CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20-779 SE5 042, 20-778 SE5 022 and 21-503 SE5 001
Submission Dates:	06/19/2003, 08/01/2003, 09/25/2003, 10/23/2003, 10/30/2003 and 03/04/2004
Brand Name:	Viracept®
Generic Name:	nelfinavir mesylate
Formulation:	250 mg tablets, 625 mg tablets and 50 mg/g oral powder
Applicant:	Agouron Pharmaceuticals, Inc, A Pfizer Company
Reviewer:	Robert O. Kumi, Ph.D.
Team Leader:	Kellie Reynolds, Pharm.D.

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I. EXECUTIVE SUMMARY

Viracept® (nelfinavir mesylate, tablets and oral powder) in combination with other antiretroviral agents is indicated for the treatment of HIV infection in children two years of age and older and in adults. Pharmacokinetic information was provided in NDAs 20-779 SE5 042, 20-778 SE5 022 and 21-503 SE5 001 to fulfill the Pediatric Exclusivity Written Request and a Phase IV Commitment. The listed NDA submissions provide the following pediatric information:

- Nelfinavir dosing for children < 2 years of age (birth to 2 years).
- New nelfinavir dosing recommendations for children between 2 and 13 years of age.
- Nelfinavir pharmacokinetics following twice daily administration of nelfinavir in children.

Six study reports were included in the current submission to support nelfinavir dosing recommendations in pediatric subjects: AG1343-524, AG1343-556, PACTG 725, PACTG 353, PENTA 7 and "German Study". The applicant sponsored only two of these studies, AG1343-524 and AG1343-556. In all studies the pharmacokinetics, safety and efficacy of nelfinavir were assessed to varying degrees.

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted to NDAs 20-779 SE5 042, 20-778 SE5 022 and 21-503 SE5 001. The NDA supplements provide adequate information to change the recommended nelfinavir dose for pediatric patients between 2 and 13 years of age **from 20 to 30 mg/kg TID with a meal to 25 to 35 mg/kg TID with a meal**. The submitted pharmacokinetic data do not support BID dosing for pediatric patients between 2 and 13 years of age; the nelfinavir exposure at the studied BID doses is higher than exposure achieved at approved doses in adults. The medical reviewer evaluated the safety data from study PACTG 377/725 to determine whether the label should include a BID dosing regimen for children between 2 and 13 years of age. The medical reviewer concluded that the safety data support a dose of 45-55 mg/kg BID. (b) (4)

The label will be updated to include pharmacokinetic data for all pediatric age groups that were studied. The inclusion of these data will make health care providers aware of the high pharmacokinetic variability associated with nelfinavir use in young children.

Pediatric Exclusivity Determination

The FDA Pediatric Exclusivity Board granted the applicant Pediatric Exclusivity on September 4, 2003. The Board determined that the applicant had adequately fulfilled the terms of the Pediatric Written Request for Viracept.

Fulfillment of Phase IV Commitment

The applicant provided sufficient data to fulfill the Phase IV commitment to evaluate the pharmacokinetics of twice daily dosing of Viracept with the oral powder in pediatric patients. PACTG 353, PACTG 725, PENTA 7 and the German Study provide BID dosing information.

B. Phase IV Commitments

There are no phase IV commitments. The review team determined that additional pharmacokinetic data in pediatric patients less than 2 years of age are unlikely to allow selection of a dose for this age group, due to the high variability observed in the submitted studies.

C. Summary of Clinical Pharmacology Findings

NDAs 20-779 SE5 042, 20-778 SE5 022 and 21-503 SE5 001 provide information from six pediatric studies in which nelfinavir was coadministered with other antiretroviral agents. These studies were submitted to aid in nelfinavir dose selection across the pediatric age range of birth to 13 years of age. Currently, dosing information is available for children between 2 and 13 years of age: nelfinavir dose is 20 to 30 mg/kg TID. Pediatric subjects received nelfinavir as tablet, crushed tablet mixed with liquid, or oral powder mixed with liquids or food. Both BID and TID regimens were evaluated: TID doses ranged from 10 mg/kg to 35 mg/kg and BID doses ranged from 14 mg/kg to 75 mg/kg. The six studies are listed below; please refer to individual study reviews for additional study information. All studies were conducted in children born to HIV-infected mothers.

1) AG1343-524, TID dosing in children between 1.4 and 13 years of age (n = 17). This study was reviewed with original NDA.
2) AG1343-556, TID dosing in children between 0.6 to 12.7 years of age (n = 119).
3) PACTG 353, TID and BID dosing in children 0.02 to 0.1 years (1 week to 6 weeks) of age (n = 20).
4) PACTG 725, BID dosing in children between 3.4 and 11 years of age (n = 6).
5) PENTA 7, TID and BID dosing in children between 0.2 to 0.7 years (2.4 to 8.5 months) of age (n = 16).
6) "German Study", TID (n = 17) and BID (n = 18) dosing in children between 2 and 15 years of age.

<u>Key Clinical Pharmacology Findings</u>

- Pharmacokinetic results from all pediatric studies were characterized by high inter-individual pharmacokinetic **variability,** as is observed in the adult population. In most pediatric studies, variability, measured by CV %, was > 50 %. The sources of variability were not identified, but are likely due to myriad factors, such as nominal vs. actual dose administered, varying absorption, dosing conditions (e.g. food type), compliance, and small numbers of patients. Data were most variable in Study 556, which employed a sparse sampling population pharmacokinetic approach.

(b) (4)

- The tablet and oral powder had similar **bioavailability** in children; generally pediatric patients preferred receiving the intact or crushed tablet rather than the oral powder.
- (b) (4)
- (b) (4)

(b) (4)

(b) (4) The Office of Clinical Pharmacology does not agree with the applicant's conclusion (b) (4)

- (b) (4)

  .

Food increases nelfinavir exposure; thus, Viracept should be taken with food to optimize therapy.

Table II: Nelfinavir Steady State Exposure Measures in Adult and Pediatric Patients (b) (4)

(b) (4)

Age group	Study ID	Approximate Dose (mg/kg)	AUC_{24} (µg·hr/mL)	AUC Conclusion Comment
Adults and older children				
> 18 years (n =10)	542	18 mg/kg BID^	52.8 ± 15.7	Target exposure
> 18 years (n = 11)	542	11 mg/kg TID^	43.6 ± 17.8	Target exposure
2 –13 years (n = 14)	524	22 ± 3 TID	56.1 ± 29.8	Acceptable
3 – 11 years (n = 6)	725	53 ± 4 BID	101.8 ± 56.1	High
2 - 15 years (n = 18)	German	40 ± 9 BID	72.7#	High
2 - 15 years (n = 17)	German	24 ± 5 TID	47.7#	Acceptable
6 weeks to 2 years				
6 weeks to < 2 months	No studies conducted in this age group			
2 – 9 months (n = 12)	PENTA 7	66 ± 8 BID	37.2 ± 19.2	Low
2 – 9 months (n = 4)	PENTA 7	39 ± 4 TID	33.8 ± 8.9	Low
10 months to 2 years	PK data (Study 556) were not reliable for this age group			
Birth to 6 weeks				
6 weeks (n = 10)	353	37 ± 7 BID	44.1 ± 27.4	Acceptable, but highly variable
6 weeks	TID regimen was not evaluated			
1 week (n = 10)	353	29 ± 12 BID	45.8 ± 32.1	Acceptable, but highly variable
1 week	TID regimen was not evaluated			
Birth (0 weeks)	Neither the TID nor the BID regimen were evaluated			

^ dose approximated by dividing 1250 mg by 70 kg or 750 mg by 70 kg

median values reported and range not available

_____ Date_____

Robert O. Kumi, Ph.D.,
Clinical Pharmacology Reviewer

Concurrence:

_____ Date_____

Kellie Reynolds, Pharm.D.
Clinical Pharmacology Team Leader

II. QUESTION BASED REVIEW

Although, the Question Based Review (QBR) approach was employed in the review, a complete QBR section was not required for this Efficacy Supplement. The key QBR sections used in dose selection and making labeling recommendations follow; for additional details please refer to individual study reviews.

A. What are the general attributes of nelfinavir in the pediatric population?

1. **Regulatory Background**

In the original Viracept NDA, NDA 20-779, sufficient data and information were provided to make nelfinavir (NFV) dosing recommendations for adults and children ≥ 2 years of age. The approved dose for these children was 20 to 30 mg/kg TID. Study 524 provided the main basis for the approval. The current submission provides safety, efficacy and pharmacokinetic data in children from birth to 15 years of age; children participating in the trials were born to HIV infected mothers. (b) (4)

2. **Drug Formulation**

A pediatric Viracept oral powder formulation is available for NFV administration; however, the majority of pediatric subjects preferred receiving the intact 250 mg Viracept tablet or crushed tablet rather than the oral powder. The applicant provided two reasons for this preference:

a) poor taste of oral powder
b) large amount of oral powder that needed to be swallowed to obtain dose

3. **Overview of Pediatric Studies**

Pharmacokinetic, efficacy and safety data sources provided in the submission are as follows:

a) AG1343-524, TID dosing (20 –30 mg/kg/dose) in HIV-infected children between 1.4 and 13 years of age (n = 17). Open label multi-center trial with Viracept and antiretroviral therapy including zidovudine, lamivudine, stavudine, didanosine, or zalcitabine (22- month duration). PK samples obtained on Day 14.

b) AG1343-556, TID dosing (25 – 35 mg/kg/dose) in HIV-positive children between 0.6 to 12.7 years of age (n = 119). Multi-center, randomized, double-blind, placebo-controlled trial with Viracept or placebo coadministered with zidovudine or didanosine (48-week duration). PK samples obtained throughout the trial (sparse sampling approach).

c) PACTG 725, BID dosing (55 mg/kg/dose) in HIV-infected children between 3.4 and 11 years of age (n = 6). PK substudy of a multi-center, randomized trial with four treatment arms. Children participating in the PK sub-study received NFV with lamivudine and stavudine (48-week duration). PK samples obtained at Week 4.

d) PENTA 7, TID (40 mg/kg/dose) and BID (65 mg/kg/dose) dosing in HIV-infected children between 0.2 to 0.7 years (2.4 to 8.5 months) of age (n = 16). Multinational, multi-center, open label trial with Viracept and stavudine and didanosine (72-week duration). PK samples obtained after Week 4.

e) "German Study", TID (25 mg/kg/dose) and BID (40 mg/kg/dose) dosing in HIV-infected children between 2 and 15 years of age (n = 17). Multi-center, open label trial with Viracept and stavudine, didanosine, zidovudine or abacavir (one subject received efavirenz). Maximum of three PK samples obtained (3-month duration).

f) PACTG 353, TID (10 mg/kg/dose) and BID (40 mg/kg/dose) dosing in children 0.02 to 0.1 years (1 week to 6 weeks) of age (n = 20). Multi-center, open label trial with Viracept and lamivudine and zidovudine (6-month duration). PK samples were obtained at Week 1 and Week 6.

None of these studies were adequately powered to definitively show efficacy. However, Study 556 was blinded, had a comparator arm, and included a relatively large number of subjects.

B. What are the General Clinical Pharmacology characteristics of nelfinavir in the adult and pediatric populations?

NFV is a protease inhibitor that is indicated for treatment of HIV in combination with other antiretroviral agents. Please refer to NDA 20-779 for general information on NFV's mechanism of action and pharmacokinetics (PK). General clinical pharmacology characteristics relevant to the current review are provided in the following section.

Exposure-Response Information

Historical Data in Adults

Exposure-response (ER) relationships for NFV and other protease inhibitors have been reasonably demonstrated in previous studies in adults; typically, these analyses are conducted retrospectively. Because antiretroviral therapy requires multi-drug combinations it is difficult to ascribe efficacy to a specific drug; however, protease inhibitors are known to contribute significantly to antiretroviral activity. With appropriate study designs, such as single substitution regimens (e.g. control = background regimen of NRTIs and NNRTIs vs. same background + NFV) an ER relationship can be elucidated.

The following ER findings for NFV do not necessarily meet the "appropriate study design" criteria, but are useful in evaluating the pediatric dosing recommendations.

1) (b) (4)

2) (b) (4)

3) **Diarrhea (Safety):** Patients with AUC_{24} > ~ 60 µg hr/mL have increased likelihood of diarrhea (frequency and severity); this relationship was evaluated in NDA 21-503 (625 mg tablet formulation) because the 625 mg tablet was more bioavailable than the approved 250 mg tablet. The applicant discontinued evaluation of the 1000 mg TID regimen (NDA 20-779) because of unacceptable diarrhea (AUC_{24} ~ 90 µg hr/mL and C_{max} ~ 5 µg/mL).

The majority of the quantitative methods involve logistic regression approaches that attempt to define an exposure threshold, typically AUC. Consequently, at the minimum, the pediatric exposure should achieve comparable exposure to that obtained in the adult on the 750 mg TID regimen.

Historical PK data that are relevant to the current review are summarized in Table 1 (excerpted from NDA 20-779)

Table 1. Mean ± SD Nelfinavir PK Measures (Day 28) from CPB Review for NDA 20-779^

Pharmacokinetic Measure	500 mg TID (n = 10)	750 mg TID (n = 10)	1000 mg TID (n = 9)
AUC_8 (µg hr/mL)	15.86 ± 5.51	16.30 ± 7.71	29.67 ± 9.31
C_{max}(µg/mL)	3.52 ± 1.30	2.93 ± 1.29	5.11 ± 1.63
C_{trough} (µg hr/mL) on Day 21	1.72 ± 0.63	2.02 ± 1.28	2.79 ± 2.30
CL/F (L/hr)	30.7 ± 4.8	36.4 ± 3.7	40.5 ± 14.6

^ Data obtained from Study 503: HIV positive patients ≥ 12 years of age

Pediatric Data in Current Submission

(b) (4)

[redacted]

Two Major Potential Shortcomings of Study 556 Results

(b) (4)

[redacted]

Proposed Labeling: Impact of Exposure Response Analyses

The applicant had proposed the following labeling language (b) (4)

[redacted]

Pediatric Pharmacokinetic Data

As shown in Table 2, some of the pediatric dosing regimens evaluated produced nelfinavir exposure that was comparable to that in adults receiving approved adult dosing regimens (particularly the TID regimen).

Table 2. Nelfinavir Steady State Exposure Measures in Adult and Pediatric Patients

Age group	Study ID	Approximate Dose	AUC_{24}	C_{max}	$C_{trough, AM}$	$C_{trough, PM}$
		(mg/kg)	(µg hr/mL)	(µg/mL)	(µg/mL)	(µg/mL)
> 18 years (n =10)	542	18 BID^	52.8 ± 15.7	4.0 ± 0.8	2.2 ± 1.3	0.7 ± 0.4
> 18 years (n = 11)	542	11 TID^	43.6 ± 17.8	3.0 ± 1.6	1.4 ± 0.6	1.0 ± 0.5
2 –13 years (n = 14)	524	22.1 ± 2.7 TID	56.1 ± 29.8	3.5 ± 1.6	Not done	Not done
3 – 11 years (n = 6)	725	53.3 ± 4.2 BID	101.8 ± 56.1	7.5 ± 4.4	1.7 ± 1.3*	NA
2 – 15 years (n = 18)	German	39.5 ± 9 BID	72.7#	3.6#	NA	NA
2 – 15 years (n = 17)	German	24.3 ± 4.7 TID	47.7#	2.5#	NA	NA
2 – 9 months (n = 12)	PENTA 7	66.1 ± 8.3 BID	37.2 ± 19.2	3.2 ± 1.6	0.6 ± 0.6*	NR
2 – 9 months (n = 4)	PENTA 7	39.1 ± 3.7 TID	33.8 ± 8.9	2.3 ± 0.2	0.8 ± 0.6*	NR
6 weeks (n = 10)	353	37 ± 7 BID	44.1 ± 27.4	2.4 ± 1.2	1.1 ± 0.9*	NA
1 week (n = 10)	353	29 ± 12 BID	45.8 ± 32.1	3.0 ± 2.1	0.6 ± 0.6*	NA

^ dose approximated by dividing 1250 mg by 70 kg or 750 mg by 70 kg
# median values reported and range not available
* C_{min} values, C_{trough} values were not available
NA- not available; NR- not reliable

C. What intrinsic factors influence nelfinavir exposure and/or response?

Age, weight, and body surface area appeared to affect NFV exposure in children; some of these correlations are depicted in Figure 1. (b) (4)

Figure 1.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Table 3 also provides nelfinavir dose-exposure information.

Table 3: Nelfinavir Steady State Exposure Measures in Adult and Pediatric Patients (b) (4)

Age group	Study ID	Approximate Dose (mg/kg)	AUC_{24} (µg·hr/mL)	AUC Conclusion Comment
Adults and older children				
> 18 years (n =10)	542	18 mg/kg BID^	52.8 ± 15.7	Target exposure
> 18 years (n = 11)	542	11 mg/kg TID^	43.6 ± 17.8	Target exposure
2 –13 years (n = 14)	524	22 ± 3 TID	56.1 ± 29.8	Acceptable
3 – 11 years (n = 6)	725	53 ± 4 BID	101.8 ± 56.1	High
2 – 15 years (n = 18)	German	40 ± 9 BID	72.7#	High
2 – 15 years (n = 17)	German	24 ± 5 TID	47.7#	Acceptable
6 weeks to 2 years				
6 weeks to < 2 months	No studies conducted in this age group			
2 – 9 months (n = 12)	PENTA 7	66 ± 8 BID	37.2 ± 19.2	Low
2 – 9 months (n = 4)	PENTA 7	39 ± 4 TID	33.8 ± 8.9	Low
10 months to 2 years	PK data (Study 556) were not reliable for this age group			
Birth to 6 weeks				
6 weeks (n = 10)	353	37 ± 7 BID	44.1 ± 27.4	Acceptable, but highly variable
6 weeks	TID regimen was not evaluated			
1 week (n = 10)	353	29 ± 12 BID	45.8 ± 32.1	Acceptable, but highly variable
1 week	TID regimen was not evaluated			
Birth (0 weeks)	Neither the TID nor the BID regimen were evaluated			

^ dose approximated by dividing 1250 mg by 70 kg or 750 mg by 70 kg
# median values reported and range not available

Reviewer's Notes

Two to 13 years of age

The currently approved nelfinavir dosage for these children is 20 to 30 mg/kg TID and appears to provide adequate nelfinavir exposure. The increase in dose is supported by the following:

- According to the Medical Reviewer, many clinicians indicate that nelfinavir activity is suboptimal in children receiving the approved pediatric regimen, 20 – 30 mg/kg nelfinavir TID. It is unclear if these observations are for all age groups or for children ≥ 2 years to 13 years. However, the clinical observation suggests that a higher nelfinavir exposure may be required for children in this age range or other age ranges.
- The 25-35 mg TID dose was evaluated in Study 556 and was associated with adequate safety and efficacy; therefore, increasing the nelfinavir to 25-35 mg/kg is supported by clinical evidence. As noted previously, the reliability of the PK information in Study 556 is unclear.

Based on the two factors discussed, this reviewer considers the 25 – 35 mg/kg TID dose in children ≥ 2 years to 13 years acceptable, even though exposure information from Study 556 may not be accurate.

2. Body weight and Body Surface Area

The following correlations were observed:

- Body weight (BW) and body surface area (BSA) were correlated with CL/F.
- BW and BSA were correlated with each other
- BW and BSA were correlated with age.

These correlation findings suggest that either BW or BSA could be used in pediatric dosing of NFV in an attempt to minimize variability in NFV exposure. Generally, BW is more accurately determined than BSA, and NFV dosing by BW has been shown to be effective (children ≥ 2 years old). Consequently, all pediatric subjects receiving NFV will be dosed according to body weight.

D. What extrinsic factors influence nelfinavir exposure and/or response?

Food was the only extrinsic factor that was considered to have potentially affected NFV exposure. In adults, the type of meal profoundly affects NFV exposure (Table I). Other extrinsic factors that can affect NFV exposure include formulation and concomitant medications. Please see NDA 20-779 for a complete discussion of these factors. For this application, food and formulation are the two main extrinsic factors that could influence NFV exposure.

Food

Assuming that the NFV food effect is comparable in adults and children, the type of meal would have a great impact on NFV exposure. The meal types were not closely monitored or recorded in the pediatric studies. Generally the amount of meals or food ingested by children is erratic, thus the high variability in exposure results (especially in neonates) may be explained largely by the food effect.

Table 4: 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

As discussed above, food plays an important role on nelfinavir exposure, therefore pediatric children should also take NFV with food or a meal, if possible. This recommendation is consistent with the recommendation for adults receiving nelfinavir.

Formulation

NFV was administered in one of three forms: oral powder, crushed tablet or intact tablet. All NFV forms were found to be equally bioavailable across the pediatric dose range; thus, the dosage form did not affect nelfinavir exposure.

E. What are the general biopharmaceutics properties of nelfinavir?

Biopharmaceutics properties of NFV are provided in the CPB Review for NDA 20-779; no additional biopharmaceutics information was provided in the current submission.

F. What analytical methods were used to identify and measure nelfinavir concentrations?

In all submitted pediatric studies an HPLC method was used to quantify NFV concentrations. These methods are summarized in Table 5.

Table 5: Nelfinavir Assay Methods

Study	Method	Reviewer Comment on Assay Validity
524	HPLC UV	Acceptable- sufficient information provided
556	HPLC UV	Acceptable- sufficient information provided
PENTA 7	LC/MS	Acceptable- sufficient information provided
PACTG 725	HPLC UV	Acceptable- sufficient information provided
PACTG 353	HPLC UV	Acceptable- sufficient information provided
German^	LC/MS	Insufficient data provided to make assessment

^ Applicant provided study results as supportive information (BID regimen), but does not intend to use this information for labeling. Study results not reliable as incomplete plasma concentration-time profiles obtained.

III. Detailed Labeling Recommendations-
Based on the Clinical Pharmacology and Biopharmaceutics Review, the following changes to the applicant's original labeling proposal were made. These changes apply to the Clinical Pharmacology and Dose and Administration sections of the label.

Clinical Pharmacology Section

Comments
1. Delete (b) (4) information from the PK table (Table 3)

2. In Table 3, provide dose ranges for each study

3. In Table 3, provide more specific age ranges (instead of <2 or ≥2 years)

4. In Table 3, provide mean ± SD PK data, rather than geometric mean data, to facilitate comparison with adults exposure data.

5. Delete the following sentence (b) (4)

New label text for Clinical Pharmacology, Pediatrics Section (Applicant and DAVDP agree)

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 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. (see PRECAUTIONS Pediatric USE; DOSAGE AND ADMINISTRATION).

Dosage And Administration Section

Comments

1. (b) (4)

2. The PK data do not support a BID dose recommendation for pediatric patients between 2 and 13 years of age. (Note: Safety review by Medical Officer supports a BID regimen for the 2-13 year old, so this comment was not sent to the sponsor).

3. The dosing instructions need to state that all doses must be taken with a meal.

New label text for Dosage and Administration Section (Applicant and DAVDP agree)

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 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**
Kg.	**Lbs.**	# of tablets (250 mg)	# of tablets (250 mg)
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

IV. INDIVIDUAL STUDY REVIEWS

Study 524- page 16
Study 556- page 18
German Study- page 23
PRAM-2 or PACTG 377/725- page 26
PENTA 7- page 29
PACTG 353- page 34

Title of Study: A phase I study of safety, tolerability, and pharmacokinetics of Viracept in HIV-1-infected children and exposed infants (Study 524)
Investigators: Multiple investigators
Centers: Four US sites.
Study Period: 08/1996 – 07/1998

Reviewer's Note
The pharmacokinetic (PK) study results were previously reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (Reviewer: Dr. Kellie Reynolds) as part of the original Viracept submission, NDA 20779 and 20778, submitted in December 1996. Consequently, the study will not be reviewed in depth; however, salient sections of the study report will be revisited to aid in dose selection for the current application, NDA 20779 SE5 042. The current review is focused on the multiple-dose PK component of the study (Phase B).

Study Overview
For study details such as study objectives (pharmacokinetic, safety and efficacy), study design, blood sampling, bioanalytical assay, pharmacokinetic analyses, safety and efficacy assessments, and conclusions, please refer to Dr. Kellie Reynolds' Review for NDA 20-779.

Excerpts from Dr. Reynolds' Review
- Children between 2 and 17 years receiving 20 mg/kg TID (target dose- some children received higher doses) had similar nelfinavir (NFV) plasma concentrations as adult patients in Phase II studies who received doses of 750 mg TID
- Following multiple doses of NFV, the body-weight corrected apparent NFV oral clearance was approximately double that observed in adults.

Selected multiple dose data supporting the above statements are tabulated below:

Age (yr)	N	F*	TID Dose (mg/kg)	$AUC_{0\text{-}8\ hr}$ (μg hr/mL)	C_{max} (μg/mL)	C_{min} (μg/mL)	CL/F (L/hr)	CL/F (L/hr/kg)
2-7	8	P	20	20.2 ± 8.2	4.03 ± 1.33	1.68 ± 1.08	22.3 ± 8.8	1.25 ± 0.55
7-13	6	T	20	16.7 ± 12.5	2.69 ± 1.63	1.74 ± 1.42	67.0 ± 41.8	2.08 ± 1.41
> 18 (adults)	30	T	750 mg	18.5 ± 7.6	3.16 ± 1.21	1.50 ± 0.82	50.1 ± 29.8	0.72 ± 0.43

F* = formulation, P for powder and T for tablet (the tablet and powder were equally bioavailable)

Dose Selection (Variability in Clearance)
Based on mean values, the order of decreasing clearance (weight normalized) was 7-13 year olds, 2-7 year olds and adults. This finding suggests that the optimal dose for the two pediatric age groups may be different. However, the high degree of variability in clearance appears to obscure potential exposure differences in the two pediatric age groups and the need for different doses. Ultimately, the exposure resulting from a 20 – 30 mg/kg NFV dose TID in children 2 to 13 years was considered sufficiently comparable to exposures in adults receiving 750 mg TID (only approved adult regimen at the time). A dose range, rather than one dose, was proposed because only one dose strength of the NFV formulations was available: 250 mg tablet and 50 mg/g (scoop) powder.

Pharmacokinetic Conclusions (Dosing Recommendation)
A Viracept dose of 20 to 30 mg/kg TID in children 2 to 13 years of age achieves plasma NFV concentrations similar to those in adults receiving a standard 750 mg TID regimen

Appendix to Study 524

Individual Subject Demographics and Steady State (Day 14) PK data (20 mg/kg TID) for Study 524

Race	Form	Subject	Cmax	CL/F	$AUC_{0\text{-}24hr}$	WT	AGE (yr)	Dose (mg/kg)	$AUC_{0\text{-}8\ hr}$
Caucasian	Powder	1	6.77	0.550943	109.53	17.4	4.02	20.11494	36.51
Caucasian	Powder	2	4.77	0.926441	69.39	17.5	2.97	21.42857	23.13
Hispanic	Tablet	3	1.55	1.766329	32.046	53	12.5	18.86792	10.682
Hispanic	Powder	4	2.42	2.383511	26.391	15.5	6	20.96774	8.797
Caucasian	Powder	5	3.63	1.244601	50.427	23.9	6.68	20.9205	16.809
Hispanic	Powder	7	3.76	1.141819	55.77	21.2	7.19	21.22642	18.59
Black	Tablet	8	3.95	1.057366	68.865	30.9	9.76	24.27184	22.955
Caucasian	Tablet	9	2.82	1.375001	49.14	33.3	10.31	22.52252	16.38
Caucasian	Powder	10	4.07	0.879301	73.11	17.5	5.24	21.42857	24.37
Black	Tablet	11	0.945	4.28201	13.071	26.8	8.34	18.65672	4.357
Hispanic	Tablet	12	5.21	0.675044	114.54	19.4	8.5	25.7732	38.18
Hispanic	Powder	13	2.82	1.372517	44.913	14.6	4.45	20.54795	14.971
Hispanic	Tablet	16	3.99	1.506591	56.25	17.7	7.18	28.24859	18.75
Hispanic	Tablet	17	1.67	3.312563	22.053	30.8	9.5	24.35065	7.351

Title of study:	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 (Study 556)
Investigators:	Multiple investigators
Study centers	Five study centers located in Brazil and Argentina
Study period:	August 1998 to April 2000 (data cutoff)

Reviewer's Note
Based on inspection of data by this Reviewer and the findings of a Pharmacometrics Consult by Dr. Jenny J. Zheng, the pharmacokinetic (PK) information from Study 556 provides supportive rather than definitive nelfinavir (NFV) PK information in the pediatric population. The comment below was conveyed to the sponsor and provides the rationale for our conclusion. It should be noted that there were no major shortcomings in the sponsor's study design or analyses.

Comment conveyed to Sponsor on Study AG1343-556 (Study 556)
Based on a preliminary review of the pharmacokinetic (PK) data from Study 556, it appears that data from this study will provide supportive PK information in the pediatric population. However, we do not think that PK data from this study will be useful in selecting a NFV pediatric dosing regimen. Generally, PK data from Study 556 were more variable than data from other studies in the pediatric population. The source of variability in Study 556 is probably multi-factorial, but may be due to the "uncontrolled" nature of the study with respect to meal consumption and dosing compliance. We consider the population pharmacokinetic approach (sparse sampling) a viable and significant tool in drug development and dose selection, but results from Study 556 do not appear useable in the stated context. Therefore, NFV dose selection for the pediatric population will be based primarily on the other submitted pediatric studies (PACTG-353, AG1243-524, PACTG-725, and PENTA7).

Due to the limited utility of the study results in determining a NFV pediatric dose, the study was not reviewed in detail by this Reviewer or the Pharmacometrics Reviewer. The remainder of this report highlights the sponsor's study procedures and conclusions. Additionally, reviewer comments are included to address some relevant study findings.

Objectives
- To evaluate the efficacy and safety of Viracept administered in combination with zidovudine (AZT) and didanosine (ddI), as compared with AZT and ddI alone, in HIV-positive children.
- To determine the population pharmacokinetics of nelfinavir in the pediatric population

Study design
This was a randomized, double blind, placebo-controlled study in 120 HIV positive children. Children who were antiretroviral naïve (less than 1 month of therapy or less than 6 weeks of AZT therapy if they received AZT to prevent vertical transmission) were randomized to 1 of 2 groups: Viracept with AZT and ddI or placebo with AZT and ddI. Randomization was stratified by three factors based on the patient's status at screening:
1) Age group- < 2 years old versus ≥ 2 years old
2) Baseline HIV RNA viral load- $< 50,000$ copies/mL versus $\geq 50,000$ copies/mL
3) Disease status based on Centers for Disease Control and Prevention (CDC) classification.

Patients were followed on study through week 48 and could continue on study through week 96. Patients received Viracept doses (targeted at 25 to 35 mg/kg TID) based on their body weight. AZT and ddI were given at doses recommended by the respective manufacturers.

Patient demographics and baseline characteristics (per Clinical Study Report):
The placebo and Viracept groups were similar in their distribution of age, gender, race, weight, and other baseline characteristics.

- Mean age was 3.9 years (range 0.6 to 12.7 years) in both the placebo and Viracept groups.
- Approximately an equal number of males (52 %) and females (48 %).
- Race- 53% were of mixed racial origin, 41% were white, and 6% were black.
- Mean duration of HIV infection was 14.6 (placebo) and 15.9 (Viracept) months.
- Mean calculated baseline log-transformed HIV RNA values were 5.1 (placebo) and 5.0 (Viracept) logs.
- Mean CD4 percentage was 19.7 % (placebo) and 20.2% (Viracept).

Drug Formulations and Mode of Administration
Nelfinavir

- Nelfinavir mesylate powder and tablets, Viracept, was administered three times daily: either as a powder (mixed with milk, formula, ice cream, pudding, or water) or as a tablet (crushed or intact) with food (e.g., full meal, light meal, or snack). The lot numbers for Viracept tablets (250 mg) were 028564, 028565, 048595, 048596, and TBQ002. The lot numbers for Viracept oral powder (50 mg/g) were 08015C, 08250B, 08338C, 08386B, and 08475B.
- Matching placebo powder and tablets were administered in a manner identical to that of Viracept. The lot numbers for placebo tablets were PL088, PL091, and TBA005. The lot numbers for placebo oral powder were 08046B, 08134B, and 08233B.

Other study drugs*

- Zidovudine liquid and capsules, Retrovir.
- Didanosine liquid or tablets, Videx.

* See Study Appendix for listing of Videx and Retrovir lot numbers

Blood Sampling for Pharmacokinetic Analyses
Blood samples for pharmacokinetic (PK) profiles of NFV were collected at baseline and during weeks 4, 8, 12, 24, 32, and 48. For weeks 8 and 24, samples were collected pre-dose and at approximately 3 hours post-dose. The remaining weeks had 1 pre-dose sample collected during that week. Placebo patients who reached virologic failure and switched to Viracept had additional blood samples (both pre-dose and at approximately 3 hours post-dose) taken during weeks 8 and 24 after initiation of Viracept therapy.

Reviewer's Comment
The majority of samples were obtained between two and four hours post dose, however a significant number of samples were obtained outside the two- to four-hour window.

Assay
An HPLC UV assay was used; the assay performance was acceptable.

Pharmacokinetics/Pharmacodynamic Analyses
Oral clearance (CL/F) and area under the curve (AUC) values were estimated for each patient. Additionally, the possible relationship between NFV exposure and virologic suppression was explored by examining the correlation between response data at week 48 and AUC values. This correlation was analyzed with a chi-square test and logistic regression (using the Statistical Analysis System™ [SAS], Version 8.0). Other analyses explored the relationship between NFV PK parameters and age, formulation, metabolic phenotype (M8/NFV ratio) and concomitant medications.

Efficacy and Safety Assessments.
Efficacy assessments were performed every four weeks throughout the study. Safety assessments were performed every four weeks for the first 24 weeks of treatment, every eight weeks until week 48, and every 12 weeks thereafter. Safety assessments were also performed two weeks after the end of treatment. Key study assessments included blood draws for measurement of plasma HIV RNA levels, CD4 lymphocyte count, as well as monitoring of adverse events (AEs), clinical laboratory assessments, physical examinations, and vital signs.

Pharmacokinetics and Pharmacodynamic Results
Pharmacokinetic measures obtained from the population pharmacokinetic analyses are summarized in Table I. Sparse PK samples were available from 119 patients.

Table I: Selected Pharmacokinetic Results in Study 556 (per Population Pharmacokinetics Report)

	Age < 2 years	Age ≥ 2 years	Pooled Data
Number of subjects	N = 33	N = 86	N = 119
Age^ (years)	(b) (4)		
Dose^ (mg/kg) TID			
CL/F* (L/hr/kg)			
AUC*$_{8\ hr}$ (µg hr/mL)			
AUC*$_{24\ hr}$ (µg hr/mL)			

* results are reported as geometric mean and 95 % confidence intervals
^ results reported as mean ± SD

(b) (4)

See the Medical Officer's review for more details.

Reviewer's Comment on Population Pharmacokinetic/Dynamic Analyses

(b) (4)

(b) (4) Generally, the disease process and disease progression model for HIV is assumed to be comparable in adults and children, therefore adult exposures are targeted to select dosing regimens in children in the absence of an adequately well-controlled clinical trial in children. From a practical perspective, Study 556 provides substantial clinical evidence to support a NFV pediatric dosing regimen because:

- An adequate number of paired (ER) data were available to conduct PK/PD or ER analyses
- There are a limited number of pediatric patients infected with HIV thus it is difficult to conduct a fully powered clinical efficacy trial in the pediatric population.

(b) (4)

This reviewer recommends that only doses that potentially achieve targeted adult exposure (AUC) be considered for inclusion in the label because:

- The PK/PD based dosing may result in sub-optimal NFV therapy in children
- The PK/PD findings have shortcomings (see Discussion below).

(b) (4) The Clinical Division agrees with the recommendation due to the shortcomings of the PK/PD analyses.

Discussion: Potential Shortcomings of the PK/PD Analyses

Study 556 vs. Study 524

A comparison of the Study 556 PK data to that of Study 524 provides the most compelling evidence that the PK/PD findings may be flawed. (b) (4)

Study 524 was a well-controlled clinical study whereas Study 556 was not a well-controlled study (b) (4)

(b) (4)

(b) (4)

Extrinsic, Intrinsic and Miscellaneous Factors

Various intrinsic, extrinsic, and miscellaneous factors may have impacted the PK/PD model; not all of these factors may have been accurately captured in the analyses. Some of these factors include the presence and activity of concomitant medication and patient adherence. The applicant's analyses attempted to capture these factors to varying degrees, but may have been limited, particularly in relation to patient adherence.

Reviewer's Conclusions and Recommendations

Several PK findings from Study 556 are consistent with other nelfinavir pediatric studies, as listed below.

- High degree of PK variability
- Clearance in children < 2 years is greater than that in children ≥ 2 years
- Tablet and powder have similar bioavailability

The study results provide supportive pediatric dosing information. However, the dosing conclusions from the PK/PD analyses are not acceptable. (b) (4)

Study Appendix

- Retrovir capsules (100 mg): 8ZP0206; 8ZP0507; 9ZP0374
- Retrovir syrup (50 mg/5 mL): 7J2124; 8H1772; 8M708; 9G606
- Videx tablets (25 mg): MBN19; MBN20; MKS31; MMH16
- Videx tablets (100 mg): MCN96; MJN28; MMN39
- Videx oral solution (2 g/100 mL): MCS89; MDN56; MES93; MHN66; MHS05
- Zerit capsules (15 mg): MCN07; MES09; MHH06; MJN08
- Zerit capsules (20 mg): MCN52; MCS61; MEN53; MFS65; MLN57; MMH44
- Zerit oral solution (1 mg/mL): 131064; 131746; MBS52; MCS54; MDN23; ME562; MFS64; MJS77; MKN42
- Epivir tablets (150 mg): 8ZP0408; 8ZP1155; 9ZP0026; 9ZP1219; 9ZP0346; 9ZP0630
- Epivir oral solution (10 mg/mL): 775; 1689; 3278; 4859; 9769; 10551673; 10514362; 10549866
- Norvir oral solution (80 mg/mL): 37714AW; 43193VA; 49801AW; 51952AW; 54098AW; 58278AW; 59300AW; 62437AW21; 49830AW

Title: Clinical case studies comparing two dosage regimens of Viracept in HIV-positive Pediatric patients (German Study)
Sites: Frankfurt and München, Germany
Investigator: Drs. Tobias Schuster Dr. Uwe Wintergerst
Period: Summer 1998

Reviewer's Note
The applicant provided the following disclaimer regarding this study:
NOTE TO REVIEWERS: Agouron Pharmaceuticals, Inc. (API) had no role in designing or conducting this study and is not responsible for the accuracy or reliability of the data. We are providing the data as part of a phase IV commitment to the FDA to provide pharmacokinetic and dosing regimen data on Viracept (nelfinavir mesylate) in pediatric patients.

The study report indicates the following: "In response to an inquiry from API, the 3 participating sites (2 clinics and 1 laboratory) agreed to make the pharmacokinetic data available so that API could perform an independent analysis of Viracept pharmacokinetics. The results of that analysis are presented". Based on the above disclaimer it appears that the PK data presented in this report were analyzed by Agouron Pharmaceuticals, but Agouron does not claim liability for the accuracy of the results.

Objective
To provide additional clinical data comparing the pharmacokinetic profiles of twice-daily and three-times-daily dosage regimens of Viracept (nelfinavir mesylate) in children.

Study Design
This was an open label clinical case study in pediatric patients infected with HIV. The patients in the study were being treated with Viracept under the care of the investigators; this research was conducted in conjunction with routine clinical patient visits. HIV-positive pediatric patients received nelfinavir (NFV) twice daily (BID) or three times daily (TID) as powder or tablets. The report indicates that the powder was not well tolerated (too bulky and unpleasant aftertaste). Therefore, the majority of patients received whole or crushed tablets. Most patients received NFV tablets or powder on a TID regimen (at study initiation) followed by a BID regimen. Patients received concomitant antiretroviral medications throughout the course of the trial.

Subject Demographics
Subject demographics are summarized in Table I.

Table I: Subject Demographics- Highly Active Antiretroviral Therapy (HAART) and Dosing Information

HAART Treatment Duration	Mean 14.5 months (range 5 to 24) receiving Viracept TID + 2NRTIs[#]	
CD4 cell count	774 cells/μL (range 0 to 1607)	
HIV viral load	Median 150 copies/mL (< 20 to 75,000)	
Concomitant ARV^	stavudine, didanosine, zidovudine, or abacavir; One subject also received efavirenz.	
Nelfinavir Regimen	BID	TID
Daily Dose (mg/kg)	79 ± 18 (range 49 to 116)	73 ± 14 (range 51 to 94)
Age (years) Range 2 to 15	9 ± 4	9 ± 4
Weight (kg)	28.2 ± 11.6	26.5 ± 9.9
Male	11	11
Female	7	6

***** Age was determined on the day of first PK sampling
^ ARV- antiretroviral agents
[#] NRTI- nucleoside reverse transcriptase inhibitors

Assay
Limited assay information was provided. The report notes that plasma NFV concentrations were determined by a validated LC/MS assay. Bioanalytical assays were performed by (b) (4)

Blood Samples for Pharmacokinetic (PK) Determinations
Blood samples for determination of NFV concentrations were collected after at least two weeks of Viracept + 2 NRTIs. The exact timelines at each site varied as follows:

- Frankfurt site- at least 3 weeks after switching to the BID NFV regimen
- Munich site- immediately after switching from TID to BID regimen

The timing of blood samples also varied among sites and between dosing regimens as follows:

- Munich site (BID and TID)- at pre-dose and at approximately 1, 2, and 4 hours post-dose
- Frankfurt site (TID group)- at pre-dose and 4 and 8 hours post-dose
- Berlin site (BID group)- at pre-dose and 4 and 12 hours post-dose

Pharmacokinetic Analysis
The following NFV PK measures were estimated: The report indicates that because complete concentration-time profiles were not obtained for all patients, the median concentration-time profiles of the BID and TID groups were calculated. Subsequently, PK of NFV was calculated for the median concentration-time profile of each group.

Reviewer's Note
The use of median plasma concentration-time data appears reasonable, but may introduce an unknown degree of error and variability. Consequently, PK results from this study should be interpreted cautiously and these results should be viewed in qualitative rather than quantitative sense.

Results
Data were obtained from 20 patients. All the subjects provided at least two sets of data from TID and BID dosing. The majority of the data were obtained with the crushed tablets.

Median NFV PK measures after TID and BID administration of Viracept are listed in Table II.

Table II: Median Nelfinavir PK Measures for BID (n = 10) and TID (n = 17) Regimens

Regimen	AUCτ (μg h/mL)	AUC_{24} (μg h/mL)	C_{max} (μg/mL)	CL/F^ (L/hr/kg)	T_{max} (h)
BID	36.3	72.7	3.56	2.18	4.0
TID	15.9	47.7	2.46	1.53	4.0

AUC_{24} = AUCτ x 2 for BID and AUCτ x 3 for TID group
^ CL/F estimated by Mean Dose/AUCτ

Reviewer's Note
Individual data were not provided, therefore it was not possible to assess the variability. However, inspection of the plasma concentration-time profiles (10^{th} and 90^{th} percentile) suggest that the PK data were highly variable.

Discussion on Dosing Proposal
According to the report, the median concentration-time curves of NFV in this study were similar to previous Agouron data from pediatric (AG1343-524) and adult patients (AG1343-542). This finding suggests that adequate NFV systemic exposure was achieved in the current study. Based on the study findings, pediatric patients from 2 to 15 years old can receive NFV as a BID or TID regimen. The applicant's rationale for arriving at this conclusion is plausible, however, the applicant's argument is weakened by the absence of individual plasma concentration-time profiles and PK data. As mentioned

previously, the use of median data and absence of complete data limits the overall impact and creditability of this study. In essence, this study provides supportive NFV PK dosing information, rather than definitive NFV PK dosing information in the pediatric population. Despite the shortcomings of the study, the current study provides potentially relevant NFV PK information that is summarized in the following section:

Key Study Results

1) The median extrapolated AUC_{24} values for BID dosing appeared greater than that for TID dosing, but the AUC_{24} for either regimen is comparable to that in adults receiving approved NFV regimens

Reviewer's Note: *There was large inter-subject variability of NFV concentrations and the concentrations after BID dosing and TID dosing overlapped each other. Consequently, it is not possible to make a definite conclusion regarding exposure differences between the two regimens.*

2) The NFV powder was not well tolerated because of the volume needed for dosing, but the powder appeared to have similar bioavailability as the tablet.

Reviewer's Note: *Although the number of patients on NFV powder was small (n =2), it appeared that the resulting pharmacokinetics of NFV were in the same range as had been observed after BID or TID administration of the tablet. Thus, pediatric patients can use either formulation.*

3) Changing NFV application from TID to BID was more effective in children over 25 kg in weight compared to children under 25 kg weight (AIDS 2000, Vol 14 no 10, page 1466 – 1468)

Reviewer's Note: *This conclusion appears reasonable, but is limited by the small number of subjects and previously described study shortcomings. The publication indicates that the PK differences in subjects < 25 kg and those > 25 kg may be due to higher drug clearance rates in small children and the authors indicate that higher NFV dosages may be required in children < 25 kg to achieve sufficient plasma levels. The authors' conclusion regarding smaller children is reasonable and consistent with study results in small children.*

Reviewer's Conclusions

- A total daily dose of approximately Viracept 80 mg/kg, given on a BID or TID schedule, in children between 2 and 15 years of age appears to provide nelfinavir exposure that is comparable to that in adults receiving Viracept 750 mg/kg TID or 1250 mg/kg BID.
- The nelfinavir exposure produced by Viracept powder (n = 5) and Viracept tablets (crushed or intact, n = 13) are comparable in children between 2 and 15 years old; thus these two formulations may be used interchangeably.
- The utility of conclusions from this study is limited because full PK datasets were not provided for review.

Study Title: A Phase I/II randomized, multicenter protocol comparing 4 antiretroviral regimens containing combinations of protease inhibitors, NRTIs, and an NNRTI (PRAM-2 or PACTG377/725)
Investigators: Multiple investigators**.**
Centers: Multiple study sites
Study period: December 1997 to July 1999

Reviewer's Note
PACTG 725 was a sub-study of a larger PACTG 377 study (summarized below). This review will focus on the pharmacokinetic findings from the sub-study. The sub-study findings were provided as an abbreviated supplementary clinical study report.

Overview of Study 377
One hundred eighty-one subjects were enrolled and randomized into four main treatment arms of the PACTG 377 study as follows:

- n = 41 received d4T + nevirapine (NVP) + ritonavir (RTV); n = 7 <2 and n = 34 ≥ 2 years old
- n = 52 received d4T + 3TC + nelfinavir (NFV); n = 7 <2 and n = 45 ≥ 2 years old
- n = 44 received d4T + NVP + NFV; n = 4 <2 and n = 40 ≥ 2 years old
- n = 44 received d4T + 3TC + NVP + NFV; n = 3 subjects <2 and 41 subjects ≥ 2 years old

In the NFV containing regimens, subjects received **30 mg/kg TID**. An additional 12 subjects were enrolled in a separate PK substudy (PACTG 725) of BID NFV dosing; NFV **55 mg/kg BID** was given with d4T and 3TC in this substudy.

All subjects were HIV-infected children and had been on stable reverse-transcriptase-inhibitor therapy for the 16 weeks before enrollment and were clinically and immunologically stable.

Objectives of Sub-study 725:

- To analyze the efficacy and safety data from the main treatment arms of study PACTG 377 between subject age strata (<2 and ≥ 2 years) within each treatment regimen that included Viracept
- To evaluate twice daily (BID) dosing of Viracept (nelfinavir mesylate, NFV) in combination with stavudine (d4T) and lamivudine (3TC) in children who weighed less than 30 kg

Design of PK Sub-Study
The sub-study assessed the virologic efficacy, safety, and pharmacokinetics (PK) of twice daily (BID) administration of Viracept in combination with stavudine (d4T) and lamivudine (3TC) in subjects who weighed less than 30 kg and could swallow tablets. Subjects received Viracept at a dose of 55 mg/kg BID in combination with d4T (1 mg/kg BID) and 3TC (4 mg/kg BID).

Subject disposition (PK Sub-study):
Twelve subjects were enrolled directly into the PACTG 725 PK sub-study; however PK data were available from only six subjects. Selected demographic characteristics for these patients were:

- Mean ± SD age = 8.3 ± 2.7 years (range 3.4 to 11.0 years).
- Mean ± SD weight = 23.45 ± 5.07 kg
- 3 males and 3 females
- 1 White, 2 Hispanics and 3 Blacks

Blood Sample Collection
After four weeks of treatment with Viracept BID, serial plasma samples were collected at pre-dose (0 hr) and 0.5, 1, 2, 4, 6, and 8 hours after an observed dose in the outpatient setting.

Plasma Assays
Plasma samples were analyzed simultaneously for NFV and its active M8 metabolite (AG-1402) using a validated HPLC method with UV detection. The report indicates that the method used was a modification of a method developed by Agouron Pharmaceuticals, Inc. The assay performed acceptably with the following characteristics:
NFV/M8 assay was linear from 50 to 10,000 ng/L, with r^2 >0.99. The inter-assay mean coefficient of variation (CV) was 7.8% for NFV and 10.6% for M8. The intra-assay mean CV was 7.6% for NFV and 9.3% for M8. Interference tests were completed and there was no cross-reactivity with other HIV protease inhibitors, including ritonavir, indinavir, and saquinavir.

Pharmacokinetic Assessments
The following NFV PK measures were estimated: $AUC_{0\text{-}12\ hr}$, CL/F, and λ_z. The sponsor indicates that the zero-hour (0-hr) measurement was used as the 12-hour time point for subjects 21 and 22. For other subjects, concentrations measured 12 hours after dosing were extrapolated from the 8-hour measurement based on the terminal rate constant. Administration times for the previous two Viracept doses, PK sampling times, and concomitant medications were recorded. It should be noted that the sponsor attempted to duplicate the PK measures estimated for the sub-study data by the PACTG. Results from Agouron analyses were similar (less than 6% difference from PACTG results for any subject), but not identical. Agouron's methods for calculating PK parameters were used for this supplemental report.

Reviewer's Comment on Blood Sampling and Pharmacokinetic Assessments
Use of the 0-hr measurement as the 12 hour time point for subjects 21 and 22 introduces some errors in the PK estimations. This is because a concentration is assigned to an unknown value that may be altered by various factors including diurnal variation. The contribution of these concentrations to the total exposure appears insignificant (<10 %): the C_{max} was ~ 5900 and imputed 12-hr point was ~1300 for subject 21 and the C_{max} was ~ 7700 and imputed 12-hr point was ~ 2275 for subject 22. Due to the limited overall available data (n = 6), exclusion of PK data from subjects 21 and 22 might jeopardize the utility of the study. Consequently, data from all six subjects were used. Finally, extrapolation of 12-hour concentrations from the 8-hour concentration is acceptable based on PK principles (constant elimination half-life in terminal phase). Ideally, a 12-hr concentration-time point would have been useful; however, clinical practically may have over-ridden the need for this additional time point.

Statistical Methods for Efficacy Analyses
Rates of undetectable HIV RNA and virologic failure were compared between age strata within each treatment group using Fisher's exact test. The Wilcoxon rank sum test was used to detect between-treatment differences in HIV RNA levels, CD4 lymphocyte cell counts and percentages.

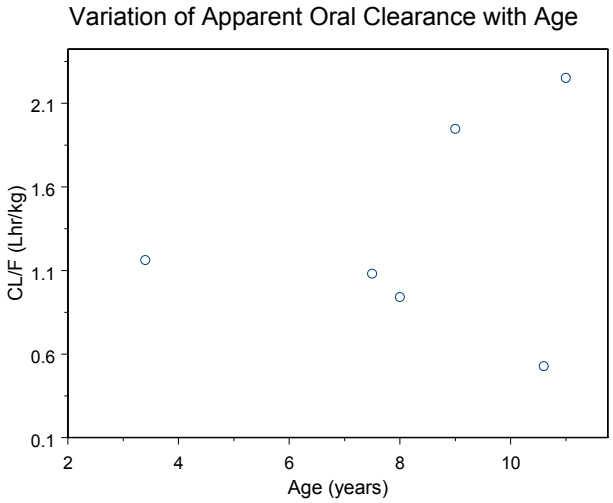
Results from PACTG 725 Sub-study
NFV PK measures (n = 6) obtained from study PACTG-725 are tabulated below:.

	BID Dose* (mg/kg)	C_{max} (μg/mL)	C_{min} (μg/mL)	AUC_{12} (μg hr/mL)	CL/F (L/hr)	AUC_{24} (μg hr/mL)	$t_{1/2}$ (hr)
Mean	53.28	7.53	1.70	50.92	1.32	101.84	5.55
SD	4.24	4.44	1.31	28.07	0.65	56.15	6.46

The maximum dose for subjects < 30 kg was 1500 mg per dose

Based on a comparison to historical NFV data, the BID regimen produced drug $AUC_{0\text{-}24\ hr}$ that was approximately twice as high as that observed in children receiving 20-30 mg TID and adult subjects receiving 750 mg Viracept TID. The sponsor indicates that the higher exposure in the PACTG 725 sub-study may have been due to the better compliance, the slightly higher daily dose administered in the BID regimen, and the small number of subjects, which may have produced atypical results. Some of the sponsor's statements have merit, but it is unclear to this reviewer why the sponsor indicates that the results were atypical; subjects in the BID received total daily doses (110 mg/kg) that were up to approximately twice as high as in the TID regimen (60 to 90 mg/kg), thus higher exposures for the BID regimen would be anticipated.

As shown in the figure below, the apparent oral clearance varied widely across the age range, but no correlation was obvious between CL/F and age.



Sponsor's Efficacy Findings

The sponsor indicated that the data obtained at week 48 indicate suggest that the virologic response rate for BID dosing is similar to that in the main study arms in PACTG 377 (55% versus 34% to 57% of subjects with RNA levels <400 copies/mL). These results suggest that the systemic exposure achieved with BID dosing of Viracept in the PACTG 725 sub-study was adequate for viral suppression. Please see Clinical Review for additional comments.

Sponsor's Safety Findings

The sponsor indicated that the interpretation of the differences in incidence of grade 2 or greater toxicity adverse events (AEs) for the Viracept TID and BID regimens is limited by the small sample sizes. However, rash and neutropenia (ANC <750/mm^3) appeared to be more common in the TID group, while fever and gastrointestinal effects appeared to be more common in the BID group. There were no deaths or other serious AEs. Please see Clinical Review for additional comments.

Conclusion

The exposure produced by the 55 mg/kg BID dose exceeds (approximately 2-fold higher) that of the standard TID regimen, 20 to 30 mg TID in children; a dose lower than 55 mg/kg BID should be used in order to avoid adverse events associated with high NFV exposure. Data from other studies will be considered in making the dosing recommendation for the age group studied in Study 377.

Study Title:	An international, multicentre, Phase I/II, nonrandomized, open-label study to evaluate the toxicity, tolerability, pharmacokinetics, and activity of triple antiretroviral combination therapy with stavudine (d4T) + didanosine (ddI) + nelfinavir (NFV) in HIV-1 vertically infected infants less than 12 weeks of age [Paediatric European Network for Treatment of AIDS (PENTA) 7]
Investigators:	Multiple investigators
Study Centers:	This was an international, multicenter study involving centers in France, Germany, Italy, Spain, and the United Kingdom.
Study Period :	August 1999 to present (ongoing, but pharmacokinetics complete)

Reviewer's Note
The PENTA group has published preliminary pharmacokinetic (PK) results. This summary report presents the PK data from the PENTA 7 Study (ANRS 087). PENTA permitted Agouron Pharmaceuticals, Inc., to perform an independent PK analysis of the PENTA 7 data.

Objectives:
- To assess the toxicity and tolerability of administering triple therapy (stavudine, didanosine, and nelfinavir) to young infants (less than 12 weeks old).
- To assess the activity (as measured by changes in HIV RNA levels, CD4 cell counts, and disease progression) of administering triple therapy to young infants

Study Design
This was an open-label, non-comparative, international, multicenter trial in infants younger than 12 weeks of age who were vertically infected with HIV-1, but who did not have AIDS. Subjects received the following combination treatment regimen:
- Stavudine suspension: 2 mg/kg per day in two divided doses just before meals
- Didanosine suspension: 200 mg/m^2 per day in two divided doses at least 30 minutes before meals
- Nelfinavir (NFV) powder (n = 5) or crushed tablets (n = 14) with food* at a dosage of: (1) 90 mg/kg per day in three divided doses (30 mg/kg TID) and at (2) 150 mg/kg/day (75 mg/kg BID) per protocol amendment.
- *Note: Most infants were >12 weeks old when PK was determined. *Food details were not provided; however, the infants probably did not consume very substantial meals.*

Subject Demographic Data
Subject demographic data are summarized in the following table:

Demographic Data for PENTA7

Regimen	NFV BID	NFV TID
Dose (mg/kg/day)	133 ± 16	117 ± 11
Gender		
Male	5	1
Female	7	3
Race		
Black	9 *	3
Caucasian	2	1
Mixed	1 *	0
Age (month)	5.57 ± 2.21	3.80 ± 1.38
Weight (kg)	6.45 ± 1.62	5.46 ± 1.19

Data are means ± SD when applicable
* one black and one mixed race patient provided two sets of PK data on different dates

Blood Sample Collection
Blood samples for the quantification of plasma concentrations of NFV, stavudine (d4T), and didanosine (ddI) were obtained at protocol-specified times at each visit from week 4 to week 72. Blood samples were collected for determination of NFV concentrations after at least two weeks on the triple treatment regimen (described previously). Collection times were at approximately 1, 2, 3, 4, 6, and 8 hours for the TID group and at pre-dose and at approximately 1, 2, 3, 4, 6, 8, 10, and 12 hours for BID group.

Assay
Plasma concentrations of NFV and its metabolite, M8, were determined by a validated LC/MS assay. The assay performed acceptably with the following characteristics:

- Nelfinavir: Inter and intra assay precision assessed by CV % were less than 6 % and the inter and intra accuracy assessed by relative error was less than 9 %.
- M8: Inter and intra assay precision measured by CV % were less than 10 % and the inter and intra accuracy assessed by relative error was less than 8 %.

Pharmacokinetic Assessments
The following NFV PK measures were estimated by non-compartmental methods: C_{max}, T_{max}, $AUC_{0\text{-last}}$, λ_z, $AUC_{0\text{-}\tau}$ (τ = 8 or 12 hours), AUC_{24} and (M8/NFV) AUC ratio. Correlations of NFV AUC with age, weight, dose, sex, race, dosing frequency, and formulation were assessed by plotting NFV AUC against these measures.

Safety Assessments
Safety was evaluated by monitoring regular clinical assessments (including measurements of head circumference, weight, and height) and laboratory test results and by recording and assessing adverse events (AEs), including AIDS-related events, deaths, and HIV-related signs and symptoms.

Efficacy Assessments
Virologic activity was assessed by measuring plasma HIV RNA levels at protocol-specified times. Plasma viral load was determined by using the Roche Amplicor HIV-1 Monitor (1.5) test, with the Standard method (sensitivity above 400 copies/mL) and the Ultrasensitive method (sensitivity above 50 copies/mL). The viral load tests were performed at a central laboratory (Covance, Geneva, Switzerland). Primary immunologic tests included CD4 cell counts and percentages.

Formulations

- Nelfinavir mesylate powder (50 mg/g) and tablets (250 mg), Viracept.
- Stavudine suspension, Zerit
- Didanosine suspension, Videx

The report did not provided any additional details regarding the formulations.

Results

<u>Pharmacokinetic Data Availability and Nelfinavir Dosing</u>
Twelve patients in the BID group had 15 sets of evaluable PK results and four patients in the TID group had four sets of evaluable PK results. Three patients from the BID group had NFV PK determined on different dates. Eight subjects began the study on TID dosing; the other 12 began on BID dosing. At week 16, all subjects were receiving BID NFV.

NFV dosing during the course of the trial was as follows:

- Range of daily NFV doses: 260 to 1750 mg and was weight based (varied weekly)

- In most cases, the total daily dose was progressively increased in increments of 125 mg (a 250-mg NFV tablet split in half). One subject received a consistent total daily dose of NFV (1000 mg) for all weeks on study.
- Total daily dose was temporarily reduced for 6 subjects during the course of the study (n = 4 subjects for decreased body weight, n = 1 for drug supply problem, and n = 1 dose was reduced when the formulation was changed).

Nelfinavir Pharmacokinetics

The PK of NFV following BID and TID dosing are summarized in Table I.

Table I: Mean ± SD (range) nelfinavir pharmacokinetic measures following BID and TID dosing

	Twice Daily Dosing (n = 15)	Three Times Daily Dosing (n = 4)
Dose (mg/kg/dose)	66.14 ± 8.31 (54.7 – 82.8)	39.08 ± 3.70 (34.07 – 42.88)
C_{max} (μg/mL)	3.15 ± 1.64 (1.75 – 7.85)	2.27 ± 0.18 (2.08 – 2.47)
$AUC_{\tau\,(12hr\ or\ 8hr)}$ (μg hr/mL)	18.6 ± 9.60 (8.72 – 46.10)	11.27 ± 2.98 (9.43 – 15.69)
$AUC_{24\ hr}$ (μg hr/mL)	37.2 ± 19.2 (17.44 – 92.2)	33.81 ± 8.94 (28.29 – 47.07)
C_{min} (μgm/L)	0.58 ± 0.58 (0.05 – 1.97)	0.75 ± 0.57 (0.23 – 1.54)
T_{max}* (hr)	3.50 (0.50 – 4.00)	3.63 (3.50 – 5.50)
$T_{1/2}$ (hr)	3.41 ± 1.90 (1.31 – 7.14)	3.37 ± 1.22 (2.24 – 4.54)
CL/F (L/hr/kg)	4.23 ± 1.78	3.36 ± 0.94

*median value

PK Variability in PENTA 7

PK values for NFV in this study varied widely as reflected by the large CV following NFV BID administration: for AUC_{12} CV = 52%, and for C_{min} CV = 101 %. Interestingly, the degree of variability with the TID regimen appeared lower than with the BID regimen despite the smaller number of subjects in the TID regimen. Typically, variability is greater with a smaller number of subjects. The sources of the PK variability remain to be defined. The report suggests that the variability may be due to differences in gastrointestinal maturity, the types and amounts of food the patients were receiving, and the degree of adherence to the dosing regimen. This explanation for the variability is reasonable.

(b) (4)

(b) (4)

Impact of Formulation: Crushed Tablets vs. Powder

According to the report, only a few patients received the NFV powder because of the large volume needed for dosing. Although the number of patients receiving NFV powder was small, the PK of NFV appeared similar after powder or tablet administration (see figure above, right panel). Historical NFV data in adults and children indicate the powder and tablet are equally bioavailable. Overall, the data obtained in the current study and the previous studies suggest that the powder and tablet are interchangeable as dosage forms for pediatric patients. Therefore this Reviewer agrees with the sponsor's recommendation that crushed NFV tablets are an acceptable alternative to the use of powder in the pediatric population.

Exploratory Analyses: Relationship between AUC and Covariates

The applicant constructed correlation plots (not shown in this review) of NFV AUC_{12} versus age, weight, dose, sex, and race. There was no clear relationship between AUC of NFV and age (for children less than 1 year old), weight, dose (per kilogram), sex, race, dosing frequency, or formulation.

Applicant's Dosing Proposal

(b) (4)

Reviewer's Comment on Dosing Proposal

This Reviewer disagrees with the applicant's recommendation (b) (4)

(b) (4)

(b) (4)

Diarrhea is the main safety concern related to high NFV exposure. (b) (4)

However, because PK and safety data are not available at the higher doses, the label will not include a dose recommendation for this age group. The PENTA 7 study did not provide data for children between the ages of 9 months and 2 years. Therefore, information from other studies will be required to make dosing recommendations for children between 9 months and 2 years of age (1 to 2 years of age).

Safety and Efficacy Results (Highlights from Sponsor's Analyses)

The applicant indicates that because of the small number of subjects who underwent TID dosing, a statistical comparison was not performed between BID and TID data for safety or efficacy. This approach seems reasonable.

Sponsor's Safety Highlights

According to the report, no NFV-related SAEs were reported, and no NFV-related AE led to discontinuation. Of the 20 enrolled subjects, 18 (90%) experienced at least 1 post-baseline AE. The most frequent AE was neutropenia (10 subjects [50%]). The applicant concludes that the data from these 20 subjects suggest a regimen of d4T, ddI, and NFV (up to 150 mg/kg per day) was well tolerated in infants. Please refer to the Medical Review for interpretation of Safety Results.

(b) (4)

Study Appendix

Baseline Characteristics (N = 20)

Median HIV RNA level ($\log_{10}$ copies/mL)	5.51 (5.40 – 5.97)
Median CD4 percentage (interquartile range)	33 (25 – 46)
Cesarean Birth	11
Vaginal Delivery	9
Gestational age in weeks	36 (24 – 40)
Mean weight at birth (kg)	2.66 (0.65 – 3.62)

Study Title: A phase I study of the safety, tolerance, and pharmacokinetics of nelfinavir mesylate (NFV) administered with zidovudine and lamivudine in HIV-infected pregnant women and their infants. (PACTG-353)
Investigators: Multiple investigators
Sites: Multiple US sites
Study Period: not defined in report

Reviewer's Note
This review focuses on the pediatric information provided in the study report; pharmacokinetics in mothers will not be presented or discussed.

Study Design (Pharmacokinetic Methodology)
This was a pharmacokinetic (PK) sub-study in HIV infected pregnant women and their infants. Patients were enrolled in one of two cohorts.

- Cohort 1 mothers received 750 mg NFV orally 3 times daily (TID) and infants received 10 mg/kg NFV orally TID.
- Cohort 2 mothers received 1250 mg NFV orally twice daily (BID) and infants received 40 mg/kg orally BID.

In both cohorts, blood samples were collected from mothers once during pregnancy, between 16 and 36 weeks gestation, and at six weeks postpartum. Blood samples were collected from infants (see Blood Sampling for Infants) during the first week of life and again at six weeks of age.

Reviewer's Note
For the PK analysis it is assumed that the mother's nelfinavir (NFV) dosage did not affect the PK of their infants. This assumption is reasonable as NFV has a relatively short half-life (< 3 hours), and infant PK samples were not obtained until at least a week after birth.

Subject Demographic Characteristics
Selected subject demographic characteristics are as follows (Cohort 2):

- Race- 7 Hispanic subjects and 3 Black subjects
- Sex- 5 males and 5 females
- Weight- week 1 = 3.05 ± 0.37 kg and week 6 = 4.38 ± 0.61 kg
- BSA- week 1 = 0.19 ± 0.02 m^2 and week 6 = 0.25 ± 0.02 m^2
- Age- week 1 = 0.023 ± 0.013 years and week 6 = 0.108 ± 0.011 years

Blood Sampling for Infants
The 1-week and 6-week infant PK blood sampling schedules were as follows:

- Cohort 1 pre-dose and 1, 2, 4, 6, and 8 hours after the dose
- Cohort 2 pre-dose and 2, 6, 8, and 12 hours after the dose

Assay
All samples were assayed for concentration of NFV and the M8 metabolite by an HPLC method with UV detection. The method was linear for both analytes over the range of 0.07 to 9.0 μg/mL Inter-assay bias and precision were acceptable.

Pharmacokinetic Analyses
The following NFV pharmacokinetic measures were estimated using non-compartmental methods: AUC_τ (τ = 8 or 12 hours), C_{max}, C_{min}, T_{max} and CL/F. Week 1 PK measures were compared to Week 6 PK measures.

Results and Discussion

Pharmacokinetic measures for 1-week and 6-week old infants are summarized in Table I. In the 40 mg/kg BID cohort, the actual doses received varied (29 ± 12 mg/kg BID at week 1 and 37 ± 7 mg/kg BID at week 6).

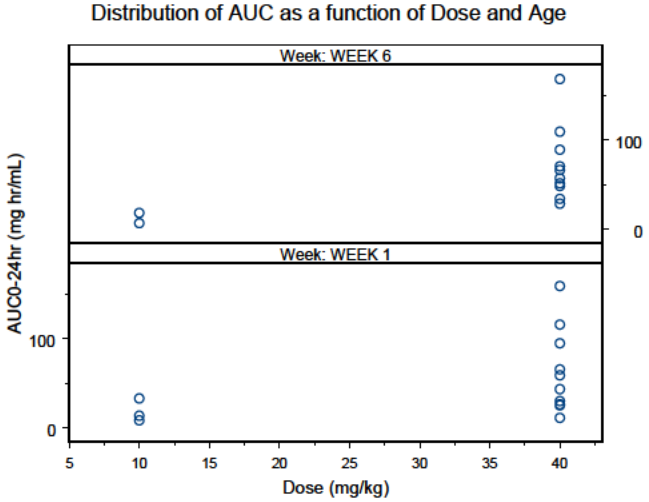
Table I: Mean ± SD or Median [range] nelfinavir pharmacokinetic measures in 1-week and 6-week old infants

		Mean ± SD Nelfinavir Pharmacokinetic Measure				
	N	$AUC_{0\text{-}24\ hr}$	C_{max} (µg/mL)	C_{min}(µg/mL)	CL/F (L/hr/kg)	$T_{1/2}$* (hr)
Week	40 mg/kg dose twice daily (mean ± SD)					
1	10	44.07 ± 27.41	2.38 ± 1.22	1.07 ± 0.92	2.36 ± 1.20	13.32 ± 11.02
6	10	45.77 ± 32.05	3.00 ± 2.09	0.56 ± 0.64	3.22 ± 3.13	5.24 ± 5.57
		Median [range]Nelfinavir Pharmacokinetic Measure				
	N	$AUC_{0\text{-}8\ hr}$	C_{max} (µg/mL)	$C_{trough,\ AM}$ (µg/mL)	$C_{trough,\ PM}$ (µg/mL)	T_{max}^
	10 mg/kg three times daily (median and [range])					
1	7	8.4 [3.5-15.7]	1.71 [0.8-3.4]	0.49 [bql-2.34]	ND	4 [4-8]
6	5	6.4 [6.5-9.3]	0.79 [0.44-1.53]	0.20 [bql-0.44]	ND	4 [1-6]
	N	$AUC_{0\text{-}12\ hr}$	C_{max} (µg/mL)	$C_{trough,\ AM}$ (µg/mL	$C_{trough,\ PM}$ (µg/mL)	T_{max}^
	40 mg/kg twice daily (median and [range])					
1	10	19.2 [8.6-56.1]	2.37 [0.95-5.20]	0.89 [bql-3.74]	1.35 [0.33-4.31]	6 [2-8]
6	10	19.4 [3.6-52.9]	2.07 [0.64-6.51]	0.50 [bql-5.96]	1.09 [0.14-2.08]	6 [2-12]

bql- below limit of quantitation; ND- not determined; ^ median value[range]

* n = 9 for determination. For week 1, variability introduced mainly by four data points, where $t_{1/2}$ > 10 hr. Without those data values, mean ± SD = 4.63 ± 2.50.

The week-1 and week-6 infant PK measures are comparable, except AM trough, suggesting that infants from birth to 6 weeks of age can receive the same NFV dosage. As expected, the 10 mg/kg TID dosage produced considerably lower exposure, particularly $AUC_{0\text{-}24\ hr}$, than the 40 mg/kg BID dosage. (b) (4)



Role of Extrinsic Factors on Nelfinavir Exposure

Two factors that could impact NFV exposure are the effect of food and the impact of concomitant medications. The potential effect of concomitant medications (inducers or inhibitors of NFV metabolism) on NFV exposure appears to have been minimal as only 3TC and AZT were allowed. Neither AZT nor 3TC affect NFV metabolism. The effect of food was not evaluated in this study; however, infants of this age typically consume only formula. Because timing of feedings may be erratic, the feedings may contribute to the large variability (CV > 60 %) in NFV PK. In addition, the effect of infant formula on NFV absorption is not known.

(b) (4)

Conclusions

- The pharmacokinetics of nelfinavir in subjects one week of age are comparable to those of subjects six weeks of age.
- The 40 mg/kg BID nelfinavir dose in children ≤ 6 weeks of age achieves mean $AUC_{0\text{-}24\ hr}$ that is comparable to that achieved in adults receiving the standard Viracept regimens (750 mg TID or 1250 BID). However, the variability was high and it is difficult to predict whether most infants will achieve adequate NFV exposure.

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Robert Kumi
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