standard therapy in North America and Europe and are gradually being adopted in more resource-poor countries as cost containment strategies are being implemented. The development of resistance to these agents continues and the need for new drugs with improved resistance profiles remains critical. Many of the currently available antiretroviral drugs also have significant adverse effects. Accurate dosing across all pediatric age groups remains an important issue in limiting the emergence of resistance and limiting the impact of adverse effects. The original pediatric dosing recommendations for nelfinavir (NFV) were established at a time when new therapies were desperately needed and were based on very limited pharmacokinetic (PK) and clinical data. The current submission attempts to fill in gaps in the dosing recommendations for children.

C. Important Milestones in Product Development

NFV as 250 mg tablets and oral powder received accelerated approval for the treatment of HIV infection in March, 1997. The pediatric dosing

recommendations to administer 20-30 mg/kg TID were based on preliminary data presented from Agouron's Study 524 and were restricted to children > 2 years of age. A Written Request for Pediatric Studies was issued for NFV on March 29, 1999, and requested PK, safety, and activity data in children < 2 years of age and PK and safety data in HIV-exposed neonates.

In November, 1999, a BID dosing schedule for NFV was approved for use in adults. At the time of approval of that supplement, the applicant agreed to evaluate the PK and safety of twice daily dosing with the oral powder formulation of NFV in pediatric patients as a Phase 4 commitment. More recently, Agouron received approval for a new 625 mg tablet for use in the adult BID dosing regimen (April, 2003).

This submission attempts to provide clinical and PK data to fulfill both the Written Request requirements and the remaining Phase 4 commitment to evaluate BID dosing in pediatric patients. The applicant requested a Pediatric Exclusivity Determination at the time of submitting the supplement and has submitted a proposal for new pediatric product labeling as required. The Pediatric Exclusivity Board met on September 4, 2003, and determined that Agouron/Pfizer had completed the studies outlined in the Written Request for NFV. Pediatric exclusivity was granted at that time and formal review of the data and proposed labeling was conducted and is included in this review.

D. Other Relevant Information

NFV tablets and oral powder have been approved for treatment of HIV infection in combination with other drugs in the European Union and many other countries.

E. Important Issues with Pharmacologically Related Agents

Many of the PIs approved for use in the treatment of HIV infection exhibit significant drug-drug interactions because of inhibition and/or induction of the hepatic cytochrome P450 enzymes. NFV is primarily metabolized by CYP2C19 and CYP3A. The ability of NFV to inhibit the cytochrome P450 enzymes has been investigated in vitro and through drug interaction studies with various antiretroviral and other drugs. Similarly, other drugs that affect the cytochrome P450 enzymes may have an impact on NFV concentrations. These interactions have been reviewed in detail during the original NDA and previous supplements and drug interaction data are prominently displayed in the product label. To date, all NFV-drug interactions studies reviewed by DAVDP have been conducted in adults. There is little information available to guide practitioners caring for very young patients receiving multiple drugs.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

This supplement contained no new information for review by Chemistry, Microbiology, or Pharmacology/Toxicology. These disciplines provided detailed reviews for the original NDA submission.

One of the major objectives of this supplement was to provide improved dosing recommendations for NFV in pediatric patients of all ages based on PK, safety, and activity data from several studies. This submission included extensive PK data for the use of NFV in pediatric patients covering different age ranges, doses, and dose schedules. These data were reviewed in detail by Dr. Robert Kumi, the Biopharmaceutics/Clinical Pharmacology reviewer. Please see Dr. Kumi's review for more complete descriptions of the PK studies, discussion of the limitations of the PK data, and interpretation of the results. His conclusions are summarized in the Pharmacokinetics and Pharmcodynamics section below.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The PK profile of NFV has been characterized in adults using both TID and BID dosing schedules. The adult approved doses have been correlated with clinical efficacy in large treatment trials. The most important PK characteristic of NFV is the remarkable variability of exposure as measured by AUC_{24}. This variability is linked to a marked drug-food effect. Taking NFV with a meal significantly increases NFV exposure and decreases variability. The effect of food on NFV exposure varies depending on meal content with higher calorie/higher fat meals increasing exposure more than low calorie/low fat meals.

It is also known that NFV is highly bound to plasma proteins and that changes in plasma proteins may have a significant impact on the amount of free NFV available. Only total NFV (and its active metabolite M8) was measured in the pediatric PK studies and there were no measures of protein binding.

The pediatric studies submitted in this supplement evaluated the PK profile of NFV given over a range of age groups, doses, and schedules. In all of the studies, there was marked variability of NFV exposure. Table 1 summarizes the steady state PK of NFV in 4 of the submitted studies. In addition to the data displayed in the table, there were also PK data available for 86 patients 2 to 12 years of age from Study 556 (NFV 25-35 mg/kg TID). Data from this study were more variable than any of the other pediatric studies, with a 95% confidence interval for

AUC_{24} of 9-121 mg*hr/L (mean AUC_{24} 38 mg*h/L). The applicant submitted summary PK data from a German pediatric study that evaluated the doses 25 mg/kg TID (mean AUC_{24} 48 mg*h/L) and 40 mg/kg BID (mean AUC_{24} 73 mg*h/L). This PK summary was submitted only as information supportive to the application and conclusions could not be confirmed but appeared to be similar to the other reviewed data.

Table 1: Summary of Steady-state AUC_{24} of Nelfinavir in Pediatric Studies

Protocol Number	Dosing Regimen*	N**	Age (years)	AUC_{24} (mg*hr/L) Arithmetic mean ± SD
AG1343-524	20 (19-28) mg/kg TID	14	2-13 years	56.1 ± 29.8
PACTG-725	55 (48-60) mg/kg BID	6	3 –11 years	101.8 ± 56.1
PENTA 7	40 (34-43) mg/kg TID	4	2-9 months	33.8 ± 8.9
PENTA 7	75 (55-83) mg/kg BID	12	2-9 months	37.2 ± 19.2
PACTG-353	40 mg/kg BID	10	6 weeks	44.1±27.4
			1 week	45.8 ± 32.1

*Protocol specified dose (actual dose range)
**N: number of subjects with evaluable pharmacokinetic results

The goal of the pediatric PK studies was to achieve the exposures that have been correlated with efficacy in adults: 44 mg*h/L for the adult TID dose and 53 mg*h/L for the adult BID dose. Not all of the pediatric studies identified doses that achieved these exposures. As noted in Dr. Kumi's review, the currently approved dose of 20-30 mg/kg TID for patients 2 years of age or older and the 40 mg/kg BID dose studied in neonates achieved the target exposures. The 55 mg/kg BID dose studied in PACTG 725 significantly exceeded the adult target exposure. Exposures achieved in PENTA 7 were suboptimal for either the TID or BID doses studied. The mean exposure achieved in Study 556 was also below the target exposure but the extreme variability in that study limited its usefulness and interpretability. Because of the marked variability in the PK data presented, dose selection required evaluating the available PK data in conjuction with the clinical

data. For additional information regarding dose selection recommendations, see Section VIII, Dosing, Regimen and Administration Issues.

B. Pharmacodynamics

No specific PK/PD studies were performed. However, efficacy of NFV in pediatrics has been assumed to be similar to that observed in adults if the appropriate exposure was achieved. The studies in this submission identify that the variability of exposure in different pediatric populations is greater than that seen in the adult PK studies and makes extrapolation of efficacy more difficult. The applicant correlated the exposures achieved in different pediatric studies with the efficacy achieved in those studies. They suggested that a mean AUC_{24} of approximately 33-37 mg*hr/L as seen in Study 556 and PENTA-7 provided adequate exposure to achieve efficacy in the pediatric population. In these studies, the proportions of patients achieving the desired target of HIV RNA < 400 copies/mL at 48 weeks were 21% (26% for patients > 2 years of age) and 37% respectively. These results do not reach either the target adult exposure (AUC_{24} of 43-53 mg*hr/L) or the same level of effectiveness (about 60% patients achieving HIV RNA < 400 copies/mL) as seen in adult trials of NFV.

IV. Description of Clinical Data and Sources

A. Overall Data

Final study reports and electronic datasets for 5 pediatric clinical studies were submitted in this NDA supplement. Three studies were submitted in response to the Written Request for Pediatric Studies issued for NFV on March 29, 1999 (amended on June 26, 2001). The studies fulfilling the request for multiple-dose PK, safety, and activity studies of NFV in HIV-infected patients < 2 years of age include Study AG1343-524 and Study AG1343-556. PACTG 353 was included to fulfill the request for a multiple-dose PK and safety study of NFV in HIV-exposed neonates. In addition, 2 studies were included to fulfill a Phase 4 commitment made by the applicant to evaluate BID dosing with the oral powder in pediatric patients. These studies include PENTA-7 and PACTG 377 (including the PK substudy PACTG 725).

This submission was provided electronically. Datasets were provided as SAS transport files for each study. Multiple errors and omissions were identified in the electronic datasets throughout the course of the review requiring re-submission of some of the laboratory and randomization datasets for Studies 524 and 556, PACTG 353, and PACTG 377. Requests for additional data and clarifications of the datasets significantly slowed the review process. Because critical data was not available in a timely way, this priority review was extended by 3 months (critical datasets requiring resubmission were considered a major amendment).

B. Tables Listing the Clinical Trials

The 5 studies submitted in this supplement represent all age ranges of pediatric patients, from birth through adolescence. The studies enrolled children of multiple nationalities, both sexes, and many races and ethnic backgrounds. The studies evaluated a variety of doses and both BID and TID dose schedules, sometimes within the same study. Table 2 summarizes some of the characteristics of the studies submitted for review.

Table 2: Characteristics of Studies Submitted

Study	Dose (mg/kg)	Dose Schedule	Ages Enrolled	Study Characteristics	Number of Patients Enrolled
AG1343-524	20	TID	< 3 months to 13 years	Open-label	65
AG1343-556	25-35	TID	3 months to 12 years	Randomized, placebo-controlled	141
PACTG 377 Substudy 725	27-33 48-60	TID BID	4 months to 17 years	Randomized, open-label	181 12
PACTG 353	10 40	TID BID	At birth	Open-label, sequential cohorts	8 23
PENTA-7	40 75	TID BID	< 3 months	Open-label, sequential cohorts	8 12

C. Postmarketing Experience

A very brief postmarketing safety update was included in the summary of this submission and will be discussed in the Integrated Review of Safety. ODSS was not consulted to review the AERS database for any specific safety concerns.

D. Literature Review

Published reports of some of these studies taken from the scientific literature were also used as additional background information. For a complete list of references consulted during the review, please see the Appendix.

V. Clinical Review Methods

A. How the Review was Conducted

Studies 524 and 556, PENTA-7 and PACTG 377 were reviewed in detail for safety and evidence of drug activity. These studies are described individually in the Integrated Review of Efficacy. PACTG 353 was primarily a PK study and contained no efficacy data and was reviewed for safety. It is described in less detail in the Appendix. Because of the differences in study design (open label vs. randomized, controlled), age ranges studied (neonates, young infants, and children up to 17 years), and doses and schedules studied, the 5 pediatric studies were reviewed individually rather than pooled.

The Medical Officers conducting the Clinical Review confirmed the applicant's efficacy and safety analyses using [redacted] software and the electronic datasets provided. Additional confirmation of the efficacy endpoints for Study 556 and PACTG 377 were provided by Dr. Susan Zhou, Mathematical Statistics Reviewer.

B. Overview of Materials Consulted in Review

Materials for this supplement were submitted to the Electronic Document Room. Study reports for the 5 studies were submitted as PDF documents. Electronic datasets for all studies were submitted as SAS transport files. No other data was reviewed.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audits of the sites or applicant were performed for this review.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The applicant notes that all studies were conducted in accordance with accepted ethical standards. The protocols were reviewed by IRBs for each participating site.

E. Evaluation of Financial Disclosure

The 5 studies in this submission were all evaluated for financial conflict of interest among investigators. Investigators in the studies sponsored by Agouron/Pfizer and those done in collaboration with the Pediatric AIDS Clinical

Trial Group (PACTG) and the Paediatric European Network for Treatment of AIDS (PENTA) were evaluated for financial information requiring disclosure. Since some of these studies were initiated prior to 1999 and there was substantial turnover of staff at some sites since the studies were conducted, not all investigators could be accounted for. No investigators participating in the Agouron-sponsored studies or the PACTG-sponsored studies reported financial information to disclose and none reported equity in Agouron/Pfizer or received significant payments of other sorts. One investigator participating in the PENTA-7 study reported receiving significant payments that required disclosure (payments of $59,100 and $36,000). It is unlikely that conflict of interest from a single investigator even in the small PENTA-7 study would have any impact on the study outcome.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The four pediatric treatment studies provide evidence of NFV's activity as part of a combination antiretroviral regimen for pediatric patients. All of the studies document that pediatric patients receiving NFV achieved significant mean decreases in HIV RNA levels over time and most also achieved increases in CD4 cell counts or percentages. From a regulatory perspective, a pediatric dosing regimen may be approved if it is supported by efficacy in adequate and well-controlled studies of the drug in adults and by data identifying a dose that achieves a similar PK profile. The original approval of NFV based on preliminary clinical and PK data from Study 524 fits this category and the follow-up data provides evidence of long-term activity of the NFV-containing regimens. The PENTA-7 study, using the highest doses of NFV studied (150 mg/kg divided in BID dosing), achieved HIV RNA < 400 copies/mL at 48 weeks in 37% of infants. In PACTG 377, the NFV-containing arms of the study achieved undetectable HIV RNA levels in 30% to 52% of patients. In the small substudy PACTG 725 evaluating a BID NFV regimen, 55% of patients achieved HIV RNA < 400 copies/mL at 48 weeks. In the placebo-controlled Study 556, the NFV-containing regimen clearly performed better than the placebo regimen with a greater proportion of patients achieving and maintaining HIV RNA < 400 copies/mL (21% compared to 3%).

The response rates varied significantly across the pediatric studies. In general, response rates were lower than those observed in treatment-naïve adults receiving NFV. Response rates for patients less than 2 years of age appeared to be worse than those in patients 2 years of age and older. Associations between the doses studied and a reasonable level of effectiveness could not be concluded for all age groups for either TID or BID dosing. The applicant has proposed TID and BID doses for pediatric patients in all age groups from birth to adolescence. Because

of the differences in study design, doses and regimens studied, and age groups studied and the PK and efficacy data obtained it is difficult to identify an effective dose in all age groups.

B. General Approach to Review of the Efficacy of the Drug

Because the pediatric studies submitted were conducted by different investigators in widely varying patient populations, the primary endpoints and efficacy analyses were different. In all of the treatment studies, some assessment of change in HIV RNA as measured by HIV RNA PCR assay was the primary endpoint and 48 weeks was the duration of treatment evaluated. In most studies, the lower limit of quantitation of the HIV RNA assay was 400 copies/mL. Additionally, change in CD4 cell count or percent over time was assessed as a secondary endpoint. The specific analyses performed for each study are described below. For each of the studies submitted, the Medical Officers attempted to confirm the applicant's efficacy conclusions. Dr. Susan Zhou, the Mathematical Statistics Reviewer, provided independent statistical analysis of efficacy for Study 556 and PACTG 377/725. Dr. Zhou's analyses and comments are referred to in the Detailed Review of Trials by Indication section below and incorporated into Appendix A.

C. Detailed Review of Trials by Indication

Study AG1343-524: A Phase I study of safety, tolerability and pharmacokinetics of Viracept in HIV-1-infected children and exposed infants

Summary of Study Design:

Study 524 was the original Phase I study of nelfinavir (NFV) in pediatric patients. It was designed as an open-label, multicenter study in two parts. The first segment of the study evaluated the safety, tolerability, and pharmacokinetics (PK) of single-dose NFV followed by an initial observation period of 6 weeks of TID dosing (multiple-dose phase). There was an optional extension of the TID dosing segment for up to 22 months. The extension period was designed to evaluate the longer-term safety and durability of response to NFV. All patients were given NFV in combination with NRTI's, although they did not have to be new NRTI's. Patients were enrolled in 4 age groups:

Group I – 7 to 13 years of age
Group II – 2 to < 7 years
Group III – 3 months to < 2 years
Group IV - < 3 months

Patients completing the single-dose PK segment (Phase A) were allowed to continue in the multiple dose segment (Phase B). After identification of the appropriate dose in Phase A, a study amendment allowed 10 additional patients to be enrolled into each age cohort for Phase B. Groups I and II were enrolled first, followed by enrollment of Group III and Group IV sequentially as the optimal dose was found for the preceding group. Target plasma concentrations of 50%-200% of the median exposure of adults receiving 750 mg single doses were used to estimate the appropriate dose for each pediatric age group.

The multiple-dose phase was to begin after completion of the single-dose phase for each age group and selection of the most appropriate dose for that age. In Phase B, patients were evaluated at baseline (Day 0), Week 1, Week 2, Week 4, Week 6, and every month thereafter to assess safety, tolerability, and efficacy of the drug regimen. Clinical adverse events (AE's) and serious AE's were recorded at each visit. Laboratory evaluation included routine hematology and serum chemistry tests, HIV RNA PCR, and CD4 lymphocyte percent and absolute numbers.

Data collected from the first 47 patients enrolled in Study 524 over a mean duration of 38 days (range 1 to 104 days) of NFV dosing were reviewed during the original review of NDA's 20-778 and 20-779 and the information was incorporated into the product label. The original review included the analysis of the single-dose PK data. The current report contains final study data collected on all patients who were enrolled and received at least one dose of NFV.

Patient Population:

The study population was planned to include HIV-1 infected pediatric patients from 3 months through 12 years of age (up to the 13th birthday). Patients in this age range were eligible to enroll in the study if they met all of the following criteria:

- Birth weight greater than 2500 g
- Absence of serious or unstable medical conditions
- Written informed consent and willingness to adhere to the study requirements by the patient's parent or legal guardian
- Patients who had taken other investigational drugs, immunomodulators, HIV-1 vaccines, glucocorticoids or "unconventional therapies" within 1 month of baseline were evaluated and included or excluded on a case-by-case basis after discussion with the study's Medical Monitor

Patients were excluded from enrollment if they met any of the following criteria:

- Current or previous treatment with a PI
- HIV-associated malignancy requiring chemotherapy
- Clinical or laboratory assessments greater than Grade 1 at the time of screening

- Potential to procreate and not practicing barrier contraception
- Pregnant or breastfeeding females

Study Results:

Since preliminary results of Phase A of Study 524 were reviewed for the original NDA, this review will focus on safety and activity through the entire study but primarily the multiple-dose segment. The study report notes a total of 64 pediatric patients were enrolled in the study and received at least one dose of NFV and were included in the safety review. Patients received either the tablet or powder formulation of NFV, and some patients received both formulations at different times during the study based on individual tolerance. There was no formal assessment of adherence. The final clinical study report was based on data collected from the initial patient enrollment in August, 1996, through July, 1998.

Table 3 summarizes the disposition of patients enrolled in Study 524 by age group as reported by the applicant in the final study report. All 22 patients enrolled in the single-dose phase completed Phase A and rolled over into Phase B. Through the end of the study report period a total of 29 patients discontinued study during the multiple-dose phase, 8 within the first 6 weeks of NFV dosing.

Table 3: Patient disposition by age group – Study 524

Patient Disposition	Group 1 (7-13 yrs)	Group 2 (2-<7 yrs)	Group III (3 mos-<2 yrs)	Group IV (< 3 mos)	Total
Single-Dose Phase					
Enrolled	6	11	4	1	22
Discontinued	0	0	0	0	0
Completed	6	11	4	1	22
Multiple-Dose Phase					
Entered	16	23	23	2	64
Discontinued	9	13	6	1	29
< 6 weeks	0	3	4	1	8
≥ 6 weeks	9	10	2	0	21
Reason for D/C*					
Related to study drug	1	0	1	1	3
Adverse Event	1	0	0	0	1
Other**	0	0	1	1	2
Unrelated to study drug	8	13	5	0	26
Death	0	0	0	0	0
Disease progression	0	1	0	0	1

Patient request	0	3	2	0	5
Noncompliance	2	1	2	0	5
Other***	6	8	1	0	15
Months of NFV exposure – mean (range)	11 (2-19)	10 (1-20)	10 (0-18)	0 (0-1)	10 (0-20)

Source: NDA 20-778, SE5-022, Final Study Report, Study AG1343-524, Section 6, Vol. 2, pgs 97,112.
*Reasons for discontinuation are displayed as reported by the investigator.
**Other reasons for discontinuation related to study drug included: taste aversion (1 patient) and inadequate PK levels (1 patient).
***Other reasons not related to study drug included: increased HIV RNA levels (10 patients), lost to follow-up (2 patients), no virologic response to study drug (1 patient), guardian request (1 patient), and too far from medical center (1 patient).

Patients were enrolled from 4 pediatric HIV centers in the U.S.: Bronx Lebanon Hospital Center (32), UC-San Diego Treatment Center (9), UCLA Department of Pediatrics (12), and University of Massachusetts (12). Three of the 4 sites participated in the initial single-dose PK phase.

Table 4 provides the demographic and disease characteristics of patients at the time they enrolled in the study. Two patients originally enrolled into Group 2 were 7 and 7.1 years of age at the time of study entry and should have been enrolled into Group 1. These enrollment errors had no impact on the results of the study.

Table 4: Demographic and baseline disease characteristics of patients enrolled by age group - Study 524

Patient Characteristic	Group I (7-13 yrs) N = 16	Group II (2-<7 yrs) N = 23	Group III (3 mos-<2 yrs) N = 23	Group IV (< 3 mos) N = 2	Total N = 64
Age – mean (range)	8.9 (7.1-12.3)	4.8 (2.3-7.1)	0.9 (0.3-1.8)	0.2 (0.1-0.2)	4.3 (0.1-12.3)
Sex –M/F	75%/25%	57%/43%	52%/48%	50%/50%	59%/41%
Race – N (%)					
Caucasian	4	6	3	0	13
Black	5	7	11	1	24
Hispanic	5	10	8	1	24
Other	2	0	1	0	3
Log HIV RNA – mean (range)	4.1 (3.2-5.3)	4.6 (3.4-5.5)	4.7 (3.2-6.1)	6.2 (5.1-7.2)	4.6 (3.2-7.2)
CD4 percent – mean (range)	19.0 (0.1-39.0)	19.9 (3.0-35.5)	28.9 (6.8-50.6)	46.2 (46.0-46.3)	23.8 (0.1-50.6)

History of HIV signs and symptoms (% with)	88%	91%	78%	50%	84%
Prior antiretroviral therapy*	15 (94%)	22 (96%)	21 (91%)	2 (100%)	60 (94%)
New antiretroviral therapy**	8 (50%)	12 (52%)	17 (74%)	2 (100%)	39 (61%)

Source: NDA 20-778, SE5-022, Final Study Report Study AG1343-524, Section 6, Vol. 2, pgs 100, 102, 105.
*Any antiretroviral therapy taken prior to initiation of the Viracept multiple-dose phase.
**Any antiretroviral therapy started for the first time within 1.5 months before (and continuing until after initiation of the Viracept multiple-dose phase) or 0.5 months after initiation of multiple-dose Viracept.

The database actually contains data from 65 patients enrolled in the study. The applicant notes that one patient in Group III was enrolled and dosed within 2 days of the original study report data cut-off and was not included in the final clinical study report. This patient's data was included in the electronic database and was included in my review. Also, the electronic dataset submitted with this supplement includes data collected after the data cut-off date reported in the final study report. Thus, the estimates of efficacy rates calculated in this review are generally slightly different than those reported in the applicant's final study report for Study 524 and shown in their Integrated Summary of Efficacy.

Efficacy Analysis

Since Study 524 was an open label trial of NFV in combination with other antiretroviral therapy, a strict analysis of NFV efficacy cannot be performed. The applicant's primary analysis of efficacy included assessments of the mean change from baseline over time in log HIV RNA levels and the mean change from baseline over time in CD4% by age group. CD4% was considered a more appropriate analysis than absolute CD4 count because the normal absolute CD4 count undergoes significant changes as an infant's immune system matures. Absolute CD4 cell counts in newborns are higher than those seen in adults, remain high during the first year of life then decline over the next few years, reaching the normal adult levels at about 4 to 5 years of age. CD4% is less subject to this physiologic variation over time and is preferred as a measurement when evaluating children over a wide age range.

The applicant calculated the mean change from baseline in the study age groups through each study visit. In their analysis, all age groups displayed an initial decrease in mean HIV RNA of about 1 log over the first 2 to 4 weeks on study drug. Mean HIV RNA levels for the age groups then reached a plateau at somewhat higher HIV RNA levels and persisted through the remainder of the study. In their analysis, similar mean change from baseline in CD4% were observed in all study age groups over time, 4-7% increase through the M11 visit (approximately one year of treatment with NFV). However, by the M11 visit only 27 of the original 64 patients had data included in the sponsor's CD4% analysis.

For my analysis, patients were analyzed according to actual age at enrollment rather than by study group. Also, only 2 patients were enrolled in the original Group IV (age < 3 months) and neither had extensive follow-up data, these patients were included with the Group III patients in my analysis. For the analysis presented below, the Baseline value used was the Day 0/Baseline measurement at the beginning of the multiple dose phase. When more than one value was available, these values were averaged to calculate the Baseline/Day 0 CD4 cell count. In this study, many patients were not followed on study after discontinuing study drug but some changed to a different therapeutic regimen and continued their study follow-up. Consequently, results shown in the following tables of CD4% and HIV-RNA levels reflect the drop-out of some patients who were responding poorly and some who began more effective therapy and may overestimate the beneficial effects of NFV.

Table 5 summarizes the mean CD4% by age groups during the course of the study. As can be seen in the table, the mean CD4% increased over time in each age group in the patients remaining on study.

Table 5: CD4% by age group - Study 524

Study Visit	≤ 2 years (N=26)	2 years to < 7 years (N=22)	≥ 7 years (N=17)	All Patients (N=65)
Baseline/Day 0				
Number with data	23	21	15	59
CD4% - mean	31.0	18.8	16.2	22.9
M6*				
Number with data	18	13	14	45
CD4% - mean	37.3	27.6	24.9	30.6
M11*				
Number with data	15	10	6	32
CD4% - mean	38.5	28.1	32.3	36.1
M18*				
Number with data	9	8	6	23
CD4% - mean	43.1	33.5	35.4	37.7

*Study visits designated as M6, M11, and M18 represent 6, 11, and 18 months of the study's extension. The "M" visits began after the initial 42 days of drug dosing. The M11 visit is the closest visit to 48 weeks on study.

Table 6 summarizes the changes in HIV RNA as measured by quantitative PCR in Study 924 according to age group. In each age group, the level of HIV RNA decreased over the course of the study for those patients remaining on study. At the M11 visit (about one year of treatment), 13 of 32 (40%) patients with data had

HIV RNA levels < 400 copies/mL, accounting for only 20% of the original study population.

Table 6: Log HIV RNA levels by age group – Study 524

Study Visit	≤ 2 years (N=26)	>2 years to < 7 years (N=22)	≥ 7 years (N=17)	All Patients (N=65)
Baseline/Day 0				
Number with data	22	22	16	60
Log HIV RNA – mean	4.76	4.62	4.08	4.53
M6*				
Number with data	19	13	14	46
Log HIV RNA – mean	3.66	3.48	3.83	3.66
Number ≤ 400 copies/mL	7 (27%)	6 (27%)	4 (24%)	17 (26%)
M11*				
Number with data	15	10	7	32
Log HIV RNA – mean	3.69	3.27	3.20	3.45
Number ≤ 400 copies/mL	4 (15%)	6 (27%)	3 (18%)	13 (20%)
M18*				
Number with data	9	6	7	22
Log HIV RNA – mean	3.72	2.83	3.12	3.29
Number ≤ 400 copies/mL	4 (15%)	5 (23%)	3 (18%)	12 (18%)

*Study visits designated as M6, M11, and M18 represent 6, 11, and 18 months of the study's extension. The "M" visits began after the initial 42 days of drug dosing. The M11 visit is the closest visit to 48 weeks on study.

The patient population in Study 524 was relatively experienced in terms of treatment with NRTIs. None had received other protease inhibitors or non-nucleoside RTIs as these drugs were just beginning to be available for children at the time the study was conducted. The applicant evaluated the response to study treatment in the subset of patients completing at least 6 weeks of dosing according to other factors that might have an impact on treatment success. In these analyses, patients with HIV RNA ≤ 4.0 log at baseline were more likely to achieve an undetectable HIV RNA than those with baseline HIV RNA > 4.0 log (38% compared to 18%). Similarly, patients with CD4% > 24% were more likely to remain undetectable than those with CD4% ≤ 24% (32% compared to 14%). Patients who initiated one or more new NRTIs at the time of study entry were more likely to achieve an undetectable HIV RNA than those who did not add a new NRTI (35% compared to 5%). Of these by-factor analyses, only the addition of new NRTI drugs at the time of study entry proved statistically significant.

The applicant concluded that Study 524 supported the efficacy of NFV as part of an antiretroviral regimen in children. Their conclusion was based on the

improved HIV RNA levels and CD4 cell counts and percentages in patients receiving NFV at a dose that achieved NFV exposure (AUC_{24}) comparable to that shown to be effective in adult treatment studies.

Study 556: A Phase III randomized, double-blind, placebo-controlled, study of Viracept in combination with zidovudine (AZT) plus didanosine (ddI) versus AZT plus ddI alone in HIV-positive children with less than 1 month or no prior antiretroviral treatment

Summary of Study Design:

Study 556 was a randomized, double-blind, placebo-controlled, Phase III study designed to evaluate the safety and efficacy of NFV given in combination with zidovudine (ZDV) and didanosine (ddI) compared with ZDV plus ddI in HIV-infected, treatment-naive children. At the time the study was designed and conducted, dual NRTI therapy was the standard HIV treatment regimen in Brazil and Argentina, the countries where the study enrolled patients. Patients were randomized to receive one of the following regimens:

NFV (25-35 mg/kg TID) + ZDV + ddI
Placebo + ZDV + ddI

ZDV and ddI were administered "according to manufacturer's recommendations." Randomization was stratified according to age (< 2 years or ≥ 2 years), HIV RNA level (< 50,000 copies/mL or ≥ 50,000 copies/mL), and CDC HIV disease status classification (Categories N3, A2, A3, B2 or B3 versus Categories C1, C2, or C3). The blinded study regimen was planned for a 48 week treatment period with the option of an extension to 96 weeks. Patients were evaluated monthly for the first 6 months, then every 2 months through 48 weeks, then every 12 weeks through 96 weeks.

At each study visit, patients were evaluated for safety and efficacy of their study regimen. Plasma HIV RNA levels and CD4 cell counts were evaluated as measures of efficacy. Serum chemistry studies, routine hematology studies, and assessment of AEs were conducted at every visit to evaluate safety.

Patients could be withdrawn from the study if the patient or family refused further study treatment or if the patient was shown to be taking ≤ 50% of the prescribed doses per month for at least 2 months. Patients could have their treatment status changed and receive the designated salvage regimen if they had unacceptable toxicity or were considered to have failed treatment. Patients were designated as having virologic failure if they did not achieve HIV RNA levels below the limit of quantitation of the assay or at least a [redacted] decrease from baseline by 16 weeks or if they achieved such a response but rebounded above 2000 copies/mL and ≥

0.5 log increase above their nadir. Patients were considered to have an immunologic failure if they experienced a protocol-defined decrease in CD4 counts from baseline based on their initial CD4 counts and age at the time of assessment. They were considered to have a clinical failure if they experienced a new AIDS-defining condition after at least 4 weeks of study treatment.

Patients who were considered treatment failures for virologic, immunologic, or clinical reasons were allowed to switch to a salvage regimen defined in the protocol and could continue to be followed on study. Patients who were considered treatment failures because of non-compliance were not eligible for switching to salvage therapy but were counseled about adherence and discontinued from the study if non-compliance persisted. For those patients failing the placebo regimen, the salvage regimen consisted of NFV + stavudine (d4T) + lamivudine (3TC). For those patients failing the NFV regimen, the salvage regimen consisted of ritonavir (RTV) + d4T + 3TC.

Patient Population:

The study was planned for 120 HIV-infected pediatric patients from 3 months to 13 years of age who had received no more than 1 month of antiretroviral therapy or less than 6 weeks of ZDV for prevention of mother-to-child transmission. Patients were eligible to enroll if they met all of the following inclusion criteria:

- Male or female patients between 3 months and 13 years of age (up to 13th birthday)
- HIV-infection documented and CDC disease category N3, A2, A3, B2, B3, C1, C2, or C3
- No serious or unstable medical condition at the time of study entry
- Parent or guardian able to give written informed consent and willing to comply with the study requirements

Patients were not allowed to enroll in the study if they met any of the following exclusion criteria:

- Previous antiretroviral therapy for more than 1 month or more than 6 weeks of ZDV for prevention of mother-to-child transmission
- Current or previous treatment with a protease inhibitor
- Any HIV-associated malignancy requiring chemotherapy
- Clinical or laboratory assessments > Grade 2 (in Toxicity Severity Scale included as appendix to the protocol) at the time of screening that made them ineligible based on a case-by-case basis
- Patient of procreative potential and not practicing barrier contraception (neither oral nor patch hormonal contraceptives alone considered acceptable)
- Patient was pregnant or nursing

Additionally, patients were included or excluded on a case-by-case basis after discussion with the medical monitor for the following reasons:

- Use of investigational agents, immunomodulators, HIV-1 vaccine, glucocorticoids, or unconventional therapy within 1 month prior to baseline
- Patients who required vaccinations were encouraged to have them between study visits and after study laboratory tests were completed. Patients were to avoid vaccinations during the first 16 weeks of study.
- Concomitant medications were evaluated for potential drug interactions with NFV. Rifampin, cisapride, terfenadine, astemizole, triazolam, midazolam, ergot derivatives, amiodarone, and quinadine were specifically excluded. Use of anticonvulsants such as phenobarbital, phenytoin, and carbamazepine were discussed with the medical monitor prior to use during the study.

Study Results:

A total of 141 patients were enrolled in Study 556 and received at least one dose of study drug, 75 randomized to the placebo group and 66 randomized to the NFV group. All 141 patients are included in the applicant's safety analysis but one patient (#2607) did not have efficacy data after the Baseline visit and is not included in their efficacy analysis. Patients were enrolled from 2 sites in Argentina (N = 66) and 3 sites in Brazil (N = 75). The last patient completed 48 weeks on study on February 25, 2000, and the applicant's clinical study report is based on data collected through April 17, 2000.

Table 7 provides the demographic and disease characteristics of patients at the time they enrolled in the study as reported by the applicant. The 2 treatment groups were similar in their demographic and disease characteristics. Patients enrolled in this study represent the range of ages, severity of clinical symptoms, and entry HIV RNA levels and CD4 counts observed in children with HIV infection. Since this study was conducted in South America, the classification of racial and ethnic backgrounds of the participants reflects the racial and ethnic diversity and reporting practices of HIV-infected children in that geographic area.

Table 7: Demographic and baseline disease characteristics of patients enrolled - Study 556

Characteristic	NFV + ZDV + ddI (N=66)	Placebo + ZDV + ddI (N=75)

Age – mean (range)	3.9 (0.3-11.8)	3.9 (0.3-11.9)
< 2 years	20	27
2 to < 7 years	36	36
7 to < 13 years	10	12
Sex		
Male	34	39
Female	32	36
Race – N (%)		
Mixed origin	34	41
White	29	29
Black	3	5
CDC classification*		
A, B	48	54
C	18	21
Log HIV RNA at entry – mean (range)	5.0 (2.6-6.6)	5.1 (2.8-6.7)
CD4 percent – mean (range)	20.2 (3-46.5)	19.7 (1-47.5)
Mean HIV duration (months)	15.9	14.6

Source: NDA 20-778, SE5-022, Final Study Report Study AG1343-556, Section 8, Vol. 9, pgs 62, 63.
*A=mild clinical signs or symptoms; B=moderate clinical signs or symptoms; C=severe clinical signs or symptoms

Table 8 summarizes the disposition of patients enrolled in Study 556 as reported by the applicant in the final study report. In this study, over 90% of patients in both treatment groups continued on study through the 48-week study period although only 58% of NFV patients and 13% of placebo patients completed 48 weeks on their originally assigned drug regimen. By the time of the data cutoff, 67 placebo patients and 19 NFV patients had failed on their original regimen and were switched to a salvage regimen.

Table 8: Patient disposition - Study 556

Patient Disposition	NFV + ZDV + ddI (N=66)	Placebo + ZDV + ddI (N=75)
Randomized	66	75
Received study drug	66	75
Completed 48-week treatment period	63 (95%)	69 (92%)
Completed 48 weeks of original randomized drug	38 (58%)	10 (13%)

Discontinued treatment by data cut-off	10 (15%)	14 (19%)
HIV-related event	2 (3%)	2 (3%)
Treatment failure	6 (9%)	9 (12%)
Noncompliance	1 (2%)	2 (3%)
Lost to follow-up	1 (2%)	1 (1%)
Death*	2 (3%)	2 (3%)
Still on study at data cut-off	56 (85%)	61 (81%)

Source: NDA 20-778, SE5-022, Final Study Report Study AG1343-556, Section 8, Vol. 9, pg 61.

*All deaths described as due to HIV-related events.

The study report notes that there were 70 patients enrolled in Study 556 who had documented protocol exemptions or violations, 42 in the placebo group and 28 in the NFV group. The most frequently reported exemption was failure of the investigator to unblind the patient or switch therapy at the time of treatment failure in 14 (19%) placebo patients and 17 (26%) NFV patients. In these cases, the investigator decided that it was not in the best interest of the patient to unblind treatment and switch to the salvage regimen. Another 14 (19%) placebo patients and 6 (9%) NFV patients had delayed unblinding or delayed therapy switch due to an error or communication difficulties. These protocol violations and exemptions are unlikely to have had any significant impact on the efficacy results since patients would still have been identified as treatment failures in the analysis even if they were not switched to salvage therapy.

Efficacy Analysis:

As noted above, 140 patients were included in the applicant's efficacy analyses, 65 in the NFV group and 75 in the placebo group. Many patients met the criteria to switch to a designated salvage regimen before completing their study follow-up but most of the patients remained on study. Data collected after a patient switched therapy were not included in the calculations of primary or secondary endpoints.

The applicant's primary endpoint for Study 556 was the calculation of the time to loss of virologic response (TLOVR) over the 48 week study period. In the applicant's primary analysis, virologic failure was defined as not achieving an HIV RNA level below the limit of quantitation of the assay (< 400 copies/mL) or at least a [redacted] crease from baseline by Week 16 or demonstrating a relapse of HIV RNA above 2000 copies/mL and a 0.5 log increase above the nadir. Patients who did not achieve virologic response by Week 16 were considered failures from Day 0. In this analysis, the proportion of patients continuing to respond at Week 48 was 9% (7 of 75) in the placebo group and 42% (27 of 65) in the NFV group. Using the study definition of time to failure, 40 patients in the placebo group and

14 patients in the NFV group were considered failures at Day 0. Median time to failure was 0 days for the placebo group and 218 days for the NFV group. Kaplan-Meier estimates of the time to virologic failure were constructed. Differences between the NFV and placebo group were statistically significant in this analysis.

The applicant also completed several secondary efficacy analyses that are included in the study report and an addendum to the study report, some of which will be described below. As part of the analysis, the proportion of patients maintaining virologic response was calculated using the same definition of virologic failure and a non-completer equals failure method. This method assumes that patients with missing data or a switch in therapy are virologic failures. This analysis is summarized in Table 9.

Table 9: Percentage of virologic responders: NC=F method

Study Visit	NFV + ZDV + ddI (N=65)	Placebo + ZDV + ddI (N=75)
Week 4	49 (75%)	35 (47%)
Week 12	46 (71%)	23 (31%)
Week 24	34 (52%)	13 (17%)
Week 36	31 (48%)	9 (12%)
Week 48	26 (40%)	7 (9%)

Source: NDA 20-778, SE5-022, Final Study Report Study AG1343-556, Section 8, Vol. 9, pg 73

In a study report addendum, the applicant provided another analysis that evaluated the percentage of virologic responders at 48 weeks according to age < 2 years or ≥ 2 years. Of the 140 patients with available efficacy data, 46 were < 2 years of age and 94 were ≥ 2 years of age. Using the same NC=F method, 3 of 27 (11%) placebo patients and 4 of 19 (21%) NFV patients < 2 years were counted as virologic responders compared to 4 of 48 (8%) placebo patients and 22 of 46 (48%) of NFV patients ≥ 2 years. The response rate in children < 2 was not statistically significantly different between the treatment groups although the study was not powered to show efficacy in each age group. The response rate in patients > 2 years of age was significantly better among those who received NFV.

The applicant was asked to repeat the efficacy analysis using a more conservative definition of loss of virologic response as the endpoint as recommended by our Medical and Statistical Reviewers. The new analysis defined virologic responders as those patients who achieved and maintained an HIV RNA < 400 copies/mL through 48 weeks of their assigned study regimen. Patients who changed or discontinued their study regimen for any reason prior to 48 weeks were considered treatment failures. This analysis conformed more closely to the algorithm for determining efficacy proposed by DAVDP. Results of this

reanalysis are summarized in Table 10 below. Although the proportion of patients identified as virologic responders in this analysis is lower than in the applicant's original efficacy analysis, the results confirm that patients receiving NFV were more likely to achieve a virologic response through 48 weeks than patients receiving placebo. Using the more stringent criteria for failure, median time to failure was 0 days (mean, 43 days) for the placebo group (ie. over half of patients failed to reach HIV RNA < 400 copies/mL by Week 16) and 122 days (mean, 181 days) for the NFV group. This difference was highly statistically significant (p=0.0026).

Table 10: Patients Achieving and Maintaining HIV RNA levels < 400 copies/mL through Week 48 – Study 556

Outcome	Placebo + ZDV + ddI (N = 75)	NFV + ZDV + ddI (N = 66)
Virologic Responders	2 (3%)	14 (21%)
Virologic Failures	62 (83%)	46 (70%)
Never suppressed through Week 48 and on study at Week 48	0	6 (9%)
Rebound after initial response	11 (15%)	22 (33%)
D/C or changed therapy due to insufficient viral load response	51 (68%)	18 (27%)
D/C study drug or added new therapy before achieving confirmed suppression	11 (15%)	6 (9%)
Death or events leading to death	2 (3%)	2 (3%)
Noncompliance	1 (1%)	1 (2%)
Changed therapy – reason not documented	8 (11%)	3 (5%)

Source: Amendment to NDA 20-778, SE5-022, dated 2//04.

In the reanalysis using more stringent failure criteria, the applicant evaluated the differences in efficacy according to age. Patients < 2 years of age again appeared to respond less well to study therapy. Only 1 of 27 (4%) placebo patients and 2 of 20 (10%) NFV patients < 2 years of age were considered virologic responders compared to 1 of 48 (2%) placebo patients and 12 of 46 (26%) NFV patients ≥ 2 years of age. As noted above, the study was not powered to show efficacy in all age strata.

Another secondary analysis included in a study addendum evaluated the mean decrease in log HIV RNA levels according to age (< or ≥ 2 years). At Week 48, placebo patients < 2 years experienced a mean 1.96 log decrease from Baseline compared to a mean 1.91 log decrease in the NFV patients < 2 years. Although these results are not significantly different, the number of patients evaluated was

small, only 3 of 27 patients remaining on placebo and 9 of 19 in the NFV group in this age group. In patients ≥ 2 years of age, the 7 of 48 remaining placebo patients experienced a mean 1.48 log decrease compared to mean 1.58 log decrease among 28 of 46 NFV patients. These data show that over half of NFV patients in the study maintained a substantial decrease in log HIV RNA levels from Baseline through 48 weeks. However, very few of these patients were able to maintain an HIV RNA below 400 copies/mL through that same time period.

The applicant also analyzed changes in CD4% and absolute numbers during the study according to treatment group. In both treatment groups, CD4% and absolute counts increased from baseline. Table 11 summarizes the applicant's calculated mean change from baseline in CD4% according to treatment groups in those patients remaining on their randomized regimen. The applicant notes that due to changes in the protocol, CD4 measurements were not consistently performed at Weeks 28, 36, and 44 and so these timepoints were not included in the summary table. No significant difference in CD4 increase was noted between the two treatment groups at any timepoint through 48 weeks.

Table 11: Mean Change from Calculated Baseline in CD4 Percentage by Treatment Group – Study 556

Study Visit	NFV + ZDV + ddI (N=65)	Placebo + ZDV + ddI (N=75)
Week 4	2.6 (n=61)	3.5 (n=72)
Week 12	5.2 (n=63)	5.3 (n=70)
Week 24	6.6 (n=57)	7.3 (n=41)
Week 48	9.4 (n=37)	11.7 (n=10)

Source: NDA 20-778, SE5-022, Final Study Report Study AG1343-556, Section 8, Vol. 9, pg 77.

Statistical review of the data confirmed the applicant's conclusions that NFV was superior to placebo in the TLOVR efficacy analysis. Stratification by age confirmed that patients > 2 years of age achieved virologic response more frequently than did those < 2 years of age in the TLOVR analysis. A more detailed description of Dr. Zhou's analyses is included in Appendix A. Her review also includes analysis of mean HIV RNA levels by study visit and the mean change from baseline in HIV RNA over time. These longitudinal assessments of HIV RNA include data from patients who switched therapy during the course of the study. Inclusion of these patients in the analysis may explain why the NFV group has lower mean HIV RNA and greater mean decrease from baseline in HIV RNA over the first 24 weeks of the study but later timepoints reveal no significant differences between treatment groups.

In my analysis including all patients remaining on study, Table 12 below shows the mean CD4% at Baseline and Weeks 24 and 48 in the two treatment groups.

Analysis confirming increases in CD4 absolute cell count in both treatment arms was performed by Dr. Zhou and is included in Appendix A. These data confirm increases in CD4 counts in both treatment groups but no significant differences between the treatment groups when all patients including those who switched to salvage therapy and continued on study were evaluated.

Table 12: CD4% over time in Study 556 - by randomized treatment group

Study Visit	NFV + ZDV + ddI (N=66)	Placebo + ZDV + ddI (N=75)
Baseline/Day 0		
Number with data	65	74
CD4% - mean	19.8	19.7
Week 24		
Number with data	64	72
CD4% - mean	26.9	26.3
Week 48		
Number with data	62	68
CD4% - mean	29.2	29.4

The applicant concluded that this study supported the efficacy of NFV in a combination antiretroviral regimen in pediatric patients. This conclusion was based on a significantly longer time to virologic failure for patients receiving NFV and a greater proportion of NFV patients achieving the defined virologic response at Week 48. The applicant notes that in some analyses, patients < 2 years of age had poorer HIV RNA responses. CD4 percentage and cell counts increased in both treatment groups over time but there was no difference in CD4 improvement between the two treatment groups.

PACTG 377: PRAM-2: A Phase I/II Randomized, Multicenter Protocol Comparing Four Antiretroviral Regimens Containing Combinations of Protease Inhibitors, NRTIs and an NNRTI
PACTG 725: A Pharmacokinetic Substudy of BID Nelfinavir dosing given as tablets to Children < 30 kg

Summary of Study Design

The PACTG Phase II Rolling Arm Master (PRAM) protocols are a series of Phase II studies for clinically stable, treatment-experienced HIV-infected children designed to serve as a "rolling screen" of new combination therapies. PACTG 377 (PRAM-2) was the second phase I/II, randomized, open label, multi-center, multi-arm clinical trial in the series. Patients were enrolled in the study and randomized to one of the 4 regimens listed below. Randomization into the study

was stratified by CD4% (< 25% or ≥ 25%) and age (< 2 years or ≥ 2 years). Initially 50 patients per treatment arm, 200 total subjects, were planned for the study.

Treatment Arms:
Trt A: d4T + Nevirapine (NVP) + Ritonavir (RTV)
Trt B: d4T + 3TC + NFV
Trt C: d4T + NVP + NFV
Trt D: d4T + 3TC + NVP + NFV

Study drug dosing:
In PACTG 377 study drugs were administered at the following doses:

- 3TC: 4 mg/kg/dose BID
- d4T: 1 mg/kg/dose BID if < 30 kg; 30 mg BID if ≥ 30 kg < 60 kg; 40 mg BID if ≥ 60 kg
- RTV: 400 mg/m^2/dose BID
- NVP: 120 mg/ m^2/dose QD for 14 days, then 120 mg/ m^2/dose bid
- NFV: 30 mg/kg TID up to a maximum dose of 1250 mg TID for patients weighing more than 37 kg. Version 3 of the protocol, dated June, 1999, changed the dose of NFV to 50-55 mg/kg BID with food, with a maximum of 2000 mg BID (doses rounded up or down to the nearest 125 mg increments)

The PACTG 725 substudy was designed to determine the virologic efficacy and safety, and pharmacokinetics of BID administration of NFV in combination with d4T and 3TC in subjects who weighed less than 30 kg dosed as follows:

- NFV in PACTG 725: 55 mg/kg BID given as tablets

Patients in both PACTG 377 and 725 were evaluated for safety and efficacy at screening, baseline, and every 4 weeks through 48 weeks. Version 3 of the protocol extended the study to 96 weeks for those patients remaining on study treatment at 48 weeks. Safety evaluation included physical examination, interim history, reporting of AEs, and laboratory monitoring. Laboratory monitoring included: routine hematology, serum chemistry tests (creatinine, total bilirubin, ALT, AST, triglycerides, cholesterol, CPK, uric acid, and glucose). Urinalysis was performed every 12 weeks.

Efficacy evaluations included determinations of absolute CD4 cell count and percentage and other lymphocyte subsets (CD3+/CD4+, CD3+/CD8+, and CD19+) and plasma HIV RNA levels by PCR.

PACTG 377 also incorporated an additional substudy evaluating the response to DTaP vaccine in children with HIV infection and intensive PK evaluation of some of the other drugs in Trts A, C, and D. These evaluations are not discussed in the submission and not included in this review.

Patient Population

Patients were eligible to enroll in PACTG 377 if they met the following inclusion criteria:

- Between 4 months and 17 years of age. Children randomized up to and on their 17th birthday are eligible.
- HIV infection according to the standard definitions employed by the Pediatric ACTG (defined in the protocol).
- Clinically and immunologically stable subjects defined as:
  - Absolute CD4 count ≥ 750 cells/mm^3 for those children < 12 month of age; ≥ 500 cells/mm^3 for those children 1-5 years of age; and ≥ 200 cells/mm^3 for those children 6-12 years of age within the last 4 months.

    OR
  - CD4 percent ≥ 15% within the last 4 months.
- Subjects must have received same continuous antiretroviral therapy for the past 16 weeks. "Continuous therapy" is defined as missing no more than total of 6 weeks of the same therapy during previous 16 weeks.
- Subjects who received immunomodulator therapy as a part of perinatal clinical trials or in trials for HIV-exposed subjects are eligible.
- Use of opportunistic infection prophylaxis, erythropoietin or G-CSF/GM-CSF, and IVIG is allowed.
- Subjects who received an antiretroviral as a part of a Phase I, or a perinatal trial are eligible, with the permission of the Lead Investigator.
- Previous ZDV, ddI, or ddC monotherapy or combination therapy with ZDV+ddI is permitted.
- Parent or legal guardian with the willingness and eligibility to provide written consent.

Patients were not eligible to enroll if they met any of the following exclusion criteria:

- Current Grade 3 or 4 clinical or laboratory toxicity as defined by the ACTG Pediatric Toxicity Tables.
- Active opportunistic infection and/or serious bacterial infection at the time of study entry.
- Current or prior antiretroviral therapy with single agent included in the treatment arms offered in this study. This includes prior treatment with d4T, nelfinavir, nevirapine, ritonavir, or 3TC. Prior treatment with any protease inhibitor is not permitted due to potential cross resistance.
- Subjects require treatment with any of the disallowed medications (listed in protocol).
- Investigational drug therapy during the 14 days before randomization.
- Current diagnosis of malignancy.

- Pregnancy: females of childbearing potential must have negative serum pregnancy test documented within 24 hours of randomization.

In addition to these criteria, patients enrolling in the PACTG 725 substudy must meet the following criteria:

- Subjects meet enrollment criteria for ACTG 377.
- Subjects must weigh <30kg.
- Subjects must be capable of swallowing tablets.

Study Results

Fifty sites participated in the study, each enrolling from 1 to 10 patients. The combined studies enrolled 193 patients between December 29, 1997, and September 30, 1998, 181 patients in the primary protocol (PACTG 377) and 12 in the PK substudy (PACTG 725). The study report includes data through the last observation on July 8, 1999. The entry characteristics of patients enrolled in PACTG 377 are summarized in Table 13.

Table 13: Baseline demographic and disease characteristics for all evaluable patients - PACTG 377

	Total	Trt A	Trt B	Trt C	Trt D
Number of patients entered	181	41	52	44	44
Median age at entry - years	5.9	4.7	6.5	6.2	7.0
Age entry					
< 2	21 (12%)	7 (17%)	7 (13%)	4 (9%)	3 (7%)
2 to < 7 years	88 (49%)	24 (59%)	21 (40%)	24 (55%)	19 (43%)
≥ 7 years	72 (40%)	10 (24%)	24 (46%)	16 (36%)	22 (50%)
Race/ethnicity					
White, non-Hispanic	19 (10%)	2 (5%)	5 (10%)	4 (9%)	8 (18%)
Black, non-Hispanic	112 (62%)	27 (66%)	35 (67%)	30 (68%)	20 (45%)
Hispanic	50 (28%)	12 (29%)	12 (23%)	10 (23%)	16 (36%)
Gender					
Male	84 (46%)	21 (51%)	24 (46%)	20 (45%)	19 (43%)
Female	97 (54%)	20 (49%)	28 (54%)	24 (55%)	25 (57%)
Prior antiretroviral therapy					
ddI	62 (35%)	14 (35%)	15 (29%)	17 (40%)	16 (38%)
ZDV+ddI	105 (59%)	24 (60%)	36 (69%)	21 (49%)	24 (57%)
Other	10 (6%)	2 (5%)	1 (2%)	5 (12%)	2 (5%)
CD% stratification					

< 25%	65 (36%)	11 (27%)	18 (35%)	18 (41%)	18 (41%)
≥ 25%	116 (64%)	30 (73%)	34 (65%)	26 (59%)	26 (59%)
Median Baseline CD4 cell count/mm3					
< 500	53 (29%)	9 (22%)	16 (31%)	14 (32%)	14 (32%)
500-999	73 (40%)	19 (46%)	15 (29%)	21 (48%)	18 (41%)
1000-1499	28 (15%)	6 (15%)	12 (23%)	2 (5%)	8 (18%)
1500-1999	15 (8%)	4 (10%)	5 (10%)	4 (9%)	2 (5%)
≥ 2000	12 (7%)	3 (7%)	4 (8%)	3 (7%)	2 (5%)
Median Baseline log HIV RNA					
< 3	9 (5%)	1 (2%)	2 (4%)	1 (2%)	5 (11%)
3 to < 4	45 (25%)	10 (24%)	11 (21%)	14 (32%)	10 (23%)
4 to < 5	89 (49%)	19 (46%)	25 (48%)	23 (52%)	22 (50%)
5 to < 6	36 (20%)	11 (27%)	14 (27%)	6 (14%)	5 (11%)
> 6	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)

Source: NDA 20-778, SE5-022, PACTG 377 Week 48 Core Analysis, Volume 21, pg 25, 26.
Trt A - d4T+NVP+RTV
Trt B - d4T+3TC+NFV (TID)
Trt C - d4T+NVP+NFV (TID)
Trt D - d4T+3TC+NVP+NFV (TID)

Patients in PACTG 725 received the same regimen as those in Trt B of the PACTG 377 except that the NFV was dosed BID instead of TID. Many of the analyses of safety and efficacy compare the 11 patients who received study drug in PACTG 725 to the 52 patients receiving Trt B in PACTG 377. Patients enrolled in PACTG 725 had a median age of 7.8 years at entry (none were < 2 years), 73% were female, 91% were black, non-Hispanic and 9% were Hispanic. Thirty-six percent of this group had received prior therapy with ddI and 64% had received ZDV + ddI therapy. The median CD4 cell count was 710 cells/mm3 and 18% of patients were < 500 cells/mm3 at study entry. The median log HIV RNA was 4.4 with 18% of patients having baseline HIV RNA levels > 5 log.

Table 14 summarizes the status of patients enrolled in PACTG 377/725 through the end of the study in October, 1999, as reported by the investigators. Most patients in the studies either remained on study treatment through that time or had completed the protocol required follow-up. In this study, patients were discontinued from study if they met a virological endpoint (did not achieve HIV RNA < 400 or at least a 2 log decrease within 12 weeks), if they experienced a protocol defined toxicity or if they had clinical progression of disease. A total of 12 patients required withdrawal from study treatment because of defined toxicity or clinical endpoints and no patients were reported withdrawn because of virologic failure.

Table 14: Disposition of Patients Enrolled – PACTG 377 and 725 (as of the study closure date)

	Trt A	Trt B	Trt C	Trt D	Trt Q
Number of patients enrolled	41	52	44	44	12
Number evaluable*	41	52	44	44	11
On study	30	28	26	37	5
Still on treatment	25	25	20	31	5
Off treatment	5	3	6	6	0
Completion of protocol	1	2	2	3	0
Toxicity defined by protocol	0	0	1	2	**
Clinical endpoint	4	1	3	1	0
Off study	11	24	18	7	6
Completion of protocol	11	17	13	7	5
Refuses further contact	0	2	2	0	0
Unable to contact	0	1	1	0	0
Other***	0	4	2	0	1
Deaths	0	0	0	0	0

Source: NDA 20-778, SE5-022, PACTG 377 Week 48 Core Analyses, Volume 21, pg 18, 19.
Trt A - d4T+NVP+RTV
Trt B - d4T+3TC+NFV (TID)
Trt C - d4T+NVP+NFV (TID)
Trt D - d4T+3TC+NVP+NFV (TID)
Trt Q – d4T+3TC+NFV (BID)
*Number evaluable includes all patients entered who had started study treatment.
**No listing
***Other includes family request, patient moved away, nonadherence, etc.

Enrollment into the study was designed to complete the PK evaluations first. This led to some initial imbalance in randomization since some patients who chose not to enroll in the intensive PK were enrolled later as the study progressed. It is unlikely that this had any significant impact on the results of the study. A discussion of protocol violations or exemptions was not included with the study report.

Efficacy Analysis

This submission contains both the original study analysis report for PACTG 377/725 and the applicant's reanalysis of some of the efficacy results. The Week 48 Core Analyses Report from the PACTG investigators and statisticians provided the original efficacy analysis defined in the protocol. In this analysis, 3 primary virologic endpoints were defined in the protocol:

- The level of "undetectable RNA" is defined to be plasma HIV RNA level of less than or equal to 400 copies/ml. A subject is classified as having "undetectable RNA" at 12/16 weeks if the subject achieves an undetectable level of RNA (≤ 400 copies/mL) on at least two of three RNA determinations taken at weeks 8, 12, and 16. A subject is classified as having "undetectable RNA" at 48 weeks if the subject achieves an undetectable level of RNA on both RNA determinations taken at 44 and 48.
- A subject is classified as having "RNA suppression" at 12/16 weeks if the subject achieves at least a 2 log decrease from baseline on at least two of three RNA determinations at weeks 8, 12, and 16 and these two lowest RNA values are both less than 10,000 copies/mL. For a subject whose baseline value is already within 2 logs of the undetectable level, a drop to "undetectable RNA" is considered to be "RNA suppression". A subject is classified as having "RNA suppression" at 48 weeks if the subject achieves at least a 2 log decrease from baseline on both RNA determinations at weeks 44 and 48 and both of these RNA values are less than 10,000 copies/mL.
- An additional primary endpoint for this study was virologic failure. A subject was classified as virologic failure at weeks 12/16 if the subject did not achieve either "undetectable RNA" at 12/16 weeks or "RNA suppression" at weeks 12/16. A subject was classified as virologic failure at week 24 or beyond if the subject experienced a value above 10,000 copies/mL (which is also rebound of 0.75 logs or more relative to the RNA nadir.

There were 4 subjects with undetectable HIV RNA at baseline who were not evaluated for the mentioned primary endpoints (2 each in Trt B and Trt D). In the investigator's report all treatment arms in PACTG 377 were analyzed. The patients enrolled in the substudy PACTG 725 were analyzed separately and compared to those patients receiving Trt B in 377. For this review, the substudy BID dose results were incorporated into the same tables as the main protocol results. Table 15 below displays the proportion of children who had detectable HIV RNA at baseline remaining on initial protocol therapy and having undetectable HIV RNA at different timepoints in the study.

Table 15: Proportion of Patients Achieving HIV RNA ≤ 400 copies/mL and Remaining on Randomized Therapy – PACTG 377 and 725

Study Visit	Trt A (N = 41)	Trt B (N = 50)	Trt C (N = 44)	Trt D (N = 42)	Trt Q (N = 11)
Week 4	18	17	17	17	6
Week 8	20	21	23	24	6
Week 12	18	22	21	29	6
Week 24	16	24	18	28	7
Week 36	15	26	15	25	6
Week 48	17 (41%)	21 (42%)	13 (30%)	22 (52%)	6 (55%)

Source: NDA 20-778, SE5-022, PACTG 377 Week 48 Core Analyses, Volume 21, pg 41.

Trt A - d4T+NVP+RTV
Trt B - d4T+3TC+NFV (TID)
Trt C - d4T+NVP+NFV (TID)
Trt D - d4T+3TC+NVP+NFV (TID)
Trt Q – d4T+3TC+NFV (BID)

The investigators provided pairwise comparisons of the 4 different treatment arms at each visit. They also compared the Trt B with the BID regimen from substudy 725 (Trt Q in the table). At Week 48, the only significant difference identified between treatment groups was that between Trt C (d4T + NVP + NFV) and Trt D (d4T + 3TC + NVP + NFV) ($p = 0.048$). Although the numbers in the BID substudy were small, there was no difference in efficacy between the similar BID and TID NFV regimens.

One of the secondary analyses performed by the original investigators included an analysis of the effect of baseline HIV RNA level on efficacy of the drug regimens. In general, the proportion of patients achieving HIV RNA levels ≤ 400 copies/mL was significantly greater among children with a lower baseline HIV RNA. For all treatment arms in PACTG 377, the proportion of patients reaching undetectable HIV RNA at 48 weeks of study therapy was 60% for those with baseline RNA < 3.9 log, 34% for those with baseline RNA 3.9 to < 4.4 log, 42% for those with 4.4 to < 4.9 log, and 30% for those with ≥ 4.9 log ($p = 0.01$).

The applicant has also included in an Abbreviated Supplementary Clinical Study Report of PACTG 377 their analyses of similar efficacy parameters stratified by age (< 2 years or ≥ 2 years). The applicant did not include analysis of Trt A (d4T + NVP + RTV) since this arm did not contain NFV. In subjects < 2 years of age, the rates of undetectable RNA at week 24 ranged from 50% (2/4 subjects) for d4T + NVP + NFV to 83% (5/6) for d4T + 3TC + NFV. At week 48, the rates of undetectable RNA ranged from 50% (3/6 and 2/4 subjects, respectively) for the d4T + 3TC + NFV and d4T + NVP + NFV regimens to 67% (2/3 subjects) for the 4-drug combination regimen. In subjects ≥ 2 years of age, the rates of undetectable RNA at week 24 ranged from 40% (16/40 subjects) for d4T + NVP + NFV to 67% (26/39 subjects) for the 4-drug combination. At week 48, rates of undetectable RNA ranged from 33% (13/40 subjects) for d4T + NVP + NFV to 56% (22/39 subjects) for the 4-drug combination. For all treatment regimens incorporating NFV, the percentage of subjects < 2 years of age who had undetectable RNA at weeks 24 and 48 was equal to or greater than the respective percentages for subjects ≥ 2 years of age, although the numbers of patients < 2 years was small.

In our statistical analysis, Dr. Zhou evaluated mean HIV RNA levels by study visit and the mean change from baseline in HIV RNA over time. The mean HIV RNA dropped from 4.5 to 3.0-3.2 $\log_{10}$ at Week 4 and was maintained through Week 48 with slightly changes. Her review confirmed the investigators' main

conclusion that there was little difference between the treatment arms but the 4-drug Trt D performed somewhat better in some analyses. At Week 12, the mean HIV RNA levels in Trt D were statistically significantly less than those in Trt A and Trt C. At Week 24, the mean HIV RNA levels in Trt D were statistically significantly less than those in Trts A, B, and C. Patients in Trt Q had the greatest reduction in plasma HIV-1 RNA and subjects in Trt C had the least reduction. However, the mean changes from baseline in HIV-1 RNA were not significantly different among treatment groups. A more detailed description of Dr. Zhou's analysis is included in Appendix A.

An analysis of CD4 cell count changes over time was also provided by the investigators although CD4 data were not included in the electronic datasets. In general, CD4 absolute cell counts and CD4 percentage increased over time in all treatment groups in PACTG 377/725. According to the investigator's report, there were no significant differences among the different treatment groups through 48 weeks. A lower baseline CD4 cell count was associated with a lower likelihood of achieving ≤ 400 copies/mL at Week 48 in a multivariate logistic regression model.

The applicant interprets these data from PACTG 377/725 to support the use of NFV as part of combination antiretroviral therapy for HIV-infected children. They suggest that the rates of response through 48 weeks were similar in patients < 2 years of age and those ≥ 2 years of age although relatively few patients < 2 years were included in PACTG 377. The applicant also believes that the results of substudy 725 supports their proposal for dosing NFV at 55 mg/kg BID in children between 2 and 13 years of age.

PENTA-7: An international, multicenter, phase I/II, nonrandomized, open-label study to evaluate the toxicity, tolerability, pharmacokinetics, and activity of triple antiretroviral combination therapy in vertically infected infants less than 12 weeks of age.

Summary of Study Design

This was an open-label, noncomparative, international, multicenter trial of nelfinavir used in combination with d4T and ddI in subjects younger than 12 weeks of age who were vertically infected with HIV-1 but did not have AIDS. 25 subjects were planned for enrollment, and the subjects were followed up for at least 72 weeks.

Each subject received the following study regimen:

- D4T suspension: 2 mg/kg per day in 2 divided doses
- ddI suspension: 200 mg/m2 per day in 2 divided doses

- NFV: Initially administered orally as a powder at a dosage of 90 mg/kg per day in 3 divided doses (30mg/kg TID). In September 1999, the protocol was amended to allow the administration of tablets instead of powder because of infants' refusal due to the taste and large volume. The tablets were crushed and dissolved into liquid or mixed into food. Amendment 3 to the protocol increased the dose given to the subjects to 120 mg/kg per day. After analysis of pharmacokinetic data suggested higher doses were necessary to achieve adequate drug exposure, Amendment 4 switched the NFV dosing to a BID regimen and increased the dosage for new subjects from 120 mg/kg per day (40 mg/kg TID) to 150 mg/kg per day (75 mg/kg BID). Previously enrolled subjects were to be kept at the same dose but with a BID dosing regimen (60 mg/kg BID).

Patients were seen at the research site at screening, baseline, Week 2, Week 4, and every 4 weeks through Week 48 , then every 6 weeks through Week 72. Patients were evaluated for efficacy of the study regimen by measurements of HIV RNA level and CD4 cell counts conducted at screening/baseline, Week 4, Week 12, and every 12 weeks thereafter. Safety was evaluated by recording AEs at each visit, documenting serious AEs and relationship to study drug. Laboratory monitoring for toxicity was performed at every visit and included routine hematology studies and serum chemistry tests (AST, ALT, alkaline phosphatase, bilirubin, triglycerides, creatinine, albumin, potassium, sodium, phosphorus, calcium, lipase, amylase). Full pharmacokinetic evaluation of NFV, d4T, and ddI were performed at Week 2. Drug concentrations were measured at a specified time at each study visit.

Patient Population

To be eligible for participation in the study, patients had to meet the following inclusion criteria:

- HIV-1 infection as documented by HIV detection on 2 separate occasions (HIV DNA PCR, culture, HIV RNA PCR, or p24 antigen)
- Aged less than or equal to 12 weeks; in case of delayed diagnosis, inclusion up to 16 weeks was considered.
- No hematological, hepatical or renal contraindication to d4T, ddI or NFV
- No exposure to any of d4T + ddI or NFV in utero,
- No AIDS defining events.
- Written informed consent signed by parents or the legal guardian after a detailed presentation of the study and before any eligibility procedure can be discussed with the trial center.

Patients were not eligible to enroll in the study if they met any of the following exclusion criteria:

- In utero exposure to ddI plus d4T combination or NFV
- Severe hepatic or renal insufficiency.

- Any abnormality of the child leading to problems of intake and absorption of the drug, such as vomiting, persistent diarrhea or serious malabsorption.
- Abnormality of hematological, hepatic, pancreatic or renal laboratory values, defined by the following thresholds:
  - Total bilirubin > 3 ULN
  - AST or ALT > 5 ULN
  - Creatinine > 3 ULN
  - Leukocytes < 1500/mm^3 and/or neutrophils < 750 mm^3.
- Need for therapy with agents contraindicated with use of NFV such as rifabutin or cisapride.
- Likely not to comply with treatment.
- Any AIDS defining event.

Study Results

A synopsis of the original investigators' clinical study report was provided in this submission, rather than the full study report. The applicant also provided a summary of the data. A total of 20 infants were enrolled in PENTA-7. Patients were enrolled from centers in France, Germany, Italy, Spain and the United Kingdom. The study period dated from the first subject's enrollment on August 25 1999 and follow-up was still ongoing at the time of submission of the study report. Ten (50%) of enrolled subject were boys, and 10 (50%) were girls. Nine (45%) of the subjects were black African, 9 (45%) were white, 1 (5%) was black Caribbean, and 1 (5%) was classified as other race. The mean age was 2.6 months, with a range of 0.9 to 4.7 months. Table 16 displays the baseline demographic and disease characteristics of the patients enrolled in the study.

Table 16: Demographic and Baseline Disease Characteristics of Patients Enrolled – PENTA-7

Characteristic	Number (%)
Age in months:	
< 1	2 (10%)
< 3	12 (60%)
> 3	6 (30%)
Mean age in months (range)	2.6 (0.9-4.5)
Sex: no. (%) of subjects	
Female	10 (50%)
Male	10 (50%)
Race: no. (%) of subjects	

White	9 (45%)
Black	10 (50%)
Other	1 (5%)
Mode of delivery	
Elective cesarean	7 (35%)
Emergency cesarean	4 (20%)
Vaginal delivery	9 (45%)
Mean gestational age (range)	36 (24-40)
Mean birth weight in kilograms (range)	2.66 (0.65-3.62)
Mean weight at entry - kg (range)	2.65 (0.65-3.62)
CDC stage at entry	
N (not symptomatic)	12 (60%)
A (mildly symptomatic)	5 (25%)
B (moderately symptomatic)	3 (15%)
Median log HIV RNA (IQ range)	5.51 (5.40-5.97)
Median CD4 percentage (IQ range)	33 (25-46)

*Source: NDA 20-779, AG1343-PENTA 7A Synopsis Report, Vol 020, Page 235.

Efficacy Analysis

The primary efficacy analyses performed by the investigators were the changes in HIV RNA levels and CD4 cell counts from baseline through 24 weeks of treatment. HIV RNA levels decreased rapidly over the first 12 weeks of treatment. The median plasma levels did not continue to decrease after week 12 but they remained below baseline levels through Week 48. Median plasma HIV RNA reduction from baseline was -2.1 log and -1.9 log at Weeks 24 and 48, respectively. The percentage of subjects with plasma HIV RNA levels < 400 copies/mL and < 50 copies/mL by week on study treatment are presented in Table 17. These calculations include the 5 infants who had extra antiretroviral drugs added to their study regimen.

Table 17: Percentage of Subjects with Plasma HIV RNA Below 400 Copies/mL or Below 50 Copies /mL by Study Week – PENTA-7

Study Week	Number of Subjects Tested	Number (%) with HIV RNA < 400 copies/mL	Number (%) with HIV RNA < 50 copies/mL
4	18	2 (11%)	0 (0)
12	19	6 (32%)	2 (11%)
24	20	8 (40%)	4 (20%)
36	17	7 (41%)	4 (24%)
48	19	7 (37%)	4 (21%)

*Source: NDA 20-779, AG1343-PENTA 7A Synopsis Report, Vol 020, Page 240.

The investigators also calculated the change in CD4 cell counts and percentage from baseline to different study timepoints. Table 18 summarizes these changes through 48 weeks of study dosing, including those patients who had extra antiretroviral drugs added to their regimens.

Table 18: Changes in CD4 Results from Baseline

Week	Absolute CD4 Count (cells/μL)		CD4%	
	N	Median (Range)	N	Median (Range)
4	19	845 (-2897-2250)	18	2.5(-23-34)
12	19	567 (-4925-2405)	19	8.0(-41-31)
24	19	626 (-4815-3065)	19	4.0(-35-33)
36	17	417 (-4845-2244)	18	4.0(-17-42)
48	20	170 (-4929-4689)	20	1.0(-41-35)

*Source: NDA 20-779, AG1343-PENTA 7A Synopsis Report, Vol 020, Page 240.

The original investigators came to several conclusions after completing their analysis of these study data. They noted that compliance with the powder formulation in infants was poor and that the crushed tablets were a viable alternative. The investigators conclude that the regimen d4T + ddI + NFV resulted in rapid decreases in HIV RNA but that long-term suppression required efforts to improve compliance and "administration of the appropriate dose of NFV." Without the full study report including discussion of analyses it is not possible to determine if they believed they had identified the appropriate dose for

this age group. However, in an abstract submitted to the 9th Conference on Retroviruses and Opportunistic Infections (Poster #809W) in 2002 and included in this submission, they express concern over the high rate of virologic failure and the difficulty in achieving undetectable HIV RNA levels. The poster text describes the development of resistance mutations to treatment in 5 of the 20 patients. The applicant does not echo these concerns but suggests that the efficacy results from PENTA-7 support the use of NFV in this age group at the doses studied.

D. Efficacy Conclusions

Collectively, the four pediatric treatment studies provide evidence of NFV's activity as part of a combination antiretroviral regimen for pediatric patients. All of the studies document that pediatric patients receiving NFV achieved significant mean decreases in HIV RNA levels over time and most also achieved increases in CD4 cell counts or percentages. These surrogate endpoints have been shown to predict improved clinical outcome in other antiretroviral drug studies. However, because of the differences in study design, doses and regimens studied, and age groups studied it was difficult to identify an effective dose in all age groups.

Two of the 4 treatment studies were open-label, single-arm studies in which the NFV-containing treatment regimen was not compared to other therapy. This type of study has been used frequently in pediatric age groups linked with PK data. From a regulatory perspective, a pediatric dosing regimen may be approved if it is supported by efficacy in adequate and well-controlled studies of the drug in adults and by data identifying a dose that achieves a similar PK profile. The original approval of NFV based on preliminary clinical and PK data from Study 524 fits this category. The longer term follow-up from Study 524 provided evidence of HIV RNA decreases in patients receiving a regimen containing NFV through 48 weeks. The proportion of patients who achieved the target viral load < 400 copies/mL was relatively low (about 20%) but patients in this study were not uniformly placed on what would now be considered an optimal NRTI background regimen. The PK profile described for children 2 to 13 years of age in this study was similar to the targeted adult PK.

The PENTA-7 study was another open-label, noncomparative study conducted in younger infants. Although patients had rapid and significant decreases in HIV RNA levels in the first 12 weeks of this study, the improvements were not continued through later visits. In spite of using the highest doses of NFV studied (150 mg/kg divided in BID dosing), only 37% of infants in this study achieved HIV RNA < 400 copies/mL at 48 weeks. This study included a patient population in whom the requirement for taking NFV with a meal may be the most difficult to accomplish and the drug-food effects may have had a significant impact. In this study, the NFV exposure achieved in the infants was below the targeted adult

exposure. This population is also most likely to have high HIV RNA levels since the young infant is encountering primary HIV infection in the face of an immature immune system unable to control viral replication. Suboptimal drug exposure (AUC_{24}) might be expected to result in virologic failure and emergence of resistance over the study period as was observed in this study.

PACTG 377 provided randomized though unblinded comparative data from 4 multi-drug treatment regimens, 3 containing NFV given TID. None of the regimens provide a direct comparison of NFV to another PI or NNRTI used in a similar background of NRTIs, however, the NFV-containing arms of the study achieved undetectable HIV RNA levels in 30% to 52% of patients. In the small substudy PACTG 725 evaluating a BID NFV regimen, 55% of patients achieved HIV RNA < 400 copies/mL at 48 weeks. In the substudy, the mean NFV exposure exceeded the target adult exposure although there was still significant variability. No PK data were available from the patients enrolled in the primary study who received the approved dose of NFV TID.

Only one of the studies, Study 556, provided efficacy results from a randomized, blinded study that allowed analysis of the contribution of NFV to the success or failure of a multi-drug regimen. This study compared NFV (TID) + ZDV + ddI to placebo + ZDV + ddI in patients with minimal prior treatment over a 48 week study period. In this study, the NFV-containing regimen clearly performed better than the placebo regimen with a greater proportion of patients achieving and maintaining HIV RNA < 400 copies/mL (21% compared to 3%) and the NFV patients achieving a longer time to loss of virologic response (median, 122 days compared to 0 and mean, 181 compared to 43). While the benefit of NFV was demonstrated with this study design, the magnitude of the virologic response rate at 48 weeks in a treatment-naïve population (21%) was disappointing. The study also demonstrated a difference in efficacy of the studied dose in patients < 2 years of age compared to those ≥ 2 years (10% compared to 26%). There are several potential explanations for the apparent poor results. First, because of the blinded, controlled study design, this study could be analyzed using the strictest definition of virologic response, similar to that used for large adult treatment studies. Using the original, less stringent, primary analysis defined in the study protocol, NFV appeared to perform better (about 40% response). This study also produced PK data that were the most variable of any of the studies submitted. It is possible that this variability in the PK in this population accounted for the low proportion of patients who achieved durable virologic response. Finally, the patients enrolled in this study had median HIV RNA levels at baseline that were higher than those generally seen in other studies.

Two of the study reports contained secondary analyses that may have implications for the response rates observed in the pediatric studies. Both Study 524 and PACTG 377 contained analyses of factors that contributed to the success or failure of the regimens being studied. In both analyses, patients with higher HIV

RNA levels at baseline were less likely to achieve virologic response as were patients with lower CD4 cell counts. As noted previously, patients enrolled in PENTA-7 and in Study 556 had mean baseline HIV RNA levels of about 5 log which were higher than those seen in many other studies of antiretroviral drugs.

Although the studies generally supported the activity of NFV as a component of antiretroviral treatment in pediatric patients, the response rates varied significantly across the studies. In general, response rates were lower than those observed in treatment-naïve adults receiving NFV. Response rates for patients less than 2 years of age appeared to be worse than those in patients 2 years of age and older. Associations between the doses studied and a reasonable level of effectiveness could not be concluded for all age groups for either TID or BID dosing. After careful review of the clinical and PK data submitted in this supplement we do not feel that we can select reliably effective doses for use in pediatric patients less than 2 years of age. We do not agree that an AUC_{24} of approximately 33-36 mg*hr/L as seen in the PENTA 7 and PACTG 353 studies can be correlated with adequate efficacy, particularly in light of the remarkable variability in exposures observed in the clinical trials. It is doubtful that variability would be less in a pediatric clinical use setting. Although the results of Study 556 were less robust than expected, data from Study 524 and PACTG 377 provide additional efficacy data at similar doses in patients 2 years of age or older.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

In general, the safety profile of NFV is similar in pediatric and adult patients with gastrointestinal adverse events observed most commonly. Diarrhea was reported in 9-15% of patients in the 2 studies of younger infants (PACTG 353 and PENTA-7) and at higher frequencies, 39-48%, in the studies enrolling a wider and older age range (Studies 524 and 556). It was also the adverse event most commonly identified as drug-related in the pediatric studies. Neutropenia appeared to be the most frequently identified laboratory abnormality in the pediatric studies. In PACTG 353 and PENTA-7, some degree of neutropenia was reported in 40-70% of infants enrolled and Grade 3 or 4 neutropenia was reported in 14-16% of older patients enrolled in Studies 524 and PACTG 377. Many of the antiretroviral drugs have overlapping toxicity profiles and since NFV was given in combination with a variety of other drugs in these studies, the contribution of NFV to toxicity is difficult to determine.

B. Description of Patient Exposure

The submission contains patient data from 5 studies conducted over a range of doses, schedules, patient populations, and time periods. Exposure to NFV was significantly different in each study and was presented in different ways in the individual study reports.

In the multiple dose phase of Study 524, all 65 patients received NFV at a dose of 20 to 30 mg/kg administered TID for up to 22 months after the initial 6 week observation period. All patients in Group I received the tablet formulation but 8 patients in Group II and 3 in Group III received tablets and powder for different periods of time during the study. As of the sponsor's data cut-off July 22, 1998, 6 of 16 (38%) Group I patients, 9 of 23 (39%) Group II patients, and 8 of 23 (35%) Group III patients had received NFV through the M11 study visit (about 1 year). Mean NFV exposure was 10 months.

In Study 556, patients received NFV at a targeted dose of 25 to 35 mg/kg administered TID for up to 48 weeks with the option to continue study through 96 weeks. The 66 patients randomized to NFV actually received doses from 22 to 35 mg/kg TID. The mean number of days on randomized therapy was 208 days in the placebo group and 350 days in the NFV group. As noted above, patients failing the placebo regimen (ZDV + ddI) could receive a salvage regimen of NFV + d4T + 3TC and those failing the NFV regimen could receive a salvage regimen of RTV + d4T + 3TC. During the course of the study, 94 patients failed their study regimen and were switched to salvage therapy, 67 placebo patients and 19 NFV patients. As noted above, a significant number of patients who were eligible to switch to salvage therapy did not.

In PACTG 377, patients randomized to one of the 3 NFV-containing arms received 30 mg/kg TID for up to 48 weeks. Patients enrolled in the substudy PACTG 724 received NFV at 55 mg/kg BID over the same study period. Through Week 48, the proportion of patients receiving assigned study treatment was 61% for Trt A (no NFV), 48% for Trt B, 45% for Trt C, 73% for Trt D, and 45% for the BID substudy. The median length of follow-up on study treatment ranged from 11.1 months to 12.0 months among the treatment groups.

In the PENTA-7 study, the first 8 patients enrolled in the study received 40 mg/kg TID. The remaining 12 patients received 75 mg/kg BID. Those patients who initially receiving TID dosing were converted to a BID dosing schedule by Week 16 but received 60 mg/kg BID to maintain the same total daily dose.

In PACTG 353, infants were enrolled in 2 cohorts with those in Cohort I (N=8) receiving 10 mg/kg TID and those in Cohort II (N=23) receiving 40 mg/kg BID for 6 weeks after birth. One infant in Cohort I and 4 infants in Cohort II were never dosed with NFV. According to the study's executive summary report, 22 infants completed the 6 week course of treatment.

C. Methods and Specific Findings of Safety Review

All patients who received at least one dose of study drug were included in the safety evaluations for each study. In PACTG 353, all infants were evaluated for safety since all had been exposed to NFV in utero. Adverse events (AEs) including SAEs and HIV-related events, laboratory monitoring, and treatment interruptions and discontinuations were reported and analyzed slightly differently for the 5 studies. Table 19 shows the number of patients available for the safety analysis from all studies and their corresponding targeted NFV dose regimens.

Table 19: Patients Evaluable for Safety in Submitted Studies

Study	NFV Dose Regimen	Ages Enrolled	Number of Patients Enrolled	Number of Patients Receiving NFV
AG1343-524	20 mg/kg TID	< 3 months to 13 years	65*	65
AG1343-556	25-35 mg/kg TID	3 months to 12 years	141	66
PACTG 377	30 mg/kg TID	4 months to 17 years	181	140
Substudy 725	55 mg/kg BID		12	11
PACTG 353	10 mg/kg TID	At birth	8	8**
	40 mg/kg BID		23	22**
PENTA-7	40 mg/kg TID or 60 mg/kg BID	< 3 months	8	8
	75 mg/kg BID		12	12

*One patient enrolled just before the data cut-off was not included in the final study report but was included in the electronic datasets and included in the review of safety.
**All patients were considered to have been exposed to NFV in utero and were evaluated for safety; 7Cohort I and 19 Cohort II infants received NFV after birth.

For Studies 524 and 556 for which complete electronic datasets were available, the reviewer's safety assessment may include more AEs or laboratory abnormalities than were reported in the applicant's final study reports since the datasets contain all reported events and the study reports used a data cut-off that excluded some of the later events. For the PACTG Studies 353 and 377 more limited datasets were available. In PACTG 353 only "targeted" AEs were reported, those that were Grade 3 or 4 or specific diagnoses. In PACTG 377, AEs were reported by category (eg. neurologic or gastrointestinal) rather than as specific events (eg. seizure or diarrhea). These differences in reporting and analysis did not alter the main conclusions related to NFV's safety profile in pediatric patients.

Adverse Events

In all studies submitted, AEs were reported in most of the patients enrolled in the studies regardless of age range or NFV dosing regimen. The AE profile for each study will be briefly described in this section. In the two applicant-sponsored protocols (Studies 524 and 556), laboratory abnormalities were recorded as AEs if the investigator believed that the event was clinically significant and reported it as an AE. Laboratory abnormalities were not uniformly reported as AEs and will be discussed in more detail in the Laboratory Abnormalities section below.

Study 524

The final study report for Study 524 notes that 14 of 22 patients in Phase A (the single-dose phase) and 59 of 64 patients in Phase B (the multiple-dose phase) reported at least one AE. The applicant reports AEs from the single-dose phase, the multiple-dose phase (up to the data cut-off), and the multiple-dose extension phase separately. The electronic dataset combines all phases of the study. Throughout the course of the study, 63 patients experienced 2017 AEs that were recorded as new or changed. Table 20 summarizes the most common AEs reported after Day 0 (baseline) of the multiple-dose phase of the study through the end of data collection.

Table 20: Treatment-emergent adverse events reported during Study 524 (N = 65) – after Day 0 of multiple-dose phase

Adverse Events	Number (%) Patients with Any AEs	Number (%) Patients with Grade 2-4 AE's	Number (%) Patients with Drug-Related AEs*
Abdominal pain	8 (12%)	1 (2%)	2 (3%)
Anemia	7 (11%)	4 (6%)	1 (2%)
Anorexia	4 (6%)	0	1 (2%)
Cough increased	30 (46%)	4 (6%)	0
Dermatitis/contact dermatitis	15 (23%)	1 (2%)	0
Diarrhea	31 (48%)	4 (6%)	16 (25%)
Ear disorder	12 (18%)	1 (2%)	0
Eczema	9 (14%)	2 (3%)	0
Fever	37 (57%)	19 (29%)	1 (2%)
Headache	9 (14%)	0	0
Hepatomegaly	8 (12%)	0	0
Injury accidental	12 (18%)	1 (2%)	0
Leukopenia	15 (23%)	12 (18%)	3 (5%)
Lung disorder	20 (31%)	4 (6%)	0
Lymphadenopathy	39 (60%)	3 (5%)	0

Monilia (oral or skin)	17 (26%)	2 (3%)	0
Otitis media	30 (46%)	9 (14%)	0
Pneumonia	12 (18%)	9 (14%)	0
Rash/maculopapular rash	30 (46%)	5 (8%)	4 (6%)
Rhinitis	58 (89%)	9 (14%)	0
Vomiting	23 (35%)	2 (3%)	0

*Drug-related AEs were those designated by the investigators as "associated with" or "possibly associated with" NFV.

As noted in the table, the most commonly reported events included rhinitis, lymphadenopathy, fever, diarrhea, cough increased, otitis media, and rash. Most of the AEs were not attributed to study drug and most were graded as mild in severity. Only 80 events reported by 22 patients were considered related or possibly related to NFV, with 60 of 80 of the drug-related AEs representing gastrointestinal complaints. Diarrhea was by far the most common AE attributed to study drug.

Study 556

In Study 556, the electronic datasets identify 125 (65 placebo, 60 NFV) of 141 patients with reported AEs after the baseline assessment (Day 0), for a total of 2258 reported events. The most commonly reported AEs are displayed in Table 21 below. When all AEs regardless of causality were evaluated, fever, increased cough, monilial infections, and otitis media occurred more frequently in patients receiving placebo (more than 10% difference between groups). This could reflect less effective treatment of underlying HIV disease. There were no significant differences between groups for events of moderate to severe intensity.

Table 21: Treatment-emergent adverse events reported during Study 556 (N = 141)

Adverse Events	Number (%) PLA Patients with Any AEs (N = 75)	Number (%) NFV Patients with Any AEs (N = 66)	Number (%) PLA Patients with Grade 2-4 AEs (N = 75)	Number (%) NFV Patients with Grade 2-4 AEs (N = 66)	Number (%) NFV Patients with Drug-Related AEs*
Anemia	27 (36%)	19 (29%)	13 (17%)	9 (14%)	0
Cough increased	18 (24%)	8 (12%)	0	1 (2%)	0
Dermatitis/contact dermatitis	3 (4%)	3 (5%)	0	1 (2%)	0
Diarrhea	32 (43%)	26 (39%)	9 (12%)	7 (11%)	10 (15%)
Fever	31 (41%)	19 (29%)	12 (16%)	4 (6%)	0
Hepatomegaly	16 (21%)	17 (26%)	1 (1%)	0	0
Hyperlipemia	6 (8%)	2 (3%)	0	0	2 (3%)
Leukopenia	9 (12%)	4 (6%)	6 (8%)	1 (2%)	0
Lung disorder	25 (33%)	19 (29%)	5 (7%)	3 (5%)	0

Monilia (skin, oral, vaginal)	26 (35%)	13 (20%)	2 (3%)	1 (2%)	0
Nausea	5 (7%)	3 (5%)	0	0	3 (5%)
Otitis media	30 (40%)	22 (33%)	10 (13%)	6 (9%)	0
Parasitic infection	18 (24%)	19 (29%)	0	0	0
Pharyngitis	24 (32%)	21 (32%)	3 (4%)	0	0
Pneumonia	19 (25%)	13 (20%)	13 (17%)	10 (15%)	0
Rash/maculopapular rash	16 (21%)	11 (17%)	4 (5%)	2 (3%)	1 (1%)
Rhinitis	20 (27%)	15 (23%)	0	0	0
Vomiting	16 (21%)	10 (15%)	4 (5%)	2 (3%)	5 (8%)

*Drug-related AEs were those designated by the investigators as "associated with" or "possibly associated with" NFV.

Presumed drug-related AEs were reported in 21 placebo patients (28%) and 18 NFV patients (27%). The most commonly designated drug related AEs included: diarrhea (in 11 placebo patients and 10 NFV patients), vomiting (3 placebo, 5 NFV), nausea (4 placebo, 3 NFV), and hyperlipidemia (3 placebo, 2 NFV). In this study, conducted in South America, patients receiving placebo had equally high rates of diarrhea as those receiving NFV but it must be remembered that these study regimens included ddI, also known to be associated with diarrhea.

PACTG 377/725

Only AEs graded as Grade 2 or higher according to the DAIDS Toxicity Table (for pediatric patients) were included in the study report analysis and in the electronic datasets for this study. AEs were grouped into categories defined in the study report. Laboratory abnormalities such as low neutrophils, low hemoglobin, or elevated ALT or AST were reported as AEs in the categories "neutropenia," "anemia," and "hepatic." This reporting system did not assign a relationship between the study regimen and the AE, so causality could not be attributed to NFV or any of the other study medications. The most commonly reported AEs overall were rash/skin events, nausea/vomiting, fever, and gastrointestinal events. AEs are summarized in Table 22 according to treatment. Few significant differences were seen among the treatment groups. Rash occurred more frequently among patients receiving a NVP-containing regimen (Trt A, Trt C, and Trt D). Among the treatment arms, Trt C appeared to have the highest rates of almost all AEs. Although rash/skin events, hepatic events, and neutropenia were more common among the Trt B TID patients and fever and gastrointestinal events were more frequent among the Trt Q BID patients (see shaded areas in Table 22), this is likely related to the small number of patients receiving the BID regimen.

Table 22: Moderate or worse toxicities (≥ Grade 2) by major category – PACTG 377/725

Adverse Event Category	Trt A (N = 41)	Trt B (N = 52)	Trt C (N = 44)	Trt D (N = 44)	Trt Q (N = 11)

Rash/skin	11 (27%)	9 (17%)	18 (41%)	14 (32%)	1 (9%)
Nausea/vomiting	12 (29%)	8 (15%)	14 (32%)	8 (18%)	2 (18%)
Fever	10 (24%)	5 (10%)	13 (30%)	9 (20%)	3 (27%)
Gastrointestinal	4 (10%)	10 (19%)	11 (25%)	8 (18%)	3 (27%)
Hepatic	5 (12%)	12 (23%)	6 (14%)	8 (18%)	2 (18%)
Respiratory	5 (12%)	8 (15%)	8 (18%)	10 (23%)	2 (18%)
Neutropenia	7 (17%)	12 (23%)	4 (9%)	6 (14%)	0
Pain/headache	4 (10%)	3 (6%)	6 (14%)	5 (11%)	1 (9%)
Anemia	4 (10%)	5(10%)	2 (5%)	5 (11%)	1 (9%)
Neurologic	1 (2%)	2 (4%)	5 (11%)	3 (7%)	1 (9%)
Edema	2 (5%)	3 (6%)	4 (9%)	1 (2%)	1 (9%)
Lymphadenopathy	2 (5%)	1 (2%)	4 (9%)	0	1 (9%)
Renal	1 (2%)	1 (2%)	0	1 (2%)	0
Other	2 (5%)	7 (13%)	3 (7%)	3 (7%)	1 (9%)

Source: NDA 20-778, SE5-022, PACTG 377 Week 48 Core Analyses, Volume 21, pg 60, 62.
Trt A - d4T+NVP+RTV
Trt B - d4T+3TC+NFV (TID)
Trt C - d4T+NVP+NFV (TID)
Trt D - d4T+3TC+NVP+NFV (TID)
Trt Q – d4T+3TC+NFV (BID)

In addition, the applicant performed an analysis of adverse events according to age (< 2 years or ≥ 2 years). Of events reported in at least 10% of subjects in either age stratum, rash/skin events and pain/headache were reported only in subjects ≥ 2 years (33% and 11%, respectively) and 4 AEs were reported at a higher incidence in subjects < 2 years: neutropenia (36% vs. 14%), hepatic events (36% vs. 17%), gastrointestinal events (36% vs. 19%), and fever (29% vs. 18%). There were relatively few patients < 2 years of age in each treatment group (3 to 7) and therefore no clear differences in the pattern of AEs according to age could be determined. Table 23 displays the Grade 2 or worse AEs from all the TID NFV regimens in PACTG 377 stratified by age. This analysis did not consider relationship of the AE to study drug.

Table 23: Moderate or worse toxicities (≥ Grade 2) by major category in patients receiving NFV*, stratified by age – PACTG 377

Adverse Event	Age < 2 years (N=14)	Age ≥ 2 years (N=126)
Rash/skin	0	41 (33%)
Nausea	3 (21%)	27 (21%)
Gastrointestinal	5 (36%)	24 (19%)
Fever	4 (29%)	23 (18%)
Respiratory	3 (21%)	23 (18%)
Hepatic	5 (36%)	21 (17%)
Neutropenia	5 (36%)	17 (14%)

Pain/headache	0	14 (11%)
Other	1 (7%)	12 (10%)
Anemia	1 (7%)	11 (9%)
Neurologic	1 (7%)	9 (7%)
Edema	0	8 (6%)
Lymphadenopathy	0	5 (4%)
Renal	0	2 (2%)

*This analysis excludes 41 patients enrolled in Trt A (d4T+NVP+RTV).

PENTA-7 Study

In PENTA-7, AEs of all grades and without regard to causality were presented. Both clinical events and laboratory abnormalities were included in the AE listings but it appears that not all laboratory abnormalities were included. This studied included younger patients than those enrolled in Studies 524, 556 and PACTG 377/725 and it is interesting that there are no reports of illnesses that would be commonly seen in young infants (eg. otitis media, respiratory illness). Consequently, there are some concerns about the completeness of the AE reporting. Table 24 displays the AEs reported during PENTA-7 that occurred in at least 2 patients.

Table 24: Non-serious adverse events reported in at least 2 patients (all grades and all causality) – PENTA-7

Adverse Event	Number of Patients (%)
Anemia	6 (30%)
Diarrhea, loose stool, unspecified or < 30 days	3 (15%)
Neutropenia	10 (50%)
Other biochemical abnormality*	9 (45%)
Raised AST, ALT, GGT, or bilirubin	4 (20%)
Raised alkaline phosphatase	8 (40%)
Vomiting	4 (20%)

Source: NDA 20-779, AG1343-PENTA 7A Synopsis Report, Vol 020, Page 237
*Other biochemical abnormality" includes increased calcium (7 patients), increased phosphorus (1 patient), increased lactate (1 patient), increased triglycerides (1 patient), and increased sodium (1 patient). Some patients experienced multiple abnormalities.

Of the 62 AEs reported during the study, 13 events occurring in 8 patients were considered drug-related. These events included: 3 episodes of vomiting, 2 episodes of diarrhea, 2 episodes of neutropenia, and one episode each of anemia, leukopenia, anorexia, rash/erythema, abdominal pain, and urticaria. Alternate etiologies for the AEs considered not related to study drug were not provided.

PACTG 353

The safety analysis for PACTG 353 included "targeted" AEs as defined in the protocol. These appear to be any events that were Grade 3 or 4 or ungraded specific diagnoses. Events were recorded only once per patient. A total of 83 AEs observed in 27 infants were included in the study report and datasets. Events occurring in at least 2 patients without regard to causality are displayed in Table 25.

Table 25: "Targeted" adverse events reported in at least 2 patients (all causality) – PACTG 353 (infants)

Adverse Event	Number of Patients with Event (%*)
Bronchiolitis	3 (14%)
Candida – oral (thrush)	7 (32%)
Cradle cap	2 (9%)
Diaper rash (including candida)	3 (14%)
Diarrhea	2 (9%)
Hemoglobin (low)	11 (50%)
Neutropenia	6 (27%)
Peripheral pulmonic stenosis	2 (9%)
Potassium (high)	5 (23%)
Seborrhea/seborrheic dermatitis	3 (14%)
Upper respiratory infection	3 (14%)

*Calculations based on 22 patients with any follow-up data.

Events were classified by the investigators as treatment-related, possibly treatment-related or not treatment-related. During the study, 17 infants reported 25 clinical or laboratory events that were considered at least possibly related to study drug. These events included: decreased hemoglobin (11 patients), neutropenia (5 patients), and increased bilirubin, increased creatine phosphokinase, low birth weight/small for gestational age, clinical sepsis, suspected pneumonia, pulmonary hypertension, diarrhea, and peripheral pulmonic stenosis (each reported in 1 patient). More details regarding the laboratory abnormalities are presented in the Laboratory Abnormalities section below.

Serious Adverse Events

Serious adverse events (SAEs) are a specific grouping of events that result in hospitalization, permanent disability or incapacity, cancer, congenital anomalies, or other medically important events. These events were reported for some but not all of the 5 studies included in this submission.

In Study 524, 17 patients documented in the dataset experienced 37 SAEs. All of the events were considered serious because they resulted in hospitalization. Four patients had hospitalizations documented that were not coded as SAEs in the database. NFV was not discontinued in any of these cases but other treatment was frequently administered (27 events). None of the SAEs were considered related to NFV use but were attributed to either underlying HIV disease (9 events), another condition (26 events), or another medication (2 events). SAEs reported in 2 or more patients included: gastrointestinal complaints (4 events, 3 patients), pneumonia (3 events, 3 patients), fever (3 events, 2 patients), and otitis media (2 events, 2 patients). There did not appear to be a pattern to the reported SAEs that suggested any contribution from study drug.

For Study 556, there was a discrepancy noted in the datasets related to the reporting of SAEs. The electronic dataset identifies 50 patients as requiring or prolonging hospitalization related to AEs, 22 NFV patients and 28 placebo patients. Only 46 of these patients are identified as having SAEs by the applicant. The most commonly reported SAE was pneumonia with 9 NFV patients and 13 placebo patients hospitalized for this reason, some more than once. Among the other SAEs observed most frequently were varicella zoster virus infection (3 NFV and 4 placebo patients), diarrhea (2 NFV, 4 placebo), thrombocytopenia (2 NFV, 2 placebo), otitis media (1 NFV, 3 placebo), gastrointestinal disorder (2 NFV, 1 placebo), and fever, vomiting, sepsis, and urinary tract infection (each in 2 placebo patients). None of these SAEs were considered related to study drug. Most were attributed to HIV disease or some other condition.

Three patients in PENTA-7 experienced SAEs. One of these patients, a pre-term infant with significant respiratory disease, experienced 2 SAEs – Grade 4 bronciolitis and Grade 4 dyspnea and shortness of breath – and subsequently died. Two other infants were hospitalized during the study, one for planned placement of a central venous catheter and one for suspected hip arthritis. None of the SAEs were considered related to study drug.

In PACTG 377/725, SAEs were not identified in the electronic datasets or the summary study report. Since specific events were not reported but were grouped into body system categories, it was not possible to distinguish events that might have been SAEs.

The investigators' study report for PACTG 353 did not identify SAEs. The applicant's summary notes that 6 events could be categorized as SAEs: 1 musculoskeletal congenital anomaly, 1 neoplasm (fetal cysts), 1 fetal disorder (intrauterine growth retardation), 1 pulmonary hypertension with sepsis and pneumonia, 1 abortion, and 1 still birth. The 2 events reported as "peripheral pulmonic stenosis" should also be considered SAEs since they may represent cardiac congenital anomalies.

Deaths

There were no deaths reported in Study 524 or in PACTG 377/725.

Four patients in Study 556 died, 2 in each of the randomized treatment arms. These deaths are described in brief below.

- Patient #03-2607 – This mixed race, female patient enrolled in the study at 18 months of age and was randomized to the NFV arm. She was admitted to the hospital on Day 8 of study with respiratory distress and left lower lobe infiltrate on chest x-ray. Study medications were discontinued on that day. She required mechanical ventilation, pressor support, and antibiotics. She died due to multi-organ failure and Pneumocystis carinii pneumonia (PCP) on study Day 21. The events leading to death were considered not related to NFV, PCP was considered associated with HIV.

- Patient #04-1209 – This mixed race, male patient enrolled in the study at 6 months of age and was randomized to the NFV arm. The patient switched to treatment with NVP, d4T, and 3TC on study Day 139 and continued on study. He was hospitalized on study Day 201 for meningococcemia, presenting with purpura, tachypnea, shock, anemia and thrombocytopenia. He received antibiotics, aggressive fluid therapy, and fresh frozen plasma and required mechanical ventilation but his condition continued to deteriorate. He experienced a cardiac arrest and died later the day of admission, study Day 201. The events leading to death were considered not related to NFV but associated with HIV.

- Patient #04-1210 – This mixed race, male infant enrolled in the study at 5 months of age and was randomized to the placebo arm. He had a history of gastroesophageal reflux, septicemia or endocarditis, neurodevelopmental delay, hepatomegaly, and pneumonia. The patient had 4 hospitalizations for gastroesophageal reflux and pneumonia (one complicated by malnutrition and hepatitis). He was switched to salvage treatment with NFV, d4T, and 3TC on Day 149 and continued on study. One week following his last hospitalization for pneumonia, he was admitted to the hospital in cardiac arrest. He did not respond to resuscitation efforts and died on study Day 328. The cause of death was described as bacteremic bronchopneumonia, possibly due to Pseudomonas, resulting in cardiac arrest. The events leading to death were considered not related to NFV but associated with HIV.

- Patient #05-1814 – This white, male patient enrolled in the study at 8 years and 6 months of age and was randomized to the placebo arm. On study Day 21 he was admitted to the hospital for a bone marrow aspirate to confirm hemophagocytic syndrome. The pathology report identified Hodgkin's lymphoma and the patient was withdrawn from the study. He died on study

Day 22. The events leading to death were considered not related to NFV and associated with HIV.

One infant enrolled in the PENTA-7 study died. Patient F-03001 died at 17 months of age after 60 weeks of study treatment. This patient was born at 30 weeks gestation and began study treatment at 15 weeks of age. The cause of death was identified as acute respiratory distress due to bronchiolitis obliterans ("obliterant bronchiolitis") related to prematurity. The death was not considered related to study drug or to HIV and the patients last measurement of HIV RNA level was 50 copies/mL.

In PACTG 353 one infant died of sepsis at 4 days of age with reported bilateral pneumonia and pulmonary hypertension. This infant was never dosed with study drug but had received NFV in utero. The study summary also reports as in utero deaths one case of therapeutic abortion and one case of obstetrical complications resulting in fetal demise. The 2 cases of in utero death were included in the applicant's Integrated Summary of Safety but the neonatal death was not.

Interruptions or Discontinuations of Study Drug

Although many patients were reported to have AEs, very few patients were reported to discontinue their study drug because of AEs. Treatment interruptions were not included in the datasets or study reports for all studies. Because of differences in reporting for the 5 studies, it was not possible to determine the total number of patients who interrupted or discontinued study drug because of AEs. Information available from each study will be discussed briefly.

According to the study report for Study 524, only one patient was discontinued from study drug because of an AE (diarrhea attributed to study drug). The applicant also notes that 3 additional subjects discontinued from the extended follow-up study because of AEs that were considered possibly related to study drug (diarrhea, taste aversion, and inadequate blood level).

In Study 556, a total of 4 patients, 2 in the placebo group and 2 in the NFV group, experienced AEs that resulted in treatment and study discontinuation. All 4 of these patients died within 2 weeks of discontinuation and are described in the section describing Deaths above. One additional patient required temporary interruption of study drugs because of a Grade 4 rash, initially considered possibly related to study drug. After resolution of the rash, study drugs were resumed without further problems.

The applicant's Integrated Summary of Safety notes that 19 patients enrolled in PACTG 377 and 725 discontinued the study because of AEs or clinical symptoms but does not provide relationship to study drug. In the submission, line listings generated by the study investigators identified 11 patients who "went off

treatment permanently" as of the data cut-off because of "toxicity defined by protocol." Two patients receiving Trt A, 6 receiving Trt C, and 3 receiving Trt D met this criterion. The AEs were not described. The line listings identified another 32 patients discontinuing treatment because of a "clinical endpoint," also not described.

The study report for PENTA-7 did not specify patients who interrupted or discontinued study drug because of AEs or other toxicity. The total daily dose of NFV was temporarily reduced for 6 patients during the course of the study, including 4 for whom the total daily dose was reduced because of body size change and dose recalculation, one for whom there was a problem with drug supplies, and one for whom the total daily dose was reduced when the formulation was changed.

Five infants enrolled in PACTG never started study drug. There is no indication that these infants discontinued study drug because of drug-related toxicity. The study summary noted that 2 infants in Cohort I had their treatment interrupted because of laboratory abnormalities. Four infants in Cohort II prematurely discontinued study treatment by request of the parents or investigators and 15 infants had "dose modifications" due to weight change, noncompliance, clinical toxicity, or vomiting. No further details were available.

Laboratory Abnormalities

As with other sections of the safety analysis, the evaluation and reporting of laboratory abnormalities was performed differently in the 5 pediatric studies submitted. Each study will be briefly discussed and important laboratory findings highlighted.

Study 524

All laboratory data collected in Study 524 were available for review. Table 26 summarizes the most common laboratory abnormalities observed after Day 0 (baseline) in the multiple dose phase of Study 524. In this study, cholesterol and triglyceride levels were not routinely monitored. The number of abnormal laboratory events and number of patients with abnormal laboratory values was greater when calculated from the electronic dataset than was reported in the final study report for the reasons previously mentioned. In this study, a large proportion of patients had milder laboratory abnormalities but only hypoglycemia (12%) and low absolute neutrophil count (ANC) (14%) were observed in a significant proportion of patients at Grade 3 or 4 level.

Table 26: Laboratory abnormalities observed after Day 0/Baseline of multiple dosing in Study 524 (N = 65)

Laboratory Test	Number (%) Patients with	Number (%) Patients with

(Reference range)	Any Grade Abnormality	Grade 3 or 4 Abnormality
ALT/SGPT (3-46 U/L)	21 (32%)	0
AST/SGOT (15-60 U/L)	25 (38%)	2 (3%)
Bilirubin (0-1.5 mg/dL)	7 (11%)	0
BUN (5-20 mg/dL)	7 (11%)	0*
Calcium (8.2-10.2 mg/dL)		
Hypocalcemia	6 (9%)	0
Hypercalcemia	24 (37%)	0
Creatinine (0.5-1.1 mg/dL)	2 (3%)	2 (3%)
Glucose (60-100 mg/dL)		
Hypoglycemia	37 (57%)	8 (12%)
Hyperglycemia	34 (52%)	1 (2%)
Potassium (3.5-5.3 mEq/L)		
Hypokalemia	3 (5%)	0
Hyperkalemia	18 (28%)	3 (5%)
Sodium (136-145 mEq/L)		
Hyponatremia	52 (80%)	4 (6%)
Hypernatremia	2 (3%)	0
Hemoglobin (9-15 g/dL)	15 (23%)	3 (5%)
Absolute neutrophil count ($1500\text{-}8000/mm^3$)**	41 (63%)	9 (14%)
Platelet count (140-440 x $10^3/mm^3$)	18 (28%)	4 (6%)

*No grading scale is included in protocol Toxicity Table for BUN but no markedly abnormal values were observed.

**The laboratory reference range lists 1500-8000 cells/mm^3 as the normal range for ANC however, Grade 1 toxicity was defined at 750-1200 cells/mm^3.

Study 556

All laboratory data collected in Study 556 were available for review, however the data were difficult to compile and analyze. Data from the 2 participating countries (Brazil and Argentina) were reported separately, sometimes in different units or different electronic format. Table 27 summarizes the most common Grade 3 or 4 laboratory abnormalities observed after Day 0 (baseline) in Study 556. Although not shown in the table, a large proportion of patients were noted to have milder laboratory abnormalities. Grade 3 and 4 abnormalities were identified in a relatively small number of patients in both treatment arms and there were no clear differences in severe laboratory toxicity between the 2 arms.

Table 27: Grade 3 or 4 laboratory abnormalities observed after Day 0/Baseline of multiple dosing in Study 556 (N = 141)

Laboratory Test (Grade 3 cut-off value)	Placebo Patients with Grade 3 or 4	NFV Patients with Grade 3 or 4 Abnormality

	Abnormality (N=75)	(N=66)
ALT/SGPT (≥ 460 U/L)	3 (4%)	0
AST/SGOT (≥ 370 U/L)	3 (4%)	0
GGT (≥ 350 U/L)	5 (7%)	0
Bilirubin (≥ 3.0 mg/dL)	1 (1%)	0
BUN (≥ 60 mg/dL)*	0	0
Calcium		
Hypocalcemia (< 7.0 mg/dL)	0	0
Hypercalcemia (≥ 12.0 mg/dL)	0	2 (3%)
Creatinine (≥ 1.2 mg/dL)	0	1 (2%)
Glucose		
Hypoglycemia (< 40 mg/dL)	1 (1%)	3 (5%)
Hyperglycemia (≥ 250 mg/dL)	0	1 (2%)
Potassium		
Hypokalemia (< 2.5 mEq/L)	0	0
Hyperkalemia (≥ 6.5 mEq/L)	2 (3%)	1 (2%)
Sodium		
Hyponatremia (< 130 mEq/L)	6 (8%)	3 (5%)
Hypernatremia (≥ 150 mEq/L)	1 (1%)	4 (6%)
Hemoglobin (< 7.0 g/dL)	3 (4%)	4 (6%)
Absolute neutrophil count (< 400 cells/mm^3)	4 (5%)	0
Platelet count (< 50 x $10^3/mm^3$)	7 (9%)	3 (5%)

*Test not performed at all sites.

PACTG 377/725

Full laboratory datasets were not provided for PACTG 377/725. Since there were other laboratory data available for patients in this age range, these datasets were not requested. Some laboratory abnormalities were included in the AE categories as "anemia," "neutropenia," and "hepatic" events. The most common Grade 2 or greater events were "neutropenia" reported in 16% of study patients and "anemia" reported in 9%.

PENTA-7

The laboratory data for PENTA-7 represent data from multiple sites in 5 countries. Additionally, this study evaluated a younger age group in whom normal and toxicity ranges for some laboratory tests in infants less than 3 months old vary according to age. For example, the cut-off value for Grade 1 neutopenia was ≤ 2500 cells/mm3 for infants 8 to 56 days old, ≤ 1800 cells/mm3 for infants 56 to 90 days old, and ≤ 1200 cells/mm3 for infants > 90 days old. During this study, the most frequently observed laboratory abnormality occurring after the baseline visit was neutropenia. Fourteen (70%) infants were documented to have at least Grade 1 neutropenia using the protocol defined cut-offs, although only 1

episode of Grade 3 neutropenia was identified. Low hemoglobin was documented in 10 (50%) infants, none with Grade 3 or higher toxicity. Three (15%) infants were noted to have elevated AST and ALT. These numbers do not necessarily match the number of infants with laboratory abnormalities reported as AEs.

PACTG 353

The initial supplement submission did not contain laboratory datasets for PACTG 353 but because this was the only study conducted in neonates these data were requested and submitted later in the review cycle. Since all infants were exposed to NFV in utero, all laboratory values obtained on all infants were evaluated rather than only those that occurred after the infant's first dose of NFV. In this study, the number of laboratory tests performed at each visit were more limited due to the infants' limited blood volume. Table 28 summarizes the laboratory abnormalities identified during the study. Laboratory abnormalities occurring after Week 12 are not included in this summary since it is less likely that abnormalities occurring after this time were related to study drug dosed for only 6 weeks.

Table 28: Laboratory abnormalities* observed in infants during PACTG 353 – through Week 12

Laboratory Test	Patients with any Graded Laboratory Abnormality - Number (%)**	Patients with Grade 3 or 4 Laboratory Abnormality – Number (%)**
Absolute neutrophil count	12 (40%)	6 (20%)
AST	2 (7%)	0
Bilirubin (total)	2 (7%)	1 (3%)
Calcium	1 (3%)	1 (3%)
Glucose	3 (10%)	0
Hemoglobin	19 (63%)	11 (37%)
Potassium	6 (20%)	5 (17%)
Sodium	2 (7%)	0

*Toxicity grades for some laboratory abnormalities in infants less than 3 months old vary according to age. Toxicity grades for those laboratory tests with age-dependent cut-offs were defined in the protocol.
**Percentage calculated based on N=30 infants with follow-up data

The study report did not describe the range of laboratory abnormalities observed during the study. Low ANC and hemoglobin were the laboratory abnormalities observed most frequently with 20% and 37%, respectively, of infants having Grade 3 or 4 abnormalities. All of these infants were also receiving ZDV, a drug well known to cause hematologic abnormalities, so the contribution of NFV to this toxicity remains difficult to characterize. In this study, 17% of infants were

noted to have Grade 3 or 4 hyperkalemia. These events were probably an artifact of the technical difficulty of drawing blood from small infants resulting in hemolysis of the specimens. There were no clinical events suggestive of true hyperkalemia. Also, 5 infants were noted to have serum creatinine > 1.0 mg/dL at the initial study contact prior to NFV dosing. These elevated values were observed only once per patient, declined in subsequent visits, and likely reflected maternal serum creatinine levels.

Postmarketing Analysis

The applicant provided a summary of the pediatric safety data collected from postmarketing surveillance reports. They note that almost 10,000 patients have received NFV oral powder. The most frequently reported AEs in patients 2 to 13 years of age was pneumonia. Cases of rash, diarrhea, and nausea were also reported. In patients < 2 years of age, the most frequently reported AE was neutropenia. Detailed description of the postmarketing safety reports was not provided. Because the postmarketing reports are voluntary and the total number of patients receiving NFV is not known, rates of AEs cannot be calculated.

Antiretroviral Pregnancy Registry Review

The applicant has also included a reference to data reported in the Antiretroviral Pregnancy Registry (APR), a voluntary prospective registry of women receiving any approved antiretroviral drug during pregnancy. A copy of the APR reporting events through January, 2002, was included as an attachment to the Integrated Summary of Safety data in the label.

D. Adequacy of Safety Testing

The datasets and study reports provided in this submission provide an adequate safety database to evaluate NFV in all pediatric age ranges. The data are most complete for patients between 2 to 13 years of age but data are also available for neonates and infants from 2 months to about 1 year of age. In general, the level of drug exposure in pediatric patients was somewhat lower than that observed in adult clinical trials but the safety profile was very similar. The length of follow-up was sufficient to evaluate the effects of chronic dosing of NFV.

E. Summary of Critical Safety Findings and Limitations of Data

The applicant noted that the safety profile of NFV has been evaluated in approximately 400 pediatric patients receiving a variety of doses and regimens in clinical trials. In general, the safety profile of NFV is similar in pediatric and adult patients with gastrointestinal events observed most commonly. There appeared to be little difference in the safety profile across the pediatric age range studied although laboratory monitoring in young infants was less intensive than in older children and some laboratory events may be less well-characterized in infants < 3 months old.

Diarrhea was reported in all of the pediatric studies but was reported at different frequencies. It was observed in 9-15% of patients in the 2 studies of younger infants (PACTG 353 and PENTA-7) and at higher frequencies, 39-48%, in the studies enrolling a wider and older age range (Studies 524 and 556). Rates of diarrhea were highest in Study 556, a study in which NFV was given in combination with ddI, another drug associated with diarrhea. However, ddI was also a component of the regimen in PENTA-7. Based on the submitted studies and the observed variability in drug exposures, it is difficult to identify whether the rate of diarrhea was correlated with drug exposure in pediatric patients although this has been suggested in adult studies.

Neutropenia appeared to be the most frequently identified laboratory abnormality in the pediatric studies. Study 556 was the only study not reporting Grade 3 or 4 neutropenia in patients receiving NFV. As previously noted, neutropenia was defined and reported differently across the studies. In some studies, "neutropenia" was reported as an AE while in others it was included in the laboratory data and the grading system for levels of neutropenia also differed. In PACTG 353 and PENTA-7, some degree of neutropenia was reported in 40-70% of infants enrolled. The cut-off values for all grades of neutropenia in infants < 3 months of age are very conservative (Grade 1 < 2500 cells/mm3 in the youngest infants) and may account for reporting increased laboratory abnormalities in this group. However, neutropenia was also reported in studies enrolling older children with Grade 3 or 4 abnormalities reported in 14-16% of patients in Studies 524 and PACTG 377. Some of the studies used NFV in combination with ZDV, another antiretroviral drug known to cause hematologic abnormalities.

Only one of the studies (Study 556) allowed direct assessment of the contribution of NFV to the toxicity of the antiretroviral regimen. In this study there were few differences in the safety profile of the NFV regimen compared to the placebo regimen. Many of the other approved antiretroviral drugs used in these studies have overlapping toxicity profiles and the contribution of NFV to the occurrence of clinical AEs and laboratory toxicities is difficult to determine.

The current product label displays adult AEs that are treatment emergent, moderate or severe intensity, and possibly/probably related to study drug (excluding HIV-related conditions). Adult laboratory values defined as "marked" abnormalities are displayed, lab values representing a shift from Grade 0 to Grade 3 or from Grade 1 to Grade 4. The applicant proposes that treatment-emergent, drug-related AEs for Studies 524 and 556 be displayed in a table in the product label, stratified at age 2 years. Drug-related AEs from the other pediatric studies (PACTG 377, PENTA 7, and PACTG 353) are described in the text. No listing of pediatric laboratory abnormalities was proposed for the revised label.

Because the safety profile was similar to adults and the occurrence of moderate or severe, drug-related AEs was relatively rare in the pediatric studies, the review team believes that this detailed display of data in the label is not warranted. We recommended a more limited text description of the most common AEs highlighting the most commonly reported drug-related AEs, rates of diarrhea of all causes, and leukopenia/neutropenia.

[ ]

VIII. Dosing, Regimen, and Administration Issues

NFV was previously approved for children 2 to 13 years of age at a dose of 20-30 mg/kg TID based on data from Study 524. PACTG 377 and Study 556 evaluated doses of 30 mg/kg TID and 25-35 mg/kg TID respectively in patients the same age. Although both the PK and efficacy data from these studies were variable, the review team believed that the weight of evidence suggested that a dose of 25-35 mg/kg TID provided adequate evidence of activity and across the studies produced an acceptable PK profile. This was considered a more appropriate dose than the previously approved dose and less likely to lead to inadequate NFV exposure.

Data from PACTG 725 provided both PK and efficacy data from a small cohort [ ] a dose of 55 mg/kg BID in patients 2 years of age or older. These PK data were subject to similar variability compared to the other studies. Although the dose of 55 mg/kg BID studied in PACTG 725 was tolerated, the AUC_{24} achieved with this dose was significantly higher than the target adult AUC_{24} and the [ ] Since the primary toxicity associated with NFV was diarrhea, the review team considered it unlikely that this drug-related toxicity would remain unnoticed.

The higher exposures observed with this dose would limit the number of patients with suboptimal NFV exposure. The review team recommended a BID dose of NFV of 45-55 mg/kg BID in patients 2 to 13 years of age. Since the NFV exposures observed in the study were higher than the target, we suggested making the studied dose the upper limit of a dose range that allows for some flexibility of dosing. We would not recommend dosing that would lead to potentially even higher exposures than were studied as might result from the applicant's proposed dose c

The review team did not feel that we could select reliably effective doses for use in pediatric patients less than 2 years of age. We do not agree that an AUC_{24} of approximately 33-37 mg*hr/L as seen in the PENTA 7 and PACTG 353 studies could be correlated with adequate efficacy, particularly in light of the remarkable variability in exposures observed in the clinical trials. It is doubtful that variability would be less in a pediatric clinical use setting. We were most concerned about the potential for variable exposure in this age group where eating habits may be erratic. We believed that there might be little margin for day-to-day fluctuations in exposure if young patients failed to eat meals large enough to affect drug absorption and that it would be extremely difficult to maintain continuously adequate exposure in this age group.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The applicant did not provide a formal evaluation of gender effects in the pediatric population receiving NFV. In general, the number of patients enrolled in each study was too small to provide useful information in a subgroup analysis. To date, none of the antiretroviral drugs have been shown to have differential efficacy or safety according to gender.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The applicant did not provide a formal evaluation of the effects of race or ethnicity in the pediatric population receiving NFV. In general, the number of patients enrolled in each study was too small to provide useful information in a subgroup analysis. To date, none of the antiretroviral drugs have been shown to have differential efficacy or safety according to race or ethnicity.

C. Evaluation of Pediatric Program

This submission completes the applicant's presentation of their pediatric development program for NFV. Agouron/Pfizer was granted pediatric exclusivity

in September, 2003, as a result of submitting these studies. A full evaluation of the pediatric development program for NFV is contained in this review.

D. Comments on Data Available or Needed in Other Populations

At this time, no specific studies are needed in other pediatric populations.

X. Conclusions and Recommendations

A. Conclusions

The pediatric data submitted in this supplement is adequate to approve new dose recommendations for the use of NFV in children from 2 to 13 years of age. After thorough review of the PK, efficacy, and safety data available for each of the 5 submitted studies, the review team agreed that the weight of evidence supported revisions of the pediatric dose recommendations. NFV dose recommendations for both 25-35 mg/kg TID and 45-55 mg/kg BID in patients 2 to 13 years of age will be included in the product label. Although the NFV exposure achieved with the BID dose studied in this age group [redacted] was significantly higher than the target adult exposure, safety data was adequate to support the dosing recommendations.

The review team also agreed that the data presented for patients < 2 years of age was much less conclusive. Although NFV drug exposure was highly variable in all the pediatric PK studies, there was concern that it would be even more difficult to achieve an effective exposure in young patients (< 2 years) in whom the drug-food effect might be less easy to control with diet. The unpredictable eating patterns of young children could lead to unacceptable day-to-day variations in drug exposure resulting in emergence of HIV resistance to NFV. The study evaluating NFV [redacted] patients < 3 months of age at enrollment provided relatively low drug exposure compared to the target exposure and suboptimal efficacy results. The study evaluating [redacted] provided adequate exposure in that narrow age range but provided no efficacy or long-term dosing safety data.

B. Recommendations

The review team recommended approval of new dosing recommendations for NFV in pediatric patients 2 years of age or older: 25-35 mg/kg TID or 45-55 mg/kg BID. All doses should be taken with a meal. It was decided that PK data from all PK studies submitted should be included in the label for completeness.

The major revisions made to the product label based on this review are described below:

- Pediatric PK information was incorporated into the product label in the **CLINICAL PHARMACOLOGY, Special Populations,** *Pediatrics* section as follows:

"The pharmacokinetics of nelfinavir have been investigated in 5 studies in pediatric patients from birth to 13 years of age either receiving VIRACEPT three times or twice daily. The dosing regimens and associated AUC_{24} values are summarized in Table 3.

Table 3
Summary of Steady-state AUC_{24} of Nelfinavir in Pediatric Studies

Protocol No.	**Dosing Regimen[1]**	**N[2]**	**Age (years)**	**AUC_{24} (mg*hr/L) Arithmetic mean ± SD**
AG1343-524	20 (19-28) mg/kg TID	14	2-13 years	56.1 ± 29.8
PACTG 725	55 (48-60) mg/kg BID	6	3 –11 years	101.8 ± 56.1
PENTA 7	40 (34-43) mg/kg TID	4	2-9 months	33.8 ± 8.9
PENTA 7	75 (55-83) mg/kg BID	12	2-9 months	37.2 ± 19.2
PACTG 353	40 (14 –56) mg/kg BID	10	6 weeks	44.1±27.4
			1 week	45.8 ± 32.1

[1] Protocol specified dose (actual dose range)
[2] N: number of subjects with evaluable pharmacokinetic results
C_{trough} values are not presented in the table because they are not available for all studies

Pharmacokinetic data are also available for 86 patients (age 2 to 12 years) who received VIRACEPT 25-35 mg/kg TID in Study AG1343-556. The pharmacokinetic data from Study

AG1343-556 were more variable than data from other studies conducted in the pediatric population; the 95% confidence interval for AUC_{24} was 9 to 121 mg.hr/L.

Overall, use of VIRACEPT in the pediatric population is associated with highly variable drug exposure. The variability makes it difficult to recommend doses that will reliably achieve exposure observed in adult patients. The high variability may be due to inconsistent food intake in pediatric patients."

- The basis for the pediatric indication with relevant age group, some issues to be considered when initiating NFV in pediatric patients, and brief descriptions of the major pediatric clinical trials were incorporated into the **PRECAUTIONS, Pediatric Use** section as follows:

"The safety and effectiveness of VIRACEPT have been established in patients from 2 to 13 years of age. The use of VIRACEPT in these age groups is supported by evidence from adequate and well-controlled studies of VIRACEPT in adults and pharmacokinetic studies and studies supporting activity in pediatric patients. In patients less than 2 years of age, VIRACEPT was found to be safe at the doses studied but a reliably effective dose could not be established (see CLINICAL PHARMACOLOGY: Special Populations, ADVERSE REACTIONS: Pediatric Population, and DOSAGE AND ADMINISTRATION: Pediatric Patients).

The following issues should be considered when initiating VIRACEPT in pediatric patients:

- In pediatric patients ≥ 2 years of age receiving VIRACEPT as part of triple combination antiretroviral therapy in randomized studies, the proportion of patients achieving an HIV RNA level <400 copies/mL through 48 weeks ranged from 26% to 42%.

- Response rates in children <2 years of age appeared to be poorer than those in patients ≥ 2 years of age in some studies.

- Highly variable drug exposure remains a significant problem in the use of VIRACEPT in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing. Pharmacokinetic results from the pediatric studies are reported in Table 3 (see Clinical Pharmacology, Special Populations).

Study 556 was a randomized, double-blind, placebo-controlled trial with VIRACEPT or placebo coadministered with ZDV and ddI in 141 HIV-positive children who had received minimal antiretroviral therapy. The mean age of the children was 3.9 years. 94 (67%) children were between 2 - 12 years, and _47 (33%) were < 2 years of age. The mean baseline HIV RNA value was 5.0 log for all patients and the mean CD4 cell count was 886 cells/mm^3 for all patients. The efficacy of VIRACEPT measured by HIV RNA <400 at 48 weeks in children ≥ 2 years of age was 26% compared to 2% of placebo patients (p= 0.0008). In the children < 2 years of age, only 1 of 27 and 2 out of 20 maintained an undetectable HIV RNA level at 48 weeks for placebo and VIRACEPT patients respectively.

PACTG 377 was an open-label study that randomized 181 HIV treatment-experienced pediatric patients to receive: d4T+NVP+RTV, d4T+3TC+NFV, d4T+NVP+NFV, or d4T+3TC+NVP+NFV with NFV given on a TID schedule. The median age was 5.9 years and 46% were male. At baseline the median HIV RNA was 4.4 log and median CD4 cell count was 690 cells/mm^3. Substudy PACTG 725 evaluated d4T+3TC+NFV with NFV given on a BID schedule. The proportion of patients with detectable viral load at baseline achieving HIV RNA <400 copies/mL at 48 weeks was: 41% for d4T+NVP+RTV, 42% for d4T+3TC+NFV, 30% for d4T+NVP+NFV, and 52% for d4T+3TC+NVP+NFV. No significant clinical differences were identified between patients receiving VIRACEPT in BID or TID schedules.

VIRACEPT has been evaluated in 2 studies of young infants. The PENTA 7 study was an open-label study to evaluate the toxicity, tolerability, pharmacokinetics, and activity of NFV+d4T+ddI in 20 HIV-infected infants less than 12 weeks of age. PACTG 353 evaluated the pharmacokinetics and safety of VIRACEPT in infants born to HIV-infected women receiving NFV as part of combination therapy during pregnancy."

- An updated description of the pediatric safety data was included in the **ADVERSE REACTIONS, Pediatric Population** section, highlighting the size of the safety database, the similarity of the safety profile in adults and children, and 2 of the most commonly reported toxicities (diarrhea and neutropenia).

"VIRACEPT has been studied in approximately 400 pediatric patients in clinical trials from birth to 13 years of age. The adverse event profile seen during pediatric clinical trials was similar to that for adults.

The most commonly reported drug-related, treatment-emergent adverse events reported in the pediatric studies included: diarrhea, leukopenia/neutropenia, rash, anorexia, and abdominal pain. Diarrhea, regardless of assigned relationship to study drug, was reported in 39% to 47% of pediatric patients receiving VIRACEPT in 2 of the larger treatment trials. Leukopenia/neutropenia was the laboratory abnormality most commonly reported as a significant event across the pediatric studies."

- The new dosing recommendations for children are included in the DOSAGE AND ADMINISTRATION, Pediatric Patients (2-13 years) section. These recommendations include tables (not shown below) that provide dosing guidelines for pediatric patients of different weights taking either the 250 mg tablets or the oral powder. Instructions for mixing the powder remain unchanged. The amended text of this section is noted below:

"In children 2 years of age and older, the recommended oral dose of VIRACEPT oral powder or 250 mg tablets is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily. All doses

should be taken **with a meal**. Doses higher than the adult maximum dose of 2500 mg per day have not been studied in children. For children unable to take tablets, VIRACEPT Oral Powder may be administered. For children unable to take tablets….."

XI. Appendix

A. Other Relevant Materials – Mathematical Statistics Analysis and Comments

1. Results and Conclusions

Study 556

The 48-week efficacy data of Study 556 demonstrated that the pediatric patients receiving the VIRACEPT regimen had an 18.5% greater virologic response than those receiving the placebo regimen, with a 95% CI of (9.7,27.4)% and $p<0.0006$ by the Mantel-Haenszel Chi-Square test.

The median increases from baseline in CD4 cell count were 103 cells/mm^3 for VIRACEPT patients and 128 for placebo patients at 24 weeks, and 192 for VIRACEPT and 233 for placebo at 48 weeks, respectively. There was no significant difference in mean CD4 cell count between the VIRACEPT and placebo regimens at baseline and during 48 weeks of follow-up.

The mean baseline HIV-1 RNA values were 5.0 and 5.1 $\log_{10}$ copies/mL for VIRACEPT and placebo patients, respectively. The temporal trends in HIV-1 RNA were significantly different between VIRACEPT and placebo patients from Week 2 to Week 24: (1) the mean HIV-1 RNA values in VIRACEPT patients were statistically significantly less than those in the placebo patients; (2) patients in the VIRACEPT arm had a 0.3 to 0.8 $\log_{10}$ copies/mL greater reduction in HIV-1 RNA compared with those in placebo arm. From Week 28 on, there was no significant difference.

PACTG 377

The mean HIV RNA decreased from 4.5 to 3.0-3.2 $\log_{10}$ at Week 4 and was maintained through Week 48 with slight changes. Subjects in Group Q had greatest reduction in plasma HIV-1 RNA, and subjects in Group C had the least reduction. However, the mean changes from baseline in HIV-1 RNA were not significantly different among treatment groups.

2. Overview and Data Sources

The statistical evaluation of efficacy includes the examinations of treatment differences in plasma HIV-1 RNA, CD4+, and the change from baseline in HIV-1 RNA and CD4+ for Study 556. Time to Loss-of-Virologic Response (TLOVR) using the DAVDP-defined TLOVR algorithm was also performed.

For PACTG 377, no follow-up CD4+ data were available for review; the efficacy evaluation was limited to the examinations of treatment differences in plasma HIV-1 RNA and the change from baseline in HIV-1 RNA.

The supplemental applications under NDA 20-778 collectively contain the results of the Study 556 and PACTG 377. The original electronic datasets and revised datasets for Study 556 and PACTG 377 were reviewed by the review team. In addition, the datasets for efficacy analyses not specified in the original protocol - Time to Loss-of-Virologic Response (TLOVR) – were also received along with SAS programs. Note the TLOVR algorithm has been recommended by the DAVDP for the efficacy evaluations of HIV-1 NDAs.

The SAS transportable files can be found in five different sites/dates. The Website addresses for are as follows:

N20778\S_22\2003-06-19\crt\datasets\556\
N20778\S_22\2003-08-21\crt\datasets\556\
N20778\S_22\2003-09-02\crt\datasets\556\
N20778\S_22\2003-10-22\crt\datasets\556\
N20778\S_22\2004-02-16\crt\datasets\556\

The Website addresses for PACTG 377 are as follows:

N20778\S_22\2003-06-19\crt\datasets\pactg377\
N20778\S_22\2003-08-21\crt\datasets\pactg377\
N20778\S_22\2003-09-02\crt\datasets\pactg377\
N20778\S_22\2003-10-22\crt\datasets\pactg377\

3. STATISTICAL EVALUATION

3.1 Plasma HIV-1 RNA (Study 556)

3.1.1. Plasma HIV-1 RNA Data

Plasma HIV-1 RNA data was updated in February, 2004. Two data sets were generated after deleting one duplicated record and replacing one missing record at Week 0 by this patient's baseline HIV-1 RNA (PATID=1707). One data set includes 3030 data points for TLOVR analysis. The second data set includes 2944 data points for graphical presentation and statistical comparisons of temporal trend in HIV-1 RNA. In the second data set, mean value of HIV-1 RNA per subject per follow-up window was used if there was more than one value in a time window for a subject.

3.1.2. Mean HIV-1 RNA and Mean Change from Baseline in HIV-1 RNA

Mean, standard deviation, and median plasma HIV-1 RNA by follow-up visit and study arm are listed in Table A1. P-values were obtained based on non-parametric Kruskal-Wallis test for the comparisons of mean ranks of HIV-1 RNA between the two treatment regimens. The mean HIV-1 RNA of 48 weeks was shown in Figure 1. Legend name 'NFV' denotes 'Viracept'

regimen. The mean change from baseline in HIV-1 RNA was summarized in Table A2 and Figure 2.

The findings are as follows:

1. For the Viracept group, the mean HIV-1 RNA declined from 5.0 to 3.2 $\log_{10}$ at Week 8 and was maintained through Week 48 with slightly changes. For the placebo group, the mean HIV-1 RNA declined from 5.1 to 3.6 $\log_{10}$ at Week 2, increased to 4.2 at Week 20, decreased again to 3.5 at Week 28, then maintained through Week 48.

2. The temporal trends in change from baseline in HIV-1 RNA were different between the treatment groups. Between Week 2 to Week 24, subjects in the Viracept arm had a statistically significantly greater reduction in plasma HIV-1 RNA from baseline than those in the placebo arm. From Week 28 on, the mean change from baseline were similar between treatment arms.

    a. For the Viracept group, the mean change from baseline in HIV-1 RNA declined and was stable between 1.6 to 1.9 $\log_{10}$ during the entire study period. For the placebo group, there were more fluctuations prior to Week 28.

    b. During the study, the change from baseline HIV-1 RNA viral load (ΔHIV-1 RNA) in the placebo arm was slightly less than that in the Viracept arm. Between Week 2 to Week 24, ΔHIV-1 RNA values in the placebo arm were statistically significantly less than those in the Viracept arm. From Week 28 on, ΔHIV-1 RNA values were similar between the two treatment arms.

3.1.3. Imputation of Missing Data in HIV RNA (LVCF)

Sensitivity analyses on HIV-1 RNA data were performed using the Last Value Carried Forward (LVCF) approach to impute missing HIV-1 RNA values during 0 to 48 weeks of follow-up. Percentages of subjects with at least one missing HIV-1 RNA value were similar: 36% (27/75) in the placebo group and 32% (21/66) in the Viracept group, $p>0.05$ by the Chi-square test.

Mean and median HIV-1 RNA and those for the change from baseline in HIV-1 RNA were summarized in Table A3 and Figures 3 and 4. Slight changes were observed after imputations using LVCF approach. For example, Week 24 ΔHIV-1 RNA (LVCF) between Viracept and Placebo arms was no longer significantly different, $p>0.05$. Initially, subjects in the Viracept arm had greater mean ΔHIV-1 RNA than the subjects in the Placebo arm, $p=0.0328$.

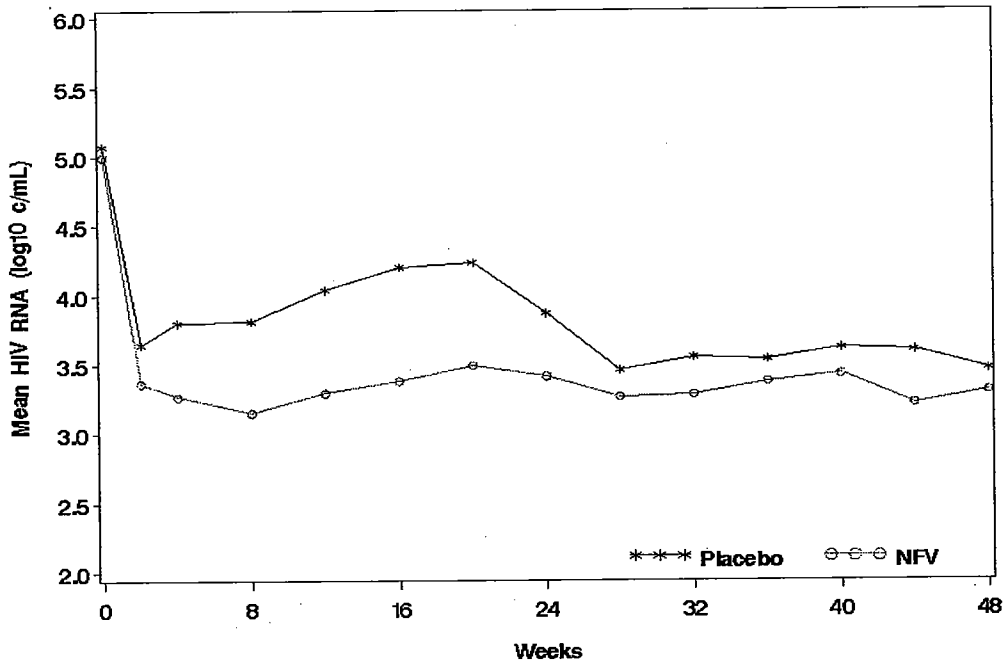

Figure 1: Study 556: Mean Plasma HIV RNA Curves by Treatment Regimens

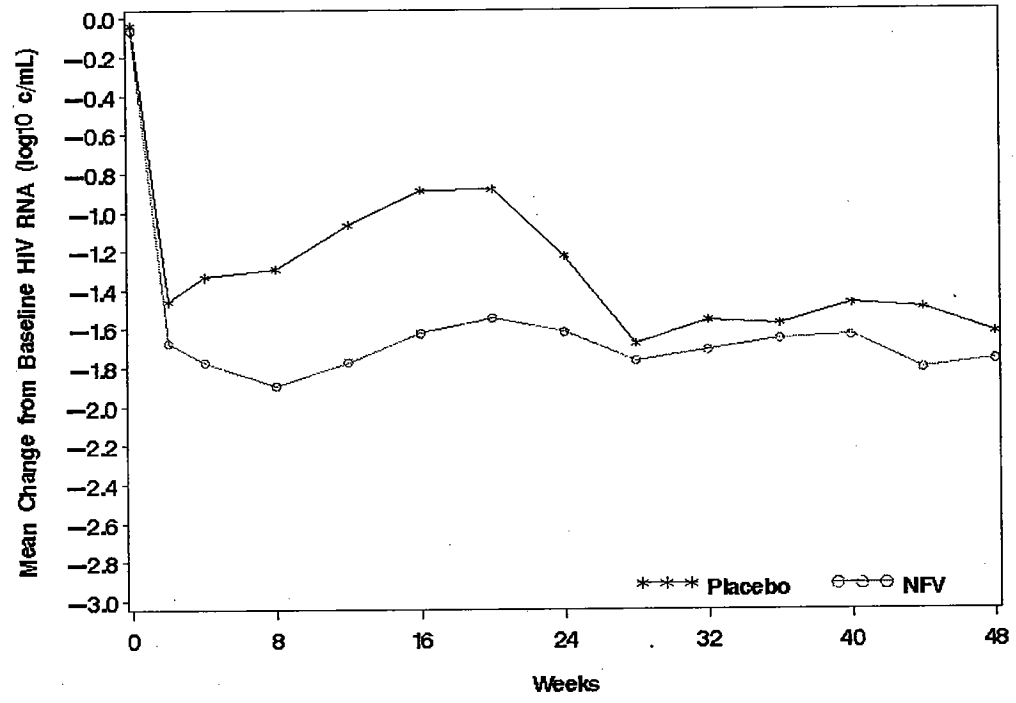

Figure 2: Study 556: Mean Change From Baseline in Plasma HIV RNA

Table A1: Study 556: Mean and Median Plasma HIV-1 RNA by Study Arm

	Viracept				Placebo				
Week	n	median	mean	std	n	median	mean	std	p-value
0	66	4.98	4.99	0.84	75	5.14	5.07	0.79	NS
2	62	3.25	3.36	0.80	70	3.46	3.64	0.99	NS
4	63	2.98	3.24	0.84	73	3.56	3.79	1.01	0.0004
8	62	2.77	3.14	0.80	71	3.91	3.83	0.95	<0.0001
12	63	2.73	3.29	0.95	72	3.98	4.03	1.00	<0.0001
16	63	2.90	3.39	0.99	68	4.28	4.20	1.13	<0.0001
20	61	3.14	3.49	0.98	69	4.32	4.18	0.97	<0.0001
24	64	3.02	3.39	0.92	72	3.66	3.85	1.08	<0.0001
28	61	2.73	3.27	0.95	68	3.14	3.46	1.02	NS
32	60	2.91	3.29	0.89	72	3.18	3.55	1.08	NS
36	59	2.94	3.37	1.02	72	3.24	3.55	1.07	NS
40	59	3.13	3.39	0.89	70	3.46	3.62	1.03	NS
44	61	2.79	3.22	0.83	70	2.81	3.60	1.20	NS
48	59	2.94	3.29	0.90	66	3.08	3.50	1.08	NS
52	46	2.93	3.25	0.75	58	2.85	3.39	1.00	NS
56	59	2.90	3.32	0.89	63	2.60	3.32	0.99	NS
60	58	3.13	3.40	0.89	66	2.72	3.33	0.94	NS
64	58	2.90	3.23	0.84	62	2.73	3.34	0.93	NS
68	61	2.82	3.30	0.86	66	2.98	3.47	1.03	NS
72	54	2.82	3.27	0.87	57	2.60	3.20	0.89	NS
76	53	2.80	3.21	0.83	48	2.60	3.27	0.94	NS
80	43	2.60	3.14	0.80	46	2.66	3.29	0.90	NS
84	32	2.83	3.24	0.78	36	2.60	3.18	0.85	NS
88	24	2.60	2.90	0.55	30	2.71	3.22	0.80	NS
92	21	2.60	2.93	0.57	25	2.63	3.24	0.88	NS
96	10	2.80	2.98	0.48	14	2.96	3.27	0.86	NS

Table A2: Study 556: Mean and Median Change From Baseline Plasma HIV-1 RNA

	Viracept				Placebo				
Week	n	median	mean	se	n	median	mean	se	p-value
2	62	-1.76	-1.67	0.74	70	-1.58	-1.46	0.81	NS
4	63	-1.86	-1.79	0.86	73	-1.43	-1.35	0.82	0.0016
8	62	-2.04	-1.90	0.78	71	-1.38	-1.30	0.77	<0.0001
12	63	-1.93	-1.77	0.93	72	-1.11	-1.07	0.81	<0.0001
16	63	-1.82	-1.65	1.04	68	-1.01	-0.90	0.94	<0.0001
20	61	-1.58	-1.55	0.90	69	-0.92	-0.92	0.95	0.0004
24	64	-1.79	-1.64	1.02	72	-1.31	-1.24	1.08	0.0328
28	61	-1.86	-1.77	1.00	68	-1.89	-1.68	1.04	NS
32	60	-1.75	-1.70	0.92	72	-1.75	-1.56	1.15	NS
36	59	-1.78	-1.64	1.03	72	-1.70	-1.55	1.17	NS
40	59	-1.66	-1.66	0.99	70	-1.57	-1.48	1.19	NS
44	61	-2.00	-1.79	1.00	70	-1.76	-1.50	1.29	NS
48	59	-1.96	-1.77	1.00	66	-1.80	-1.58	1.22	NS
52	46	-1.89	-1.87	0.90	58	-1.92	-1.65	1.24	NS
56	59	-1.95	-1.74	1.03	63	-1.91	-1.72	1.16	NS
60	58	-1.78	-1.67	1.00	66	-1.86	-1.71	1.12	NS
64	58	-1.90	-1.80	1.00	62	-1.86	-1.70	1.10	NS
68	61	-1.92	-1.73	1.05	66	-1.68	-1.58	1.19	NS
72	54	-1.86	-1.74	0.95	57	-1.93	-1.80	1.12	NS
76	53	-1.96	-1.80	0.99	48	-1.89	-1.74	1.16	NS
80	43	-1.94	-1.80	1.01	46	-1.80	-1.68	1.17	NS
84	32	-1.65	-1.70	0.69	36	-1.89	-1.75	1.03	NS
88	24	-1.91	-1.79	0.90	30	-1.82	-1.76	1.03	NS
92	21	-1.85	-1.82	0.68	25	-1.78	-1.65	1.07	NS
96	10	-1.75	-1.87	0.53	14	-1.78	-1.77	0.89	NS

Table A3: Study 556: Plasma HIV-1 RNA using Last Value Carried Forward

	Viracept (n=66)			Placebo (n=75)			
Week	median	Mean	std	median	mean	std	p-value
Mean and Median Plasma HIV-1 RNA							
0	4.98	4.99	0.84	5.14	5.07	0.79	NS
2	3.32	3.49	0.92	3.56	3.75	1.06	NS
4	3.06	3.33	0.92	3.55	3.76	1.01	0.0048
8	2.79	3.24	0.89	3.89	3.81	0.98	0.0001
12	2.79	3.36	1.03	4.01	4.05	1.02	<0.0001
16	2.94	3.49	1.07	4.28	4.21	1.11	0.0001
20	3.29	3.61	1.06	4.32	4.18	0.98	0.0007
24	3.05	3.47	1.00	3.67	3.87	1.10	0.0216
28	2.77	3.33	1.02	3.11	3.51	1.08	NS
32	2.94	3.38	0.98	3.16	3.56	1.10	NS
36	2.95	3.48	1.12	3.26	3.58	1.09	NS
40	3.13	3.45	0.96	3.46	3.66	1.08	NS
44	2.91	3.34	0.97	2.84	3.62	1.22	NS
48	2.97	3.37	0.97	3.22	3.68	1.23	NS
Mean and Median Change From Baseline Plasma HIV-1 RNA							
2	-1.69	-1.57	0.84	-1.55	-1.36	0.87	NS
4	-1.82	-1.72	0.90	-1.43	-1.35	0.81	0.0062
8	-1.99	-1.82	0.84	-1.38	-1.30	0.77	<0.0001
12	-1.87	-1.69	0.98	-1.09	-1.06	0.82	<0.0001
16	-1.74	-1.57	1.09	-0.97	-0.90	0.91	0.0001
20	-1.56	-1.44	0.98	-0.92	-0.93	0.93	0.0025
24	-1.75	-1.59	1.05	-1.29	-1.24	1.07	NS
28	-1.84	-1.72	1.03	-1.88	-1.60	1.10	NS
32	-1.75	-1.67	0.98	-1.73	-1.55	1.14	NS
36	-1.74	-1.58	1.06	-1.65	-1.53	1.16	NS
40	-1.66	-1.62	1.04	-1.56	-1.45	1.17	NS
44	-1.94	-1.71	1.05	-1.74	-1.49	1.27	NS
48	-1.91	-1.68	1.09	-1.61	-1.43	1.27	NS

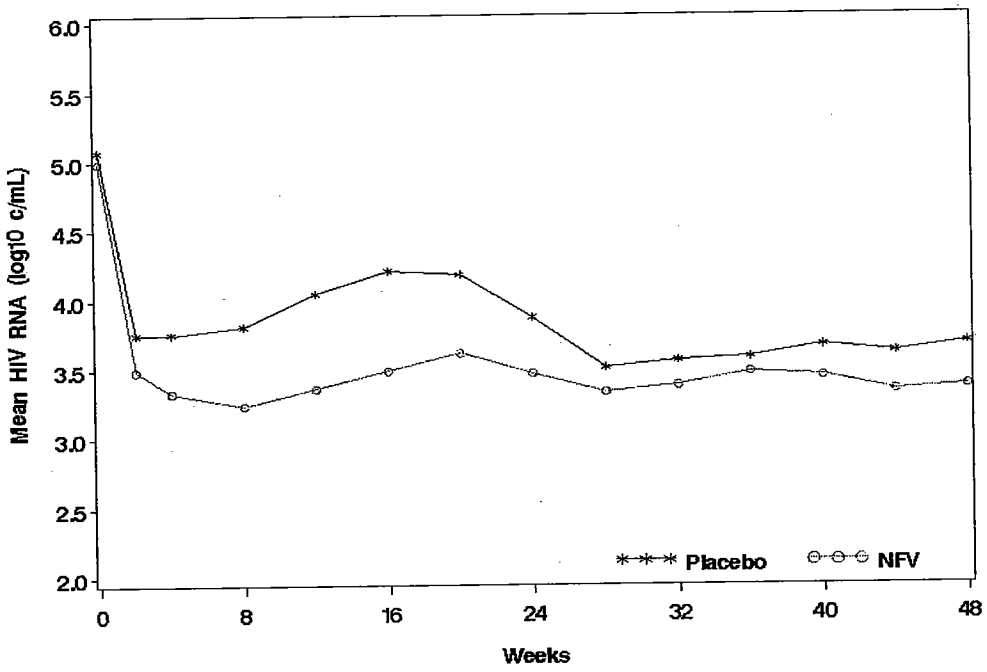

Figure 3: Study 556: Mean Plasma HIV RNA by Treatment Arm (LVCF)

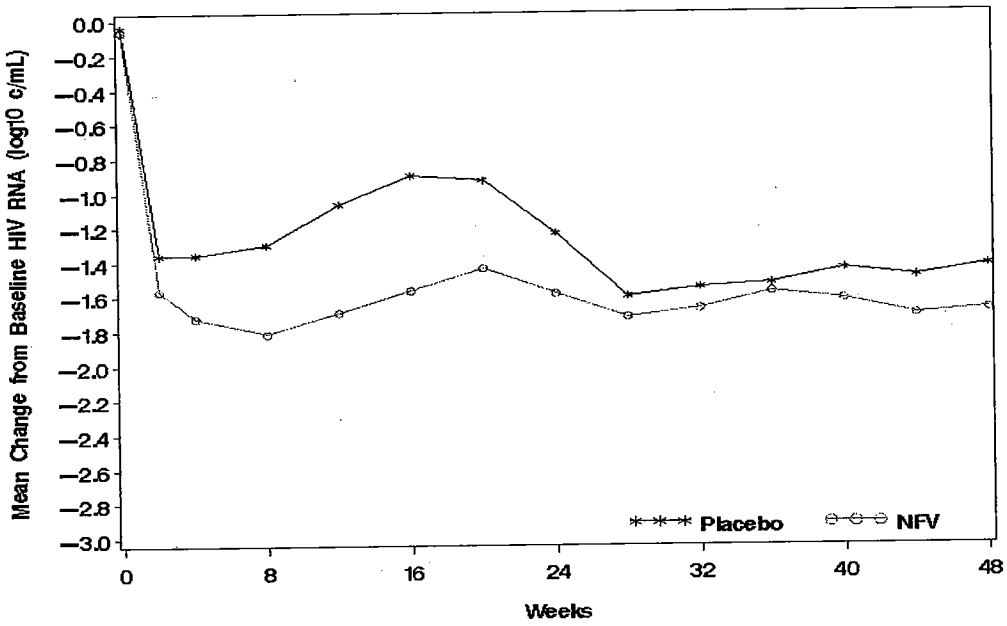

Figure 4: Study 556: Mean Change from Baseline in Plasma HIV RNA (LVCF)

3.2 Plasma HIV-1 RNA (PACTG 377)

3.2.1. Plasma HIV-1 RNA Data

There were 1277 data points including baseline or Week 0 data. No duplicates or multiple values per time-window per-subject were observed. In the text below, symbols A,B,C,D,Q denote the following treatment arms:

Trt A- d4T+NVP+RTV
Trt B- d4T+3TC+NFV
Trt C- d4T+NVP+NFV
Trt D- d4T+3TC+NVP+NFV
Trt Q- d4T+3TC+NFV (PACTG 725)

3.2.2. Mean HIV-1 RNA and ΔHIV-1 RNA

Mean, standard deviation, and median plasma HIV-1 RNA and ΔHIV-1 RNA by follow-up visit and study arm are listed in Table A4. Summary statistics were not listed in Table A4 for Week 84 since this visit included only 2 subjects in Group B and 4 subjects in Group D with HIV-1 RNA values. P-values using non-parametric Kruskal-Wallis test and F-test in Analysis of Variance (ANOVA) were obtained and listed in Table A5 for the comparisons of treatment differences in HIV-1 RNA (ΔHIV-1 RNA). The mean HIV-1 RNA curves and the mean ΔHIV-1 RNA were also plotted in Figures 5 and 6. The findings are as follows:

1. The patterns of temporal trend in HIV-1 RNA appear to be similar between the treatment groups. The mean HIV RNA dropped from 4.5 to 3.0-3.2 $\log_{10}$ at Week 4 and maintained through Week 48 with slight changes.

2. Cross-sectional comparisons show that there were significant treatment differences at Week 12 and Week 24. At Week 12, the mean HIV RNA levels in Group D were statistically significantly less than those in Groups A and C. At Week 24, the mean HIV RNA levels in Group D were statistically significantly less than those in Groups A, B and C. When comparing the mean HIV RNA, pairwise t-tests (LSD) approaches were employed.

3. Subjects in Group Q had the greatest reduction in plasma HIV-1 RNA and subjects in Group C had the least reduction. However, the mean changes from baseline in HIV-1 RNA (ΔHIV-1 RNA) were not significantly different among treatment groups.

3.2.3. Imputation of Missing in HIV RNA (LVCF)

Sensitivity analyses on HIV-1 RNA data were performed using the Last Value Carried Forward (LVCF) approach to impute missing HIV-1 RNA values during 0 to 48 weeks of follow-up. Percentages of missing data points (ever/never) in HIV-1 RNA were similar: Trt A- 32%

(13/41), Trt B-31% (16/52), Trt C- 43% (19/44), Trt D- 36% (16/44) and Trt Q- 18% (2/11), Chi-sq=3.30, p=0.51.

Mean and median HIV-1 RNA and ΔHIV-1 RNA using LVCF approach are summarized in Table A6 and Figures 7 and 8. Slight changes in mean values were observed between the LVCF approach and observed HIV-1 RNA and change from baseline in HIV-1 RNA. However, when comparing mean HIV-1 RNA among treatment arms, no significant treatment differences were observed using either the non-parametric approach or ANOVA.

Table A4: PACTG 377: Mean and Median Plasma HIV-1 RNA and ΔHIV-1 RNA

			HIV-1 RNA			ΔHIV-1 RNA		
Group	week	N	mean	std	median	mean	std	Median
A	0	41	4.45	0.79	4.38	0.00	0.00	0.00
A	4	38	3.23	0.91	2.82	-1.18	0.87	-1.29
A	8	39	3.23	1.01	2.60	-1.21	0.92	-1.31
A	12	40	3.40	1.01	2.72	-1.05	0.97	-0.79
A	24	38	3.38	0.95	2.72	-1.06	0.96	-0.80
A	36	34	3.32	0.87	2.60	-1.07	0.79	-0.89
A	48	38	3.22	0.78	2.60	-1.14	0.77	-0.87
A	60	3	3.26	1.00	2.76	-1.39	0.82	-1.60
A	72	1	2.60	2.60		-0.21	-0.21	
B	0	52	4.47	0.75	4.54	0.00	0.00	0.00
B	4	50	3.23	0.70	2.97	-1.24	0.76	-1.33
B	8	49	3.18	0.82	2.73	-1.28	0.87	-1.27
B	12	49	3.15	0.84	2.60	-1.32	0.94	-1.25
B	24	49	3.26	0.91	2.60	-1.23	0.97	-1.13
B	36	40	3.10	0.78	2.60	-1.37	0.91	-1.23
B	48	46	3.12	0.71	2.65	-1.38	0.88	-1.31
B	60	8	2.91	0.88	2.60	-1.92	0.78	-2.04
B	72	8	2.60	0.00	2.60	-1.93	0.64	-1.90
C	0	44	4.28	0.71	4.32	0.00	0.00	0.00
C	4	40	3.11	0.87	2.71	-1.23	0.85	-1.32
C	8	34	2.97	0.80	2.60	-1.41	0.75	-1.45
C	12	41	3.28	1.02	2.60	-1.03	1.03	-0.97
C	24	40	3.40	0.93	3.06	-0.91	0.89	-0.86
C	36	35	3.45	1.02	2.82	-0.93	0.92	-0.91
C	48	39	3.31	0.75	3.14	-0.98	0.75	-0.91
C	60	5	3.41	1.07	2.70	-1.09	0.88	-1.40
C	72	2	3.52	1.10	3.52	-0.96	1.44	-0.96
D	0	44	4.28	0.88	4.38	0.00	0.00	0.00
D	4	42	2.92	0.52	2.63	-1.31	0.82	-1.47
D	8	38	2.94	0.80	2.60	-1.34	0.97	-1.43
D	12	42	2.84	0.63	2.60	-1.40	0.93	-1.48

D	24	40	2.84	0.50	2.60	-1.40	0.92	-1.46
D	36	37	2.96	0.68	2.60	-1.21	1.01	-1.31
D	48	40	2.90	0.61	2.60	-1.29	1.00	-1.43
D	60	8	2.86	0.56	2.60	-1.31	1.38	-0.91
D	72	2	2.60	0.00	2.60	-1.19	1.21	-1.19
Q	0	11	4.42	0.68	4.38	0.00	0.00	0.00
Q	4	11	2.91	0.57	2.60	-1.51	0.81	-1.77
Q	8	10	2.95	0.64	2.60	-1.49	0.58	-1.55
Q	12	10	3.08	0.70	2.60	-1.37	0.70	-1.30
Q	24	10	2.97	0.70	2.60	-1.47	0.75	-1.41
Q	36	9	2.92	0.57	2.60	-1.43	0.76	-1.52
Q	48	10	3.06	0.70	2.60	-1.39	0.82	-1.24
Q	60	2	2.60	0.00	2.60	-2.36	0.71	-2.36
Q	72	2	2.67	0.09	2.67	-2.54	0.27	-2.54

Table A5: P-values for the Comparisons of Plasma HIV-1 RNA (ΔHIV-1 RNA) Among Treatment Arms Using the Kruskal-Wallis Test

Week	HIV-1 RNA	HIV-1 RNA	ΔHIV-1 RNA	ΔHIV-1 RNA
	Kruskal-Wallis	ANOVA	Kruskal-Wallis	ANOVA
0	NS	NS		
4	NS	NS	NS	NS
8	NS	NS	NS	NS
12	0.0417	0.0543	NS	NS
24	0.0170	0.0162	NS	NS
36	NS	NS	NS	NS
48	NS	NS	NS	NS

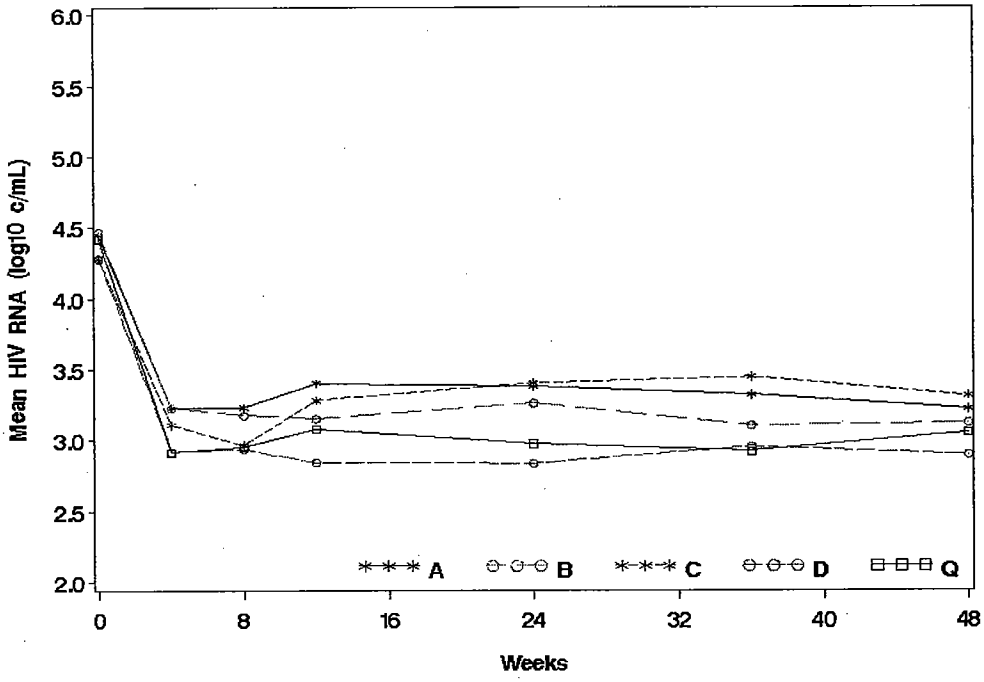

Figure 5: PACTG 377: Mean Plasma HIV RNA

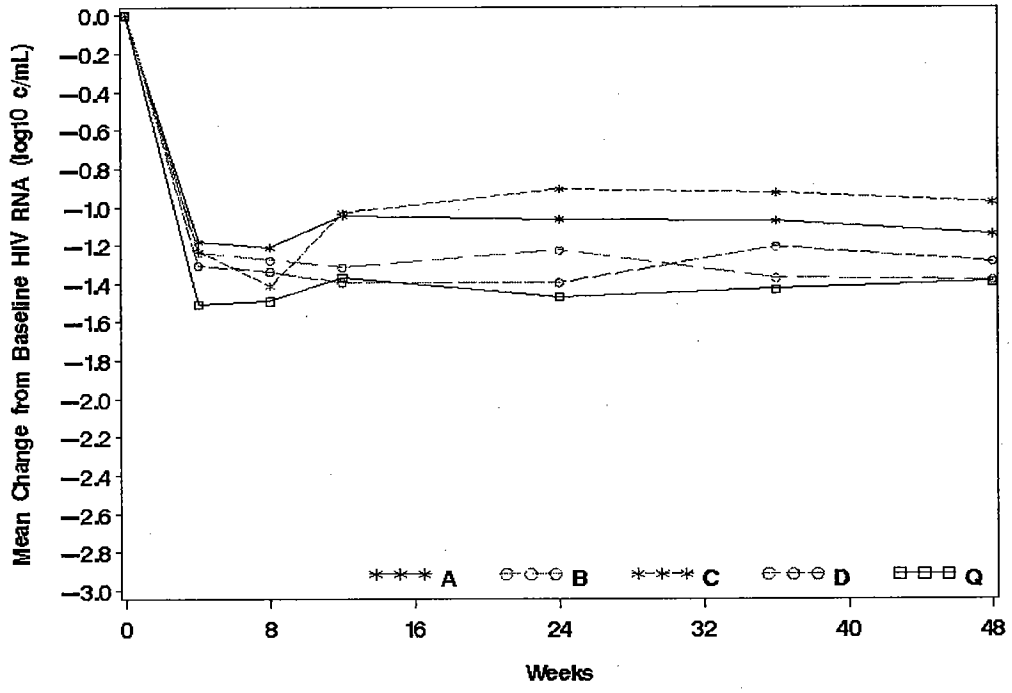

Figure 6: PACTG 377: Mean Change From Baseline in Plasma HIV RNA

Table A6: PACTG 377: Plasma HIV-1 RNA and ΔHIV-1 RNA (LVCF)

			HIV-1 RNA			ΔHIV-1 RNA		
Group	week	N	mean	std	median	mean	std	Median
A	0	41	4.38	4.45	0.79	0.00	0.00	0.00
B	0	52	4.54	4.47	0.75	0.00	0.00	0.00
C	0	44	4.32	4.28	0.71	0.00	0.00	0.00
D	0	44	4.38	4.28	0.88	0.00	0.00	0.00
Q	0	11	4.38	4.42	0.68	0.00	0.00	0.00
A	4	41	2.84	3.35	0.99	-1.11	-1.10	0.89
B	4	52	3.05	3.28	0.74	-1.29	-1.19	0.78
C	4	44	2.80	3.16	0.85	-1.17	-1.12	0.89
D	4	44	2.66	3.03	0.76	-1.39	-1.25	0.84
Q	4	11	2.60	2.91	0.57	-1.77	-1.51	0.81
A	8	41	2.60	3.26	1.03	-1.31	-1.19	0.92
B	8	52	2.79	3.21	0.82	-1.26	-1.26	0.89
C	8	44	2.60	3.04	0.83	-1.23	-1.24	0.80
D	8	44	2.60	2.93	0.76	-1.43	-1.35	0.93
Q	8	11	2.60	3.09	0.76	-1.55	-1.33	0.77
A	12	41	2.67	3.38	1.00	-0.86	-1.06	0.96
B	12	52	2.67	3.19	0.84	-1.23	-1.28	0.94
C	12	44	2.60	3.26	0.99	-1.07	-1.03	1.01
D	12	44	2.60	2.93	0.80	-1.41	-1.35	0.94
Q	12	11	2.60	3.20	0.79	-1.08	-1.22	0.83
A	24	41	2.64	3.38	0.97	-0.80	-1.06	0.94
B	24	52	2.60	3.28	0.91	-1.11	-1.18	0.95
C	24	44	3.31	3.42	0.91	-0.79	-0.86	0.89
D	24	44	2.60	3.00	0.81	-1.30	-1.28	0.95
Q	24	11	2.60	3.11	0.80	-1.29	-1.31	0.89
A	36	41	2.60	3.37	0.92	-0.84	-1.08	0.83
B	36	52	2.60	3.30	0.90	-1.10	-1.17	0.95
C	36	44	2.91	3.41	0.97	-0.90	-0.87	0.88
D	36	44	2.60	3.04	0.86	-1.34	-1.24	1.00
Q	36	11	2.60	3.22	0.83	-1.00	-1.21	0.87
A	48	41	2.60	3.27	0.82	-0.89	-1.17	0.82
B	48	52	2.70	3.23	0.81	-1.22	-1.23	0.93
C	48	44	3.07	3.34	0.83	-0.90	-0.94	0.77
D	48	44	2.60	3.01	0.83	-1.43	-1.28	1.01
Q	48	11	2.60	3.19	0.79	-0.95	-1.24	0.93

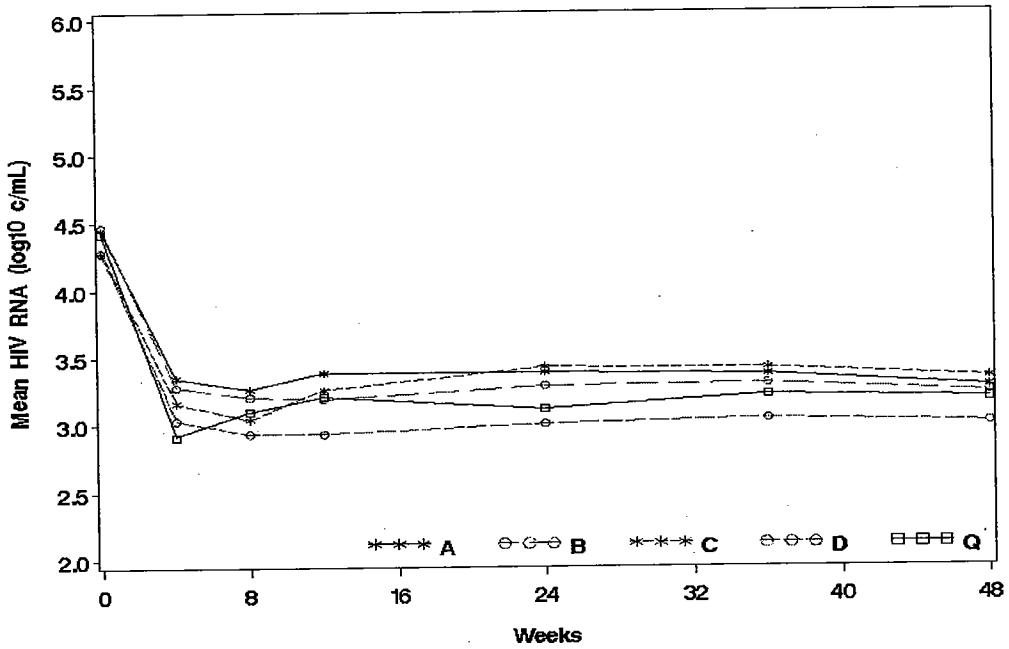

Figure 7: ACTG 377: Plasma HIV RNA (LVCF)

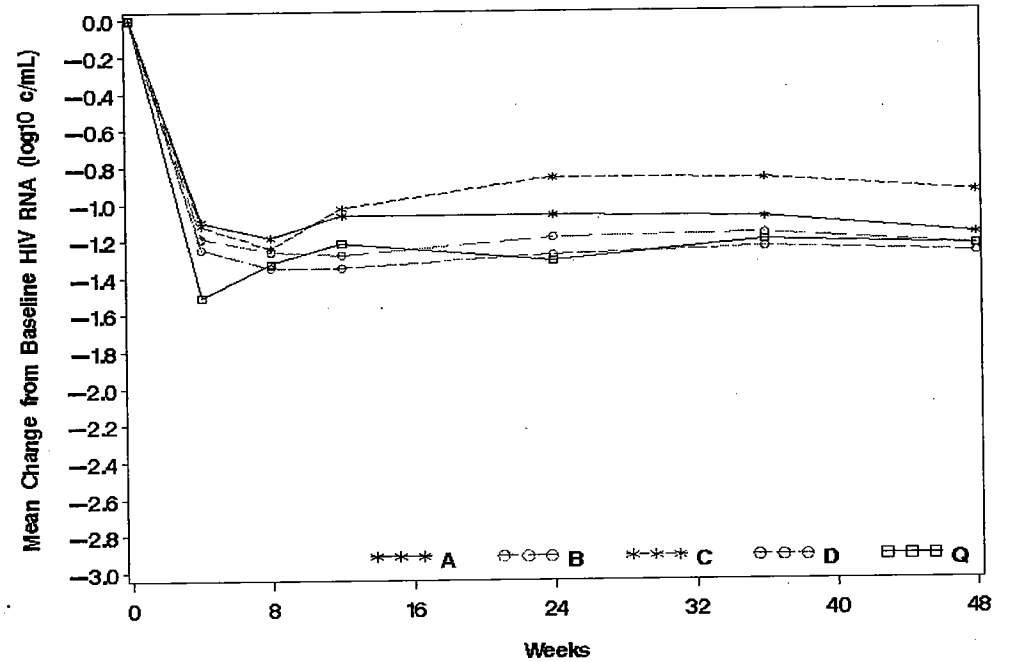

Figure 8: ACTG 377: Mean Change from Baseline in Plasma HIV RNA (LVCF)

3.3 CD4+ (Study 556)

3.3.1. CD4+ Data

CD4+ data were generated from two source files: FLEULAB.XPT and HEMAT.XPT. One subject (PATID=1109) had no baseline CD4+, the Week 2 CD4+ was added as the Week 0 CD4+. After deleting duplicates, the sample size was 2563 for the study period Week ≥0. The distribution of CD4+ is skewed to the left and the mean value is greater than the median for most of the follow-up visits. The difference between mean and median ranges from -87 to 301 cells/mm^3. Therefore, the median CD4+ curves were used for graphical presentations. In addition, large individual variations in CD4+ were observed.

3.3.2. CD4+ and ΔCD4+

Mean, standard deviation, and median CD4+ data by treatment regimen and follow-up visit are listed in Table A7, and corresponding statistics of change from baseline in CD4+ (ΔCD4+) are listed in Table A8. Figures 9 and 10 show the median CD4+ and ΔCD4+ curves respectively.

- From Week 8 to Week 40, subjects receiving Viracept had greater median or mean CD4+ than those in the placebo regimen.
- Both median CD4+ and ΔCD4+ curves show upswing trends. At Week 48, the median increase of 192 cells/mm^3 for the Viracept group and 233 cells/mm^3 for the placebo group were observed.
- The treatment difference in CD4+ or ΔCD4+ by follow-up visits was not significant, $p>0.05$ by the Kruskal-Wallis tests.

3.3.3. CD4+ and ΔCD4+ (LVCF)

Tables A9 and A10 list the statistics of CD4+ and ΔCD4+ by treatment regimen and follow-up visit after imputing missing values using the LVCF approach, and Figures 11 and 12 show the corresponding median CD4+ and ΔCD4+ curves.

- Results from the LVCF were similar to the observed one. At Week 48, a median increase of 147 cells/mm^3 for the Viracept group and 211 cells/mm^3 for the placebo group were observed.

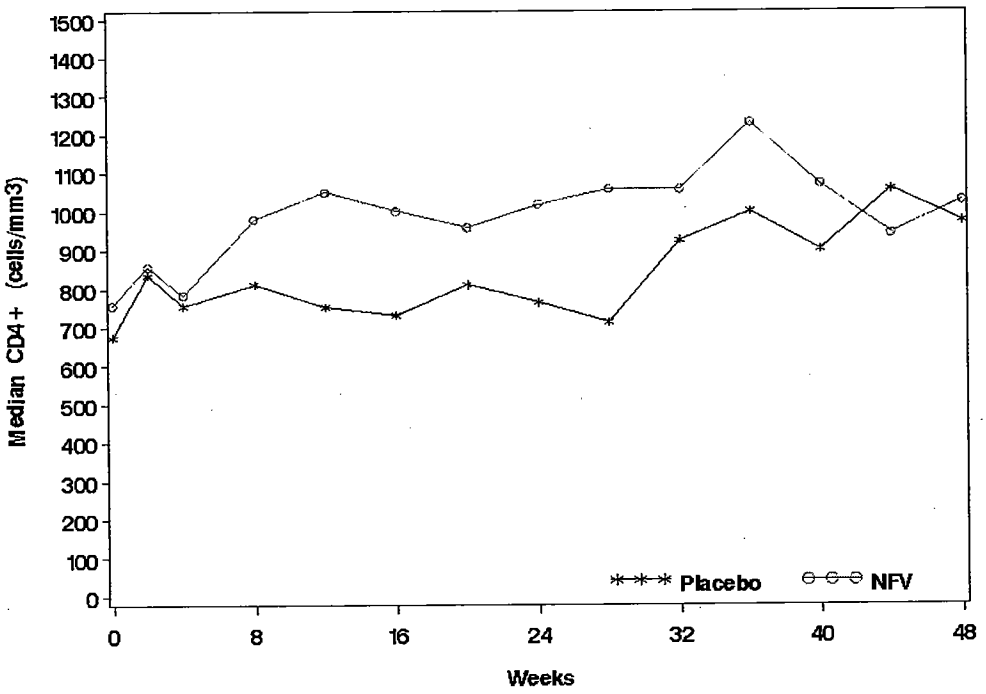

Figure 9: Study 556: Median CD4+ cells/mm^3

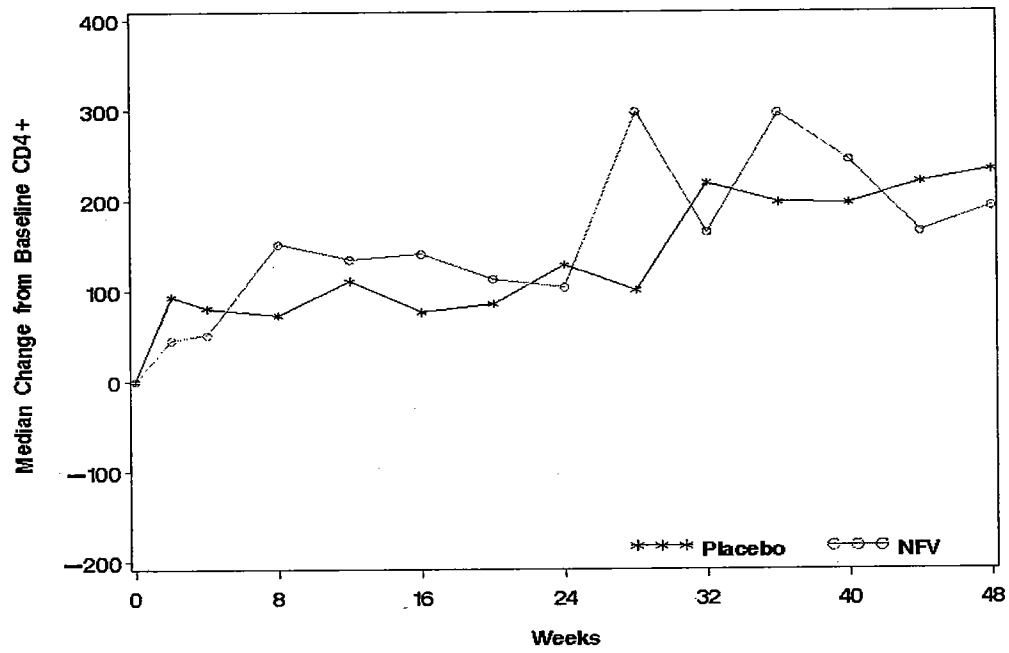

Figure 10: Study 556: Median Change from Baseline in CD4+ Cells/mm^3

Table A7: Study 556: CD4+

	Viracept				Placebo		
Week	N	Median	Mean	Std	N	Median	Mean	Std
0	66	757.5	977.9	870.3	75	675.0	871.6	763.5
2	63	857.0	1040.3	797.8	72	835.5	1015.5	806.5
4	62	784.0	928.0	703.7	72	756.0	927.0	635.7
8	64	980.5	1107.0	800.6	73	811.0	921.6	620.5
12	63	1050.0	1145.3	768.6	72	753.5	934.7	661.7
16	63	1001.0	1095.1	649.7	73	731.0	895.6	537.0
20	62	958.5	1096.0	702.8	73	810.0	958.0	592.5
24	64	1019.0	1071.6	596.3	72	764.0	948.0	601.5
28	12	1059.0	971.6	449.3	13	713.0	1014.3	823.1
32	63	1057.0	1156.8	705.0	72	925.0	1047.9	630.1
36	21	1230.0	1314.6	1023.2	23	1000.0	1105.4	656.2
40	60	1071.0	1137.1	623.5	71	901.0	1067.3	597.3
44	34	942.0	1059.4	553.8	36	1056.5	1131.8	636.6
48	62	1026.5	1164.0	724.7	68	974.0	1085.3	579.0
52	47	1120.0	1182.2	556.2	55	1105.0	1150.0	491.6
56	56	1087.0	1131.6	623.8	66	1029.5	1142.2	539.2
60	60	1005.5	1069.0	458.1	65	969.0	1108.2	520.8
64	57	975.0	1053.8	548.5	63	1073.0	1151.0	516.8
68	55	1116.0	1094.0	496.3	55	1076.0	1085.5	428.7
72	46	993.0	1073.9	468.0	50	1068.0	1107.4	534.3
76	39	837.0	1063.1	639.4	43	1100.0	1144.0	530.3
80	29	936.0	1053.2	505.3	34	989.5	1042.2	441.1
84	25	945.0	1055.6	702.8	30	1001.0	1056.8	509.9
88	16	970.0	999.4	487.7	21	1059.0	1072.8	412.8
92	9	1020.0	1122.2	438.1	14	1181.0	1213.4	540.7

Table A8: Study 556: Change from Baseline in CD4+

	Viracept				Placebo			
Week	N	Median	Mean	Std	N	Median	Mean	Std
0	66	0.0	0.0	0.0	75	0.0	0.0	0.0
2	63	45.0	50.0	555.8	72	93.5	135.1	511.9
4	62	51.0	16.7	546.7	72	80.5	98.2	497.7
8	64	151.0	182.8	448.5	73	73.0	44.4	518.9
12	63	134.0	144.7	562.0	72	110.5	52.3	521.1
16	63	140.0	87.1	489.7	73	76.0	9.9	691.0
20	62	112.5	119.2	474.1	73	85.0	70.4	560.7
24	64	103.0	73.0	507.0	72	128.0	51.5	626.6
28	12	297.0	283.3	270.2	13	100.0	-117.1	954.8
32	63	164.0	168.6	430.0	72	218.5	157.1	712.4
36	21	296.0	220.9	380.2	23	197.0	84.7	675.9
40	60	244.5	247.6	582.4	71	196.0	181.4	653.6
44	34	164.5	175.0	455.3	36	219.5	236.3	575.7
48	62	192.0	173.0	641.7	68	232.5	183.5	668.3
52	47	282.0	178.3	624.5	55	287.0	243.3	673.2
56	56	202.5	123.7	631.5	66	273.5	249.2	668.0
60	60	221.0	145.3	543.4	65	322.0	224.0	698.5
64	57	226.0	47.2	696.0	63	350.0	324.7	474.1
68	55	199.0	78.8	739.1	55	264.0	217.5	521.3
72	46	186.0	53.9	709.1	50	233.5	231.1	582.5
76	39	222.0	11.8	743.9	43	361.0	278.1	604.0
80	29	186.0	-22.6	718.6	34	295.5	233.7	527.2
84	25	96.0	-44.6	603.3	30	363.5	194.6	572.8
88	16	195.5	192.0	259.1	21	273.0	174.5	423.7
92	9	232.0	128.7	302.3	14	295.0	179.5	460.4

Table A9: Study 556: CD4+ and Change from Baseline in CD4+ (LVCF)

	Viracept (n=66)			Placebo (n=75)		
Week	Median	Mean	Std	Median	Mean	Std
CD4+						
0	759.0	984.2	875.6	675.0	871.6	763.5
2	857.0	1031.8	787.8	830.0	1001.3	797.7
4	805.0	947.3	719.1	768.0	975.4	783.5
8	980.5	1096.8	809.6	811.0	910.6	619.4
12	1050.0	1127.0	768.6	762.0	937.6	663.9
16	986.0	1064.6	660.3	731.0	884.3	537.8
20	952.0	1084.9	730.4	810.0	956.2	599.0
24	995.0	1054.9	605.2	758.0	941.9	604.8
28	995.0	1045.1	605.4	755.0	962.4	635.3
32	1057.0	1140.0	711.7	920.0	1038.8	632.8
36	1066.0	1176.0	779.2	930.0	1077.4	669.2
40	1090.0	1200.2	803.2	901.0	1043.1	610.1
44	980.0	1137.5	757.2	901.0	1045.8	635.1
48	1010.0	1139.2	727.2	931.0	1043.2	589.5
ΔCD4+						
0	0.0	0.0	0.0	0.0	0.0	0.0
2	32.0	47.7	547.2	72.0	129.7	502.1
4	20.0	-37.1	651.5	68.0	103.8	493.0
8	151.0	180.6	449.4	70.0	39.0	513.6
12	134.0	142.8	553.8	110.0	66.0	526.0
16	137.0	80.5	482.9	76.0	12.7	682.0
20	100.0	100.7	474.1	85.0	84.6	568.4
24	97.0	70.8	503.3	129.0	70.3	628.9
28	92.0	61.0	495.2	128.5	82.4	622.9
32	144.0	155.8	425.7	215.0	167.2	708.6
36	181.0	191.8	394.5	222.0	205.8	655.8
40	194.0	216.0	580.1	195.0	171.5	667.9
44	130.0	153.3	477.9	198.0	174.2	655.1
48	147.0	155.0	628.3	211.0	171.6	673.3

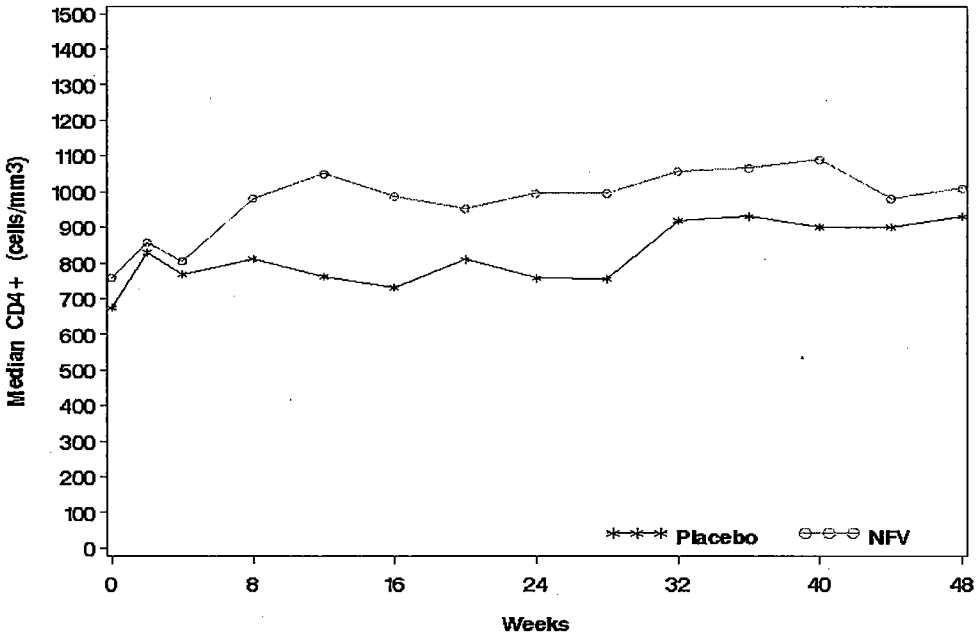

Figure 11: Study 556: Median CD4+ Cells/mm^3 (LVCF)

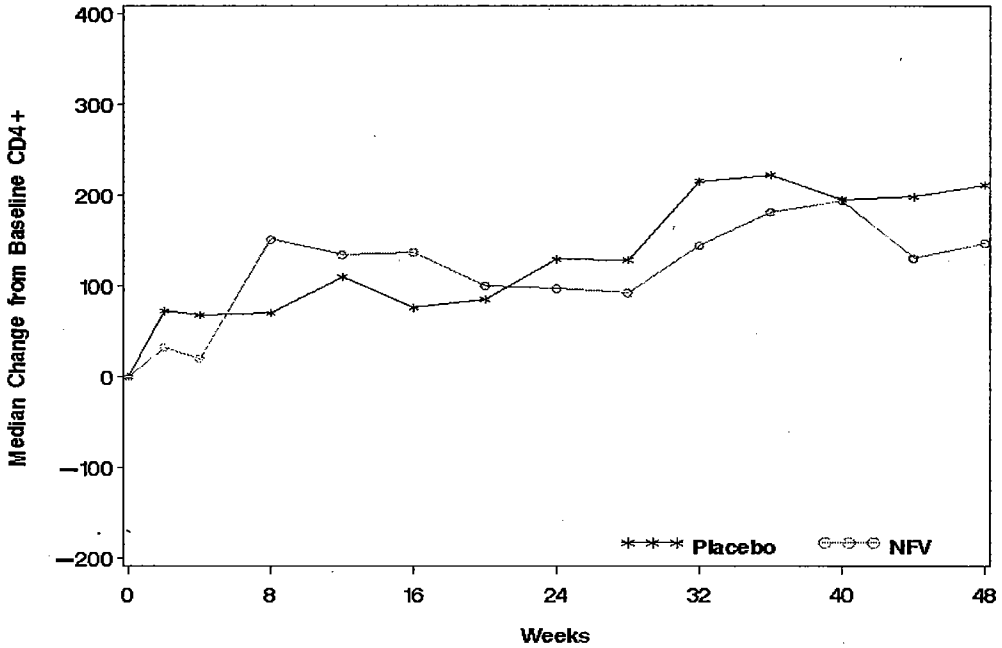

Figure 12: Study 556: Median Change from Baseline in CD4+ Cells/mm^3 (LVCF)

3.4 Time to Loss-of-Virologic-Response (Study 556)

Using the applicant's updated HIV-1 RNA data, patients' discontinuation status, and change of therapy, Time to Loss-of-Virologic-Response (TLOVR) data was generated using the DAVDP HIV efficacy algorithm. Note that the evaluation of efficacy via TLOVR analysis was a non-protocol defined post-hoc analysis.

Based on the definitions in the TLOVR algorithm, if a subject is suppressed virologically without discontinuing therapy, then the patient was classified as a success regardless of whether a CDC Class C event occurred or not. Death, loss to follow-up, and discontinuation or switching of study medications are considered as failure. Temporary discontinuation or dose reduction of study medications and discontinuation or dose reduction of background therapies in blinded studies was ignored.

In generating the TLOVR data set, a conservative approach was used. That is, the patient's earliest date of change in antiretroviral therapy, or other reasons for discontinuation, was considered as the virologic failure date.

For graphical presentation, the proportion of patients continuing to respond (1-probability of Loss-of-Virologic-Response) was computed for the comparison of the treatment regimens. Subgroup analysis by age (cutpoint = 2 years) was also performed. Figures 13 and 14 show the Kaplan-Meier (K-M) curves regarding the proportion of patients continuing to respond by treatment regimen and by age strata. Overall, the two K-M curves for the treatment regimens are significantly different, $p<0.001$ by the Logrank test.

The estimated virologic response rate or proportion of subjects with HIV RNA < 400 copies/mL through Week 48 are listed in Table A10. Overall, pediatric subjects in the Viracept group had an 18.5% greater virologic response than those in the placebo group, with a 95% confidence interval (CI) of (9.7,27.4%), $p<0.0006$ by the Mantel-Haenszel Chi-Square test. Similar results were obtained using a weighted method.

Figure 14 shows the two K-M curves for the Viracept arm (symbol = •) and the two K-M curves for the placebo arm (symbol = *). Note that the two solid lines denote K-M curves for age < 2 years subgroups, and the two dashed lines for age >=2 years groups.

Table A10: Estimated Virologic Response Rate at Week 48

	Viracept (%)	Placebo (%)	Difference (%)	95% CI (%)
Age < 2	10.0 (2/20)	3.7 (1/27)	6.3	-6.3, 18.8
Age >=2	28.1 (12/46)	2.1 (1/48)	24.0	12.8, 35.2
Total*	21.2 (14/66)	2.7 (2/75)	18.5	9.7, 27.4
Adjusted**	24.0	6.3	18.1	7.7, 28.5

*P<0.0006 by the Mantel-Haenszel Chi-Square test.

**Weighted virologic response rate adjusting for age strata using the reciprocal of variances of treatment difference in virologic response rates as weights.

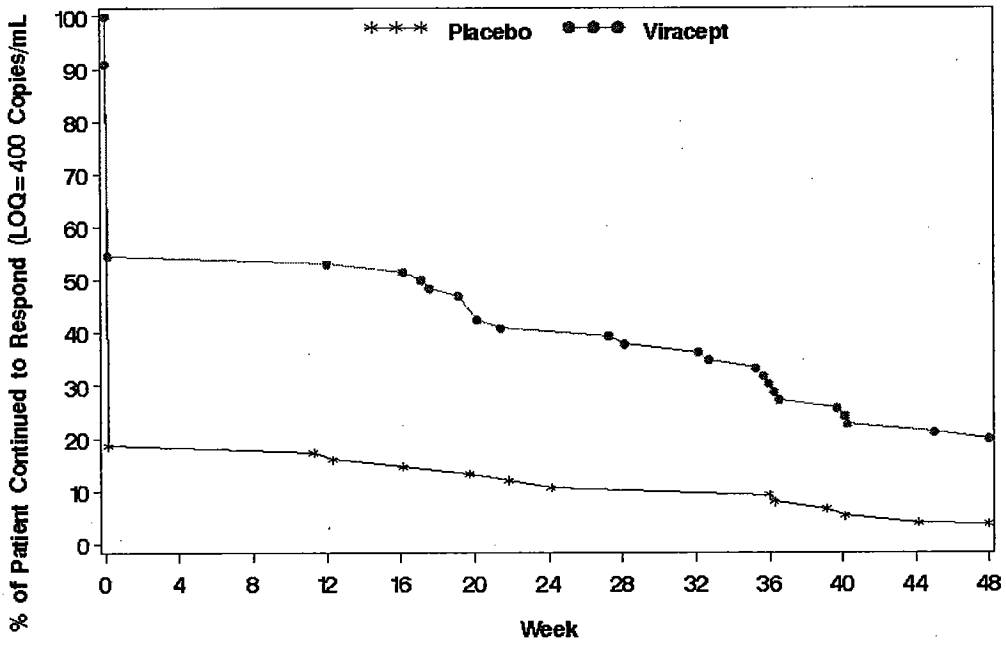

Figure 13: Study 556: Proportion of patients Continuing to Respond

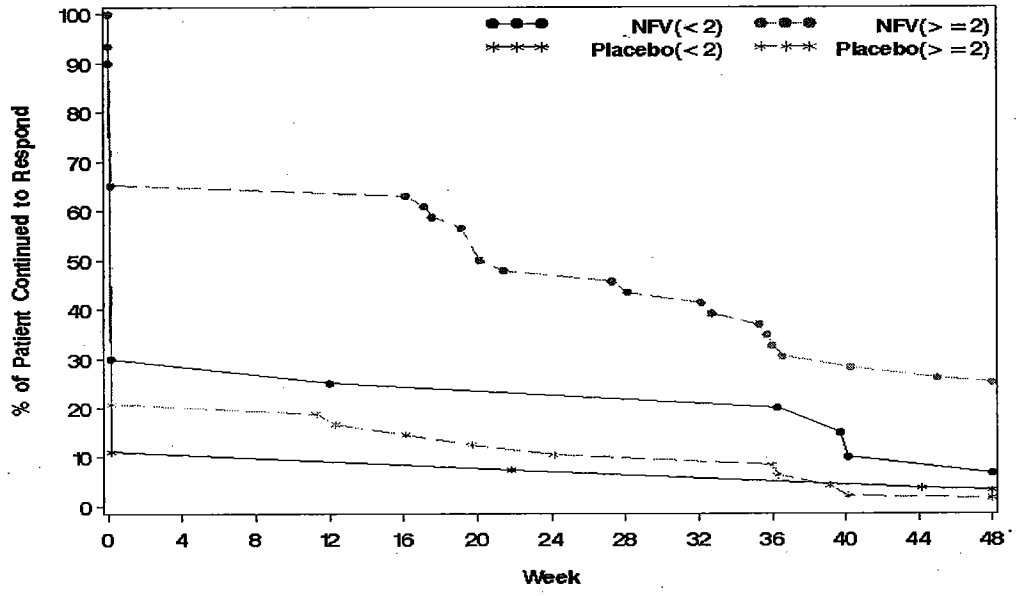

Figure 14: Study 556: Proportion of Patients Continuing to Respond by Age Groups

3.5. Time to First Change in ART

The distribution of time to first change in ART by treatment regimen for Study 556 is shown in Table 11. 58 subjects (77%) in the placebo arm and 21 (32%) in the Viracept arm received antiretroviral therapy (ART) changes during the study through 48 weeks. The greater proportion of changes in ART in the placebo arm may be the main reason for the greater probability of loss-of-virologic-response and the shortened time to failure.

The K-M analysis of time to first change in ART by treatment regimen and age groups was performed. In this analysis, other reasons for discontinuation were considered as censored. The results showed that significantly more subjects in the placebo arm had early switching and change in ART than those in the Viracept arm, $p<0.0001$ by the Log-rank test. The K-M curves are shown in Figure 15, where the two K-M curves for the Viracept arm (symbol = •) are at the top, separating from the two K-M curves for the placebo arm at the bottom (symbol = *). Note that the two solid lines denote K-M curves for age < 2 years subgroups, and the two dashed lines for age >=2 years groups.

Table 11: Study 556: First Time of Change in ART

Week	Placebo		Viracept	
	#	%	#	%
8-	1	1.33	0	0.00
12-	0	0.00	1	1.52
16-	6	8.00	0	0.00
20-	23	30.67	6	9.09
24-	13	17.33	6	9.09
28-	4	5.33	3	4.55
32-	1	1.33	0	0.00
36-	4	5.33	1	1.52
40-	0	0.00	1	1.52
44-	2	2.67	1	1.52
48-	4	5.33	2	3.03
never	17	22.67	45	68.18
total	75	100.00	66	100.00

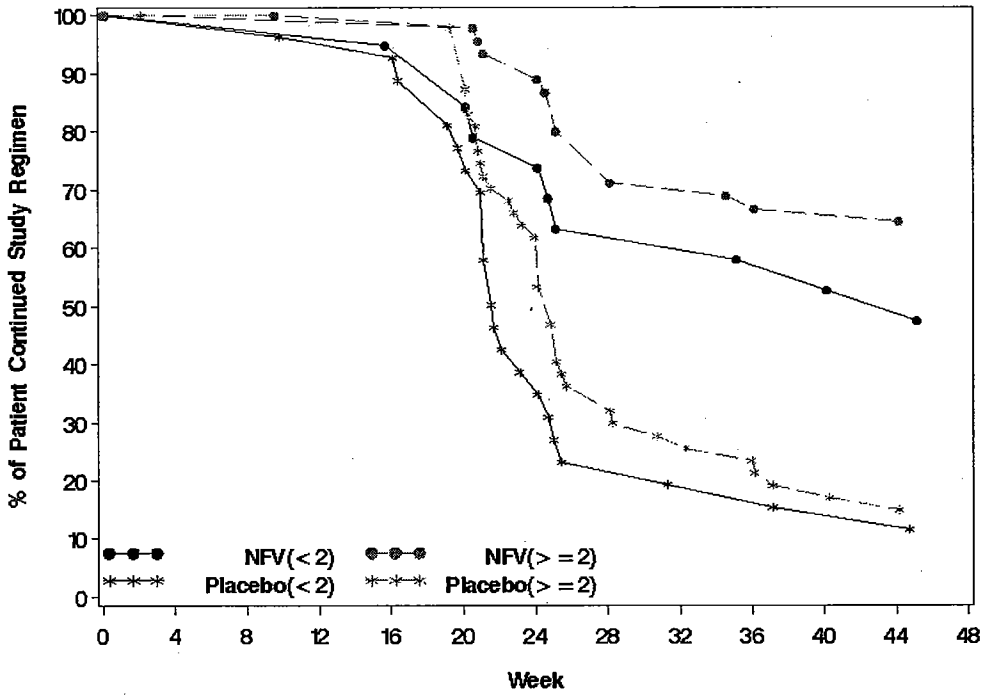

Figure 15: Study 556: Proportion of Subjects Continuing on ART without Change in Therapy

B. Individual Study Reviews

PACTG 353: A Phase I trial of the safety, tolerance, and pharmacokinetics of oral nelfinavir (Viracept) co-administered with zidovudine (ZDV) and lamivudine (3TC) in HIV infected pregnant women and their infants

Summary of Study Design

PACTG 353 was an open-label, multiple-dose, Phase I study designed to evaluate the PK, safety, and tolerance of NFV in combination with ZDV and 3TC given to HIV-infected pregnant women during pregnancy, labor and delivery, and postpartum and to their infants. The study was conducted in anticipation that NFV may be used for the treatment of HIV in pregnant women and may be used as part of a regimen to prevent mother-to-child transmission of HIV in exposed infants. At least 10 evaluable HIV-infected pregnant women between 14 and 34 weeks gestation were enrolled in each cohort.

The first cohort of women received the following oral treatment regimen:

- NFV 750 mg TID + 3TC 150 mg BID + ZDV 200 mg TID

The first cohort of infants received:

- NFV 10 mg/kg TID + 3TC 2 mg/kg BID + ZDV 2.6 mg/kg PO TID (or 2 mg/kg IV q8 hours)

After the initial evaluation of pharmacokinetic data from Cohort I, it was determined that the NFV exposures in pregnant women were lower than those previously reported in non-pregnant women. Similarly, the oral clearance of NFV in infants was higher than that reported for adults. Higher doses of NFV were studied for both pregnant women and their infants in Cohort II.

The second cohort of women received the following regimen:

- NFV 1250 mg BID + 3TC 150 mg BID + ZDV 200 mg TID

The second cohort of infants received:

- NFV 40 mg/kg BID + 3TC 2 mg/kg BID + ZDV 2.6 mg/kg PO TID (or 2 mg/kg IV q8 hours)

Pregnant women were begun on the treatment regimen at the time of enrollment and continued until 12 weeks postpartum. They were evaluated at study entry, every 2 weeks until delivery, then at 5-6 weeks and 12 weeks postpartum. At each visit, women were evaluated for safety by recording any AEs, assessing medical history and physical exam, and performing laboratory monitoring (routine hematology, serum chemistry tests, CD4 and CD8 cell counts, and HIV RNA levels).

Infants were begun on study treatment at 12 hours of life (+/- 2 hours) and received the regimen for 6 weeks. A table indicating the appropriate dose of NFV

powder or crushed tablets for infants of different weights was included in the protocol. Infants were evaluated at birth, 5 to 8 days of life, 3 to 4 weeks, 5 to 6 weeks, 3 months, and 6 months. Laboratory evaluations included HIV DNA PCR for diagnosis of HIV infection at birth (or within 2 to 3 days if born on a weekend), week 5 to 6, 3 months , and 6 months. Any positive HIV DNA assay was repeated and samples were stored for HIV RNA quantitation and HIV resistance evaluations if needed. Limited serum chemistry tests (SGOT, SGPT, direct and indirect bilirubin, BUN, creatinine, amiylase, uric acid, and cholesterol) and hematology (CBC with differential and platelet count) were performed at all study visits up to 3 months. CD4 and CD8 cell counts were also performed at each study visit.

Pharmacokinetic assessments were performed on the pregnant women 10 to 15 days after the start of study therapy and again 5 to 6 weeks postpartum. Maternal and cord blood samples were collected at the time of delivery for NFV concentrations. Blood samples were collected from the infants at intervals after delivery to determine the "washout" kinetics of NFV. More complete PK sampling in the infants was performed at 5 to 8 days after birth and again at 5 to 6 weeks. 3TC PK sampling was to be performed in the infants at the same time points.

Patient Population

Women were eligible to enroll in PACTG 353 if they met the following inclusion criteria:

- HIV infection documented by ELISA and confirmed by Western Blot
- Pregnancy at 14 to 34 weeks gestation
- Women with prior treatment with ddI, ddC, d4T, ZDV or NNRTIs are eligible. Women who had received 3TC for < 3 weeks are eligible. Women who had received 3TC for > 3 weeks were eligible under certain conditions.
- Women who had received NFV in combination with ZDV and 3TC for < 3 weeks were eligible. Women receiving > 3 weeks of NFV, ZDV and 3TC were eligible under certain conditions.
- At least 13 years of age or the local IRB age of consent, whichever was higher
- Normal level II ultrasound.
- Signed informed consent from the patient and/or her guardian. The father of the fetus (if available after reasonable attempts have been made to contact him) must also provide written consent.
- Patient must have access to a participating site and be willing to be followed at this site for the duration of the study.

Women were not eligible to enroll in the study if they met any of the following exclusion criteria:

- Women who received > 3 weeks of 3TC.

- Women who were intolerant of ZDV or 3TC
- Women requiring treatment with any anticonvulsant or antineoplastic drug or any of the following drugs: rifampin, rifabutin, terfenadine, astemizole, cisapride, triazolam, midazolam, ergot derivatives, amiodarone, or quinidine.
- Current substance or alcohol abuse
- Active opportunistic infection and/or serious bacterial infection or unstable or severe medical conditiona at the time of study entry
- Chronic malabsorption or chronic diarrhea or recent acute diarrhea
- Abnormal laboratory findings: hemoglobin < 8.5 mg/dL, ANC < 1000 cells/mm3, ALT > 3 x ULN, serum creatinine > 1.5 mg/dL, platelets ≤ 50,000, amylase > 1.5 x ULN with abnormal lipase
- Obstetrical complications in past pregnancies
- Obstetrical complications in this pregnancy
- Medical complication or conditions including: gestational diabetes diagnosed prior to enrollment, pre-gestational diabetes, hypertensive disorders requiring medications, cardiovascular disease including rheumatic or congenital heart disease, collagen vascular disease, endomyocarditis, or chronic renal disease
- Hematologic conditions including: hemoglobinopathies, coagulapathy, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, and fetomaternal blood incompatibilities with isoimmunization
- Neurological conditions that may lead to pregnancy complications including seizure disorder
- Pulmonary conditions including: moderate to severe asthma (systemic and inhaled steroids prohibited) and cystic fibrosis
- Any evidence of fetal intolerance of the intrauterine environment as measured by: intrauterine growth restriction< 10%, major fetal anomalies identified sonographically, abnormal amniotic fluid volume, elevated maternal alpha-fetal protein
- Mothers who intend to breastfeed
- Family history of PKU disease
- Participation during current pregnancy in any other therapeutic or vaccine perinatal treatment trial

Study Results

Enrollment of pregnant women into PACTG 353 began in December, 1997, and the first cohort of 10 women was completely accrued as on June, 1998. As noted above, the NFV exposures in Cohort I were lower than anticipated in both women and infants and doses were escalated for the second cohort. Cohort II enrolled 23 women between May, 1999, and July, 2001. Two women in Cohort I failed to deliver (one fetal demise and one elective abortion); all women in Cohort II delivered live infants. Eight of 10 women in Cohort I and 16 of 23 women in Cohort II completed the protocol-specified treatment from the time of entry until

6 weeks postpartum. This review focused on the infants delivered during PACTG 353 and then followed on study. The efficacy, pharmacokinetic profile, and safety of NFV in pregnant women will not be discussed further.

As noted above, there were 8 live births in Cohort I and 23 live births in Cohort II. Table B1 summarizes the demographic characteristics of the infants born during PACTG 353. One infant in Cohort I was withdrawn from the study immediately after birth and no information is available on that infant.

Table B1: Baseline Demographics of Infants – PACTG 353

Characteristic	Cohort I (N=8)	Cohort II (N=23*)	Total (N=31*)
Gender			
Male/Female	6/2	8/14	14/16
Race/Ethnicity			
White non-Hispanic	3	1	4
Black non-Hispanic	0	7	7
Hispanic (any race)	5	14	19
Newborn Classification			
Large for GA	1	0	1
Appropriate for GA	5	22	27
Small for GA	2	0	2
Gestational Age (weeks)			
Mean (range)	38.9 (36-40)	38.3 (37-41)	38.5 (36-41)
Birth Weight (grams)			
Mean (range)	3058 (2050-4210)	3010 (2150-3570)	3023 (2050-4210)
APGAR Score at 1 minute (mean)	8	8.2	8.1
APGAR Score at 5 minutes (mean)	9.1	9	9.1

Source: NDA 20-778, SE5-022, PACTG 353: Final Analysis Report (Revised), Section 6, Vol. 5, pg 53.
*One infant was withdrawn from study immediately after birth and no demographic data were recorded.

A total of 26 infants started the treatment regimen after birth. One infant in Cohort I who died at 4 days of age and 4 infants in Cohort II never received study treatment. All 7 of the infants in Cohort I who began treatment completed the study treatment period of 6 weeks. Fifteen of 19 infants in Cohort II completed the 6 week study treatment period. Four infants discontinued treatment prematurely at the request of the family or investigator. A total of 19 infants required dose modification of NFV because of weight changes, toxicity, or non-compliance. Table B2 summarizes the disposition of infants in PACTG 353 through the 6 week treatment period. Six infants in Cohort I and 18 infants in Cohort II completed the entire 6 month study follow-up.

Table B2: Treatment disposition of infants – PACTG 353

	Cohort I	Cohort II	Total
Number of live births	8	23	31
Infants never started study treatment	1	4	5
Death	1	0	1
Withdrew after birth	0	4	4
Infants off study treatment	7	19	26
Completed treatment	7	15	22
Off at request of caregiver	0	3	3
Off at request of investigator	0	1	1
Total dose modifications of study treatment (number of patients)	6 (4)	18 (15)	24 (19)
Dose increased (weight change)	4	11	15
Dose decreased (weight change)	0	1	1
Dose temporarily held	2	6	8
Clinical toxicity	2	4	6
Non-compliance	0	1	1
Vomiting	0	1	1

Source: NDA 20-778, SE5-022, PACTG 353: Final Analysis Report (Revised), Section 6, Vol. 5, pg 55.

Efficacy Analysis

Since PACTG was considered a pilot study primarily undertaken to determine the PK profile of NFV in pregnant women and their newborn infants, no efficacy analysis was conducted on the infants enrolled in the study. Infants were evaluated for mother-to-child transmission of HIV. Only one infant in Cohort II was determined to be HIV infected. All other infants completing the study were determined to be non-infected. Although this represents a small number of exposed infants, the rate of HIV transmission in PACTG 353 (1 of 24, 4%) was comparable to that observed in other recent studies evaluating perinatal transmission. This study is not adequate to support the efficacy of NFV in prevention of mother-to-child transmission. To clearly define the role of NFV in prevention of HIV perinatal transmission, a large, randomized study would be needed.

C. References

Floren LC, Wiznia A, Hayashi S, et. al. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. *Pediatrics* 2003;112:e220-e227.
(URL: http://www.pediatrics.org/cgi/content/full/112/3/e220)

Krogstad P, Lee S, Johnson G, et. al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis* 2002;34:991-1001.

Litalien C, Faye A, Compagnucci A, et. al. Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J* 2003;22:48-55.

Paediatric European Network for Treatment of AIDS (PENTA). Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS* 2004;18:237-245.

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/s/

Linda Lewis
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Susan Zhou
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-779 / S-042
20-778 / S-022
21-503 / S-001

CHEMISTRY REVIEW(S)

Chemistry Review

SUPPLEMENTAL NDA CHEMIST'S REVIEW	DUE DATE 12/17/03	1. ORGANIZATION HFD-530	2. NDA NUMBER 20-779

3. NAME AND ADDRESS OF APPLICANT

Agouron Pharmaceuticals, Inc.
10777 Science Center Drive
San Diego, CA 92121
Attn: Marie-Do Mompas, Pharm.D.

4. TYPE OF SUPPLEMENT

Efficacy supplement detailing a change to size of patient population

5. DOCUMENT(S)

NUMBERS	DATED	RECEIVED
NDA 20-779/SE5-042 (250 mg tabs)	6/19/03	6/20/03
NDA 20-778/SE5-022 (oral powder)	6/19/03	6/20/03
NDA 21-503/SE5-001 (625 mg tabs)	6/19/03	6/20/03

6. NAME OF DRUG

VIRACEPT[R] Tablets

7. NONPROPRIETARY NAME

nelfinavir mesylate tablets

8. SUPPLEMENT PROVIDES FOR:

Additional marketing exclusivity based on pediatric data.

9. AMENDMENTS/DATES

10. PHARMACOLOGICAL CATEGORY

Anti-HIV

11. HOW DISPENSED

|X| Rx | | OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM(S)

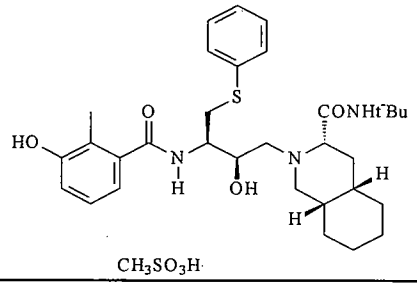
Tablets

14. POTENCY (CIES)

250 mg

15. CHEMICAL NAME AND STRUCTURE

[3S-[2(2S*,3S*,3• ;4a• ;8a•]]-N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy [(3-hydroxy-2-methylbenzoyl)amino-4-(phenylthio)butyl]-3-isoquinolinecarboxamide, monomethanesulfonate (salt)



16. MEMORANDA

17. COMMENTS

Only the labeling is changed by this supplement and none of the proposed changes affect the chemistry information. There are no CMC issues.

18. CONCLUSIONS AND RECOMMENDATIONS

This Supplement is therefore recommended for approval from a CMC perspective.

19. REVIEWER

NAME	SIGNATURE	DATE OF DRAFT REVIEW
George Lunn, Ph.D.	*[signed electronically in DFS]*	10/10/03

20. CONCURRENCE: HFD-530/SMiller *[signed electronically in DFS]*

DFS CC LIST								
L = Action Letter	R	SMiller	R	PM: JO'Neill		Micro		
R = Review		CChen		Biopharm				

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/s/

George Lunn
10/15/03 08:31:14 AM
CHEMIST

Nelfinavir pediatric labeling supplements

Stephen Paul Miller
10/22/03 11:25:14 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-779 / S-042
20-778 / S-022
21-503 / S-001

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Antiviral Drug Products
REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 21-503/SE-5-001
NDA 20-779/SE-5-042
NDA 20-778/SE-5-022

Name of Drug: Viracept® (nelfinavir mesylate)

Applicant: Agouron Pharmaceuticals, Inc. a Pfizer Company

Materials Reviewed: The approved draft labeling (first submitted June 19, 2003 and amended most recently on March 18, 2004) accompanying the approval of the above referenced applications, was compared to the last approved labeling for SLRs 002 (21-503), 041 (20-779), and 020 (20-778), approved August 27, 2003.

In addition one email correspondence dated March 18, 2004 was also reviewed.

Background and Summary

Nelfinavir is a protease inhibitor indicated for the treatment of HIV infection, in combination with other antiretrovirals, in adults and children older than two years of age. This supplement contains PK, efficacy, and safety data in pediatric subjects of all ages, and specifically in subjects < two years of age in response to the Pediatric Written Request. The Package Inset and Patient Package have been updated to incorporate the data. In these supplements the applicant provided for the addition of changes to the following sections:

Package Insert Revisions:

In addition to the changes listed below, the tables have been renumbered to reflect the addition of tables 3 and 13. There have also been some minor editorial changes throughout the document.

CLINICAL PHARMACOLOGY/Special Populations/***Pediatrics*** **(section)**

Deleted: "(see PRECAUTIONS:"

Inserted: "The pharmacokinetics of nelfinavir have been investigated in 5 studies in pediatric patients from birth to 13 years of age either receiving VIRACEPT three times or twice daily. The dosing regimens and associated AUC_{24} values are summarized in Table 3.

Inserted:

WITHHOLD 44 PAGE(S)

Draft labeling

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/s/

Jeff ONeill
3/26/04 02:17:34 PM
CSO

CSO review for Viracept NDAs 21503(001), 20779(042) and 20778(022).
Hard copy sign off 3/26/04