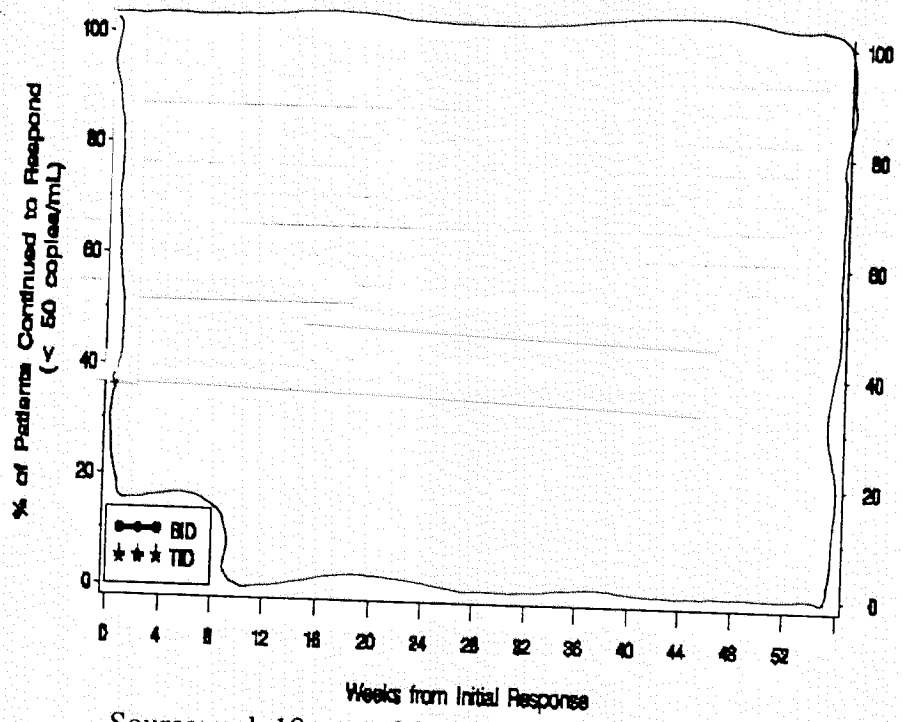
Figure 4: Duration of Suppression: UltraSenstive Assay



Source: vol. 18, page 96.

Based on the UltraSensitive PCR assay, the percent of patients who continued to respond as of Week 48 of treatment was higher for the BID regimen (48%) than for the TID regimen (36%). The lower limit of the 95% CI on the difference in these percentages (BID minus TID) was +2.0%.

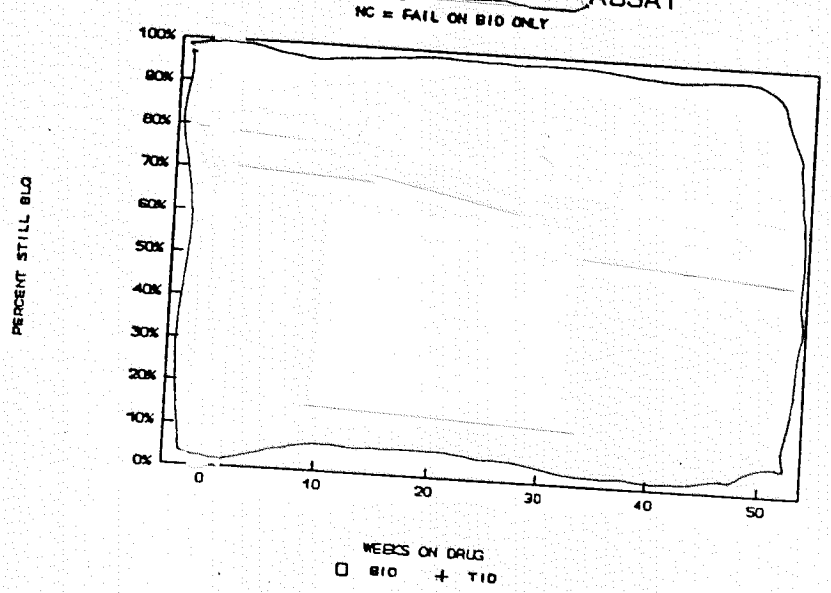
4.10 FDA's Analysis: Duration of Suppression

Only the results by the Standard PCR assay were reanalyzed.

Dr. Hammerstrom made the following adjustments for potential biases due to the open-label trial design:

Non-completers from the BID treatment group = failure
Non-completers from the TID treatment group = censored

Figure 5: TRIAL 542 [redacted] ASSAY



Based on the standard PCR assay, the percent of patients who continued to respond as of week 48 was similar for both the BID and TID regimens. The curves separate slightly after week 30 and converge again at week 48. The lower limit of the 95% CI on the differences (BID-TID) is about 15% (based on Fig. 4.3.ii in Dr. Hammerstrom's review.)

4.11 Applicant's Update of the 48 Week Analysis

In response to the Division's request, the applicant on 8/20/99 submitted an update of the 48 week analysis for study 542. In this dataset, all patients had received 24 weeks of treatment and nearly 75% of subjects received study treatment up to Week 48.

The raw dataset for this update has not been provided to FDA for review.

The results of the applicant's ITT/NC=F analyses are shown in Tables 7 and 8.

Table 7: Percent of Patients with HIV RNA <LOQ by Standard PCR Assay

Study Visit	Viracept 1250 mg BID n/N (%)	Viracept 750 mg TID n/N(%)	BID-TID(95% CI)
Week 4	83/336(24.7%)	44/206(21.4%)	3.3 (-3.9%, 10.6%)
Week 8	211/336(62.8%)	111/206(21.4%	8.9 (0.4%, 17.5%)
Week 12	250/329(76%)	143/202(70.8%)	5.2 (-2.6%, 13%)
Week 16	271/332(81.6%)	164/202(81.2%)	0.4 (-6.4%, 7.3%)
Week 24	257/333(77.2%)	164/204(80.4%)	-3.2 (-10.3%, 3.9%)
Week 32	246/335(73.4%)	160/204(78.4%)	-5.0 (-12.4%, 2.4%)
Week 40	223/321(69.5%)	143/194(73.7%)	-4.2 (-12.2%,3.7%)
Week 48	198/298(66.4%)	111/164(67.6%)	-1.2 (-10.2%, 7.7%)

Table 8: Percent of Patients with HIV RNA <LOQ by the UltraSensitive PCR Assay

Study Visit	Viracept 1250 mg BID n/N (%)	Viracept 750 mg TID n/N(%)	BID-TID(95% CI)
Week 4	6/336(1.8%)	3/206(1.5%)	0.3 (-1.8%, 2.5%)
Week 8	40/336(11.9%)	21/206(10.2%)	1.7 (-3.7%, 7.1%)
Week 12	84/332(25.3%)	56/205(27.3%)	-2.0 (-9.9%, 5.7%)
Week 16	162/336 (48.2%)	86/205(42%)	6.3 (-2.3%, 14.9%)
Week 24	207/333(62.2%)	125/204(61.3%)	0.9 (-7.6%, 9.4%)
Week 32	202/336(60%)	136/205(66.3%)	-6.2 (-14.5%, 2.1%)
Week 40	179/323(55.4%)	114/194(58.8%)	-3.3 (-12.1%, 5.5%)
Week 48	169/297 (56.9%)	92/165(55.8%)	1.1 (-8.3%, 10.6%)

Based on the Standard PCR assay, 77% of patients who received the BID regimen and 80% of patients who received the TID regimen had plasma HIV RNA levels below 400 copies/ml at Week 24. This level of suppression was present at Week 48 for 66% and 68% of patients in the BID and TID regimens, respectively. The lower limits of the 95% CI on the difference in percent of patients with plasma HIV RNA levels below LOQ between the 2 dose regimens (BID minus TID) were **–10.3**% and –10.2% at Weeks 24 and 48 respectively.

Based on the UltraSensitive assay, 62% of patients who received the BID regimen and 61% of patients who received the TID regimen had plasma HIV RNA levels below 50 copies/ml at Week 24. This level of suppression was present at Week 48 for 57% and 56% of patients in the BID and TID regimens, respectively. The lower limits of the 95% CI on the difference in percent of patients with plasma HIV RNA levels below LOQ between the 2 dose regimens (BID minus TID) were **–7.6**% and –8.3% at Weeks 24 and 48 respectively.

Results of the updated analyses showed a consistent trend of percentages of subjects with <LOQ of HIV RNA with that of the interim analysis for which an early data cutoff date was used. For an easy comparison, results of both sets of analyses are summarized in the table below.

Table 9: Summary of Percentages of Subjects with <LOQ HIV RNA

	1/11/99 Interim Report			8/20/99 Update Report		
	BID	TID	95% CI Lower bound	BID	TID	95% CI Lower bound
Standard PCR Assay						
Week 24	75%	77.8%	-12.3%	77.2%	80.4%	-10.3%
Week 48	64.2%	64%	-12.5%	66.4%	67.6%	-10.2%
UltraSensitive PCR Assay						
Week 24	60.2%	54.5%	-5.7%	62.2%	61.3%	-7.6%
Week 48	54.4%	50.7%	-9.5%	56.9%	55.8%	-8.3%

The results indicate that, with the updated analyses, the lower bounds of the 95% confidence intervals are closer to zero compared to the original interim report.

4.12 CD4 Lymphotcyte Count

The following Table and Figure present data for the mean change from baseline in absolute CD4 lymphocyte counts for patients treated with Viracept BID and TID dosing regimens.

Table 10: Mean Change from Baseline in CD4 Counts (cells/mm3)

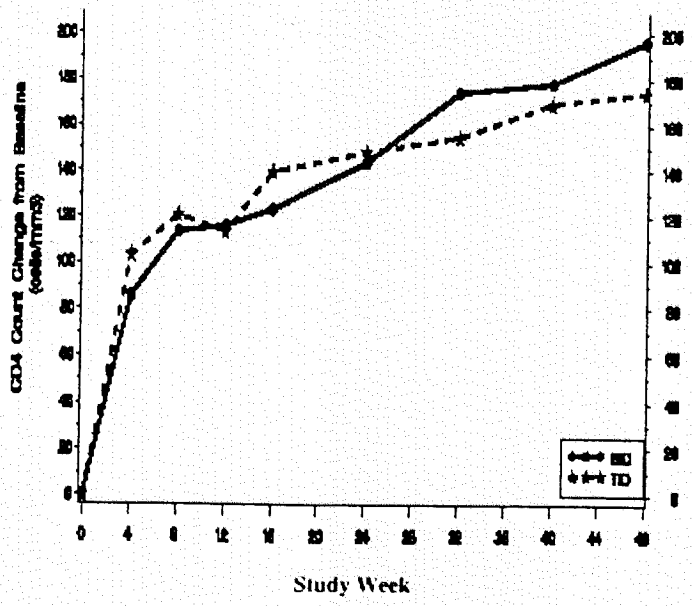
Study Visit	VIRACEPT 1250 mg BID* N=291	VIRACEPT 750 mg TID N=156
Week 4	85.5 (n=278)	103.1 (n=148)
Week 8	113.4 (n=258)	120.4 (n=136)
Week 12	115.8 (n=252)	113.3 (n=118)
Week 16	122.9 (n=235)	139.1 (n=109)
Week 24	143.5 (n=216)	147.8 (n=91)
Week 32	174.2 (n=181)	154.4 (n=63)
Week 40	178.2 (n=170)	169.5 (n=62)
Week 48	196.6 (n=165)	174.1 (n=56)
LOCF	161.8 (n=288)	147.6 (n=155)

Abstracted from Statistical Tables A.24 and Data Listing A.11.

* The majority of patients were receiving 1250 mg BID by Week 24 and all were receiving 1250 mg BID before Week 40.

LOCF=Last Observation Carried Forward.

Figure 6: Mean Change from Baseline in CD4 Counts



At Week 24, mean CD4 cells increases from baseline were 144 cells/mm3 and 148 cells/mm3 in patients receiving Viracept BID and TID regimens, respectively. At Week 48, mean increases of 197 cells/mm3 and 174 cells/mm3 for the BID and TID regimens, respectively, were observed.

4.13Safety Results

Four hundred fifty-five (455) patients who had received at least 1 dose of Viracept were included in safety analyses (296 received Viracept BID treatment and 159 received TID treatment).

4.13.1Extent of Exposure

The extent of exposure to Viracept was comparable between the 2 treatment groups as shown in Table 11.

Table 11: Extent of Exposure

Days on Treatment	Viracept BID* (n=296)	Viracept TID (n=159)
Mean (SD)	273(128)	222(130)
Median	354	205
Range	3-379	1-379

*The majority of patients were receiving 1250 mg BID by Week 24 and all were receiving 1250 mg BID before Week 40.
Source: Table 15, vol 18, page 105.

4.13.2 Drug-Related Treatment-Emergent Adverse Events

The causality of treatment-emergent events was determined by investigators. Three drug-related treatment-emergent adverse events of severity grade 2 or greater were reported by at least 2% of the patients in 1 or both of the 2 dose regimens: diarrhea, nausea and rash. The following Table depicts the results.

Table 12: Drug-Related Treatment-Emergent Adverse Events

Adverse Event	Viracept 1250 mg BID (n=296)		Viracept 750 mg TID (n=159)	
	N(%)*	Prevalence**	N(%)*	Prevalence**
Diarrhea	54(18)	63	23(15)	27
Nausea	4(1)	4	4(3)	4
Rash	6(2)	9	3(2)	4

*Percentage is based on treatment group n.
** Prevalence was defined as the total number of events.
Source: Table 16, Vol. 18, page 106

Diarrhea was the most frequently reported drug-related treatment-emergent adverse event and the incidence rates in the 2 dose regimens were similar. When the incidence rate of diarrhea was broken down according to originally assigned

BID treatment group, there was no discernable dose relationship. The incidence rates of diarrhea were 16%, 24%, and 17% for the 750 mg, 1000 mg and 1250 mg BID groups, respectively (Source: Table B30, vol. 20, page 299).

4.13.3 Treatment-emergent adverse events (regardless of severity or relationship to study drug)

Table 13: Adverse Events (Regardless Causality)

Adverse Event	Viracept 1250 mg BID (n=296)		Viracept 750 mg TID (n=159)	
	N(%)*	Prevalence**	N(%)*	Prevalence**
Diarrhea	204(69)	292	114(72%)	149
Rhinitis	69(23)	84	28(18)	36
Nausea	52(18)	67	18(11)	22

*Percentage is based on treatment group n.
**Prevalence was defined as the total number of events.
Source: Table A.29, vol 20, page 110.

Overall, equal percentages of patients in either dose regimen had treatment-emergent adverse events, regardless of severity or relationship to study drug. Diarrhea was the most frequently reported event, followed by rhinitis and nausea. The incidence rates of these events were similar between the 2 dose regimens.

4.13.4 Deaths and Other Serious Adverse Events (SAE)

Twenty-nine patients had treatment-emergent SAEs other than death (21 patients in the BID group; 8 in the TID group). Four (14%) of the 29 patients had SAEs that were considered related or possibly related to Viracept. These events included a combination of rash, fever, anorexia, nausea, somnolence; and vomiting (1 patient); diarrhea (1) anorexia (1); and obesity (1).

None of the 3 reported deaths was associated with Viracept. Causes of deaths were listed as cardiac arrest for patient 02-0202 (BID); cardiopulmonary arrest for patient 09-5962 (TID); and metastatic bronchial carcinoma for patient 04-0424 (BID).

4.13.5 Discontinuations Due to Adverse Events

A total of 23 patients discontinued the study because of treatment-emergent adverse events: 18 receiving Viracept BID treatment and 5 receiving Viracept TID treatment. The following table depicts discontinuations due to drug-related events.

Table 14: Discontinuations due to Adverse Events

Patient ID	Adverse Events
Viracept BID	
01-0015	Rash
02-0197	Fever, rash, somnolence, anemia
05-0541	Diarrhea
05-5546	Abdominal pain
21-7401	Mouth ulcer
23-2708	Asthenia, diarrhea, abdominal pain
Viracept TID	
09-5961	Leukopenia, hepatitis
18-7043	Fever, arthralgia, rash
28-3242	Obesity

Source: Table 18, vol 18, page 114

Other SAEs that led to discontinuation were carcinoma, dyspnea, fever, biliary pain, cerebrovascular accident and subdural hematoma, pancreatitis, and aspirative vomiting.

4.13.6 Treatment-Emergent HIV-Related Events

During the study, treatment-emergent HIV-related events were reported for 147(50%) of 296 patients who received Viracept BID treatment and 69(43%) of 159 patients who received the TID treatment. Events reported at least 5% incidence rate were similar in the 2 dose regimens as presented in the Table below:

Table 15: Treatment-Emergent HIV-Related Events

HIV-related events	Viracept 1250 mg BID (n=296)		Viracept 750 mg TID (n=159)	
	N(%)	Prevalence	N(%)	Prevalence
At least 1 HIV-related events	147(50)	364	69(43)	156
Viral infection	17(6)	20	8(5)	13
Diarrhea	17(6)	19	4(3)	5
Oral moniliasis	18(6)	21	4(3)	4
Lymphadenopathy	20(7)	20	7(4)	7
Folliculitis	14(5)	15	11(7)	11
Herpes simplex	24(8)	31	7(4)	10
Seborrhea	18(6)	20	11(7)	12

Source: Table 19, vol. 18, page 116

4.13.7 Lipodystrophy

While lipodystrophy was not prospectively identified in the study as a parameter to follow, a retrospective evaluation of the incidence of lipodystrophy in patients who had received at least 48 weeks of treatment was performed. The results were presented at the 4th International congress on Drug Therapy in HIV infection held in Glasgow, Scotland, 1998.

Data from 283 patients enrolled under the original protocol (Cohort 1) were included in this evaluation. A total of 228 of the 283 patients had received a minimum of 48 weeks of treatment; 3 of the 228 patients were identified as

having symptoms that were determined to be associated with lipodystropy (02-0125 (BID), 28-3331(BID), and 28-3242(TID). None of these patients developed signs or symptoms of lipodystrophy until after 40 weeks or more of treatment; however, subsequent to the week 40 visit, patient 28-3242 had a serious adverse event of central obesity with wasting of proximal muscle, which led to the patient's discontinuation from the study.

4.13.8 Abnormal Laboratory Tests

Data in this section are presented as marked changes defined as a shift in lab values from grade 0 at baseline to grade 3 or 4 during treatment, or a shift from grade 1 at baseline to grade 4 during treatment.

Marked changes in the results for hematology variables (lymphocytes, neutrophils, and platelets) occurred in <2% of the patients in either treatment regimen. Two patients had hematology-related adverse events that contributed to their discontinuation from the study. Patient 02-0197, who received Viracept BID, had a drug related adverse event of anemia and discontinued on Day 150. Patient 09-5961, who received Viracept TID, had an adverse event of leukopenia and interrupted treatment on Day 59; the patient resumed treatment 25 days later, then discontinued the study on Day 87 because of hepatitis.

The following marked hematology changes occurred in ≤ 2% of the patients in either regimen.

Table 16: Marked Hematology Changes

Variable	Viracept 1250 mg BID N(%), n=296	Viracept 750 mg TID N(%), n=159
Lymphocytes	2(1)	0
Neutrophils	6(2)	2(1)
Platelets	0	1(1)

Source: Table 20, vol 18, page 117

Overall, marked changes in chemistry values were more frequent among patients who had received Viracept BID treatment than among those who received Viracept TID treatment. A total of 15 patients had marked changes in chemistry variables. Of the 15 patients, 2 (01-0023 BID, 10-1142 TID) had marked changes that were attributed by the investigator as possibly related to Viracept therapy; both patients were co-infected with hepatitis C at baseline.

Table 17: Marked Chemistry Changes

Variable	Viracept 1250 mg BID N (%), n=296	Viracept 750 mg TID N(%), n=159
ALT	8(3)	0
AST	6(2)	1(1)
Alkaline phosphatase	1(0)	0
Serum amylase	3(1)	0
LDH	2(1)	0

Source: Table 21, vol. 18, page 118

In addition, patient 02-0187 (TID) had an elevation in glucose level to grade 3 from a grade 1 level at baseline. There were no triglyceride level measurements during the study.

4.14 Pharmacokinetic Results

For more details, please refer to Dr. Gillespie's Biopharmaceutics Review.

A total of 39 patients had available data for pharmacokinetic analysis in this study: 9 patients each in the 750 mg BID and 1000 BID groups, 10 patients in the 1250 mg BID group, and 11 patients in the 750 TID group. In this report, trough levels ($C\tau$) were measured as postdose trough concentrations, rather than predose.

The following table summarizes the pk parameters.

Table 18: Pharmacokinetic Parameters

Parameter	1250 mg BID Geometric mean (95% CI)	750 mg TID Geometric mean (95% CI)
AUC24 (mg*h/L)	51 (40-64)	40 (32-50)
C_{max} (mg/L)	3.92 (3.16-4.87)	2.62 (2.14-3.22)
$C\tau$ (mg/L)	0.56 (0.38-0.83)	0.84 (0.58-1.22)

Source:Table 23, vol 10, page 120

Summary of Dr. Gillespie's comments: The pharmacokinetics of nefinavir as parent compound and its active metabolite AG1402 were extensively studied. The AUC and Cmax after BID dosing at any of three dose levels exceeded that observed after administering 750 mg TID, whereas the trough levels ($C\tau$) were lower after administration of all of the BID regimens compared to TID dosing. Dr. Gillespie therefore recommended that the safety of higher peak and reduced trough concentrations of nelfinavir and AG1402 following BID dosing should be carefully evaluated from both clinical and microbiological aspects.

The following comments are to address Dr. Gillespie's concerns:

Clinical comment: As summarized previously under Section 4.12 of this review, the adverse event profiles of Viracept for patients receiving a BID or TID regimen were comparable. Diarrhea was the most frequently reported drug-related treatment-emergent adverse event and the incidence rates were similar in the 2 treatment groups. When the incidence rate of diarrhea was broken down according to originally assigned BID treatment groups, there was no discernable dose relationship. It does not appear that

higher peak levels of nefinavir after the BID dosing resulted in an increase in the incidence rate of diarrhea or any other adverse events.

Microbiology comment: There was no phenotypic nelfinavir susceptibility analysis performed on HIV-1 isolates obtained from plasma during the study. Therefore, one can not determine whether a correlation would exist between trough concentrations of nelfinavir (and AG1402) and phenotypic susceptibility of the HIV isolates to nelfinavir *in vitro*.

5. Reviewer's Overall Assessment and Conclusions

Study 542 is a randomized, open-label study designed to evaluate the potential benefits of administering Viracept on a BID dosing regimen compared to the standard TID regimen, each in combination with d4T and 3TC. In this interim report, when a 7/18/99 database cutfoff date was used, efficacy results from 447 patients show that the proportion of patients reaching and maintaining undetectable HIV RNA levels were comparable between the Viracept BID and TID regimens. The lower limit of the 95% confidence interval on the difference between the 2 regimens (BID minus TID) at week 48 (–12.5%) provides reasonable evidence for the statistical equivalence of the 2 regimens. This conclusion was further confirmed by an updated analysis using a later data cutoff date when a large proportion of subjects had completed 48 weeks of treatment. In this update report, the lower limit of the 95% confidence interval appears somewhat closer to zero than that reported in the interim report.

In addition to the comparable response determined by the HIV RNA levels between the two regimens, changes in CD4+ lymphocyte counts occurring in response to treatment were also comparable between the BID and TID dosing regimens.

For this equivalence trial, the FDA statistical reviewer made several comments about the methodologies employed by the applicant. Among them, two issues were of particular concern. (1) As of the 7/18/99 data cutoff, 11% and 16% of patients in the BID and TID groups, respectively, were administratively censored and counted as failures in the applicant's analyses since these patients had not been on treatment long enough to reach undetectable plasma HIV RNA levels. (2) Because this is an open-label study, a potential bias might exist in favor of the BID treatment. Because of these and other concerns, the FDA statistical reviewer felt that further adjustments to the applicant's analyses were needed. The results of the FDA's analyses, which were based on a relatively conservative approach, showed that the percentages of patients achieving HIV RNA levels of <LOQ at weeks 24 and 48 and the durability of HIV RNA suppression remained numerically and graphically comparable between the BID and TID dosing regimens. As Dr. Hammerstrom stated, the 95% confidence intervals on the difference of the primary efficacy measurement between the 2 regimens were not as narrow as that reported by the applicant (lower limits of the 95% CI: -14% to –

19%), suggesting that there existed a level of uncertainty about the conclusion. However, from a clinical perspective, the conclusion of the equivalence of the 2 regimens is deemed reasonable and can be reassured by the following:

1) This degree of uncertainty could be in part due to the extent of missing values as reflected in the interim report. It seems reasonable to expect that this degree of uncertainty would decrease as the study proceeds to completion.
2) Unlike the TID regimen, some subjects assigned to the BID regimen received a suboptimal dose of Viracept (<1250 mg) for varying lengths of time during the early phase of the study. Despite the inclusion of suboptimal treatments for the BID regimen, the numerically comparable results in plasma HIV RNA levels between the 2 regimens further reassure the conclusion of the equivalence.

The combination of 1250 mg BID or 750 mg TID Viracept with d4T and 3TC was well tolerated. Although higher C_{max} values were seen with 1250 BID compared to 750 TID Viracept, the adverse event profile and incidence rate for patients in this study were similar for each regimen. As expected, the most frequently reported treatment-emergent adverse event of moderate or greater intensity was diarrhea which was reported by 18% or the patients who received the Viracept BID regimen and 14% of patients who received the TID regimen.

6 Labeling Review

The original proposed labeling changes for Viracept underwent many revisions including organization and data presentation. The applicant has accepted and incorporated FDA's recommendations in the final version of the package insert.

7 Regulatory Action

The dosing regimen of Viracept 1250 mg BID in combination with other antiretroviral therapies is approvable as an alternate dosing regimen for the standard dose of 750 mg TID.

8 Additional Requests:

- Upon completion of the ongoing study 542, the applicant should submit a final report with full analyses of efficacy and safety to FDA for review.
- It is recommended that the applicant evaluate the pharmacokinetic parameters of the BID dosing regimen with the oral powder formulation of Viracept in children.

/S/

Teresa C. Wu, M.D., Ph.D.
Medical Officer

Concurrences:

Div Dir/Jolson /S/ 12/6/99
TL/Murray /S/ 12-3-99

CC:
Orig NDA
MO/WuT
Bioph/Reynold
Stat/Hammerstrom
PM/Lynche

Group Leader's Memorandum
Jeffrey S. Murray M.D., M.P.H.
Medical Officer, Division of Antiviral Drug Products
Nov. 19, 1999

NDA 20-778, 20-779, SE2
VIRACEPT (nelfinavir mesylate)

I concur with Dr. Teresa Wu's detailed review of this efficacy supplement. Agouron submitted this supplement in support of an alternate-dosing regimen for VIRACEPT. This efficacy supplement was based on one, ongoing, randomized, controlled, open-label study (study 542) in which VIRACEPT 1250 mg BID was compared to VIRACEPT 750 mg TID. For this supplement, all patients had received treatment for at least 24 weeks and the majority of patients had received 48 weeks of treatment. The treatment response, as evaluated by calculating the proportion of patients with HIV RNA levels below 400 copies/mL [redacted] and below 50 copies/mL [redacted] ultrasensitive), was clearly similar at both 24 and 48 weeks. The lower confidence bound for the difference in treatment response for the BID regimen compared to the TID regimen was generally in the range of –7% to –12%, depending on the assay, time point or method for handling missing data. Although this study was subject to potential bias resulting from an open-label design, there were no substantial differences between treatment arms with respect to treatment discontinuations or missing data; therefore, biases relating to knowledge of treatment regimen are of less concern. In addition, Dr. Hammerstrom's sensitivity analyses evaluating the effects of treatment discontinuations and missing data showed that the study results were robust.

As indicated in Dr. Wu's review, this study originally had four treatment arms, including three different BID dosing regimens (750, 1000, and 1250 mg BID) and the 750 mg TID regimen. A protocol amendment required that all patients on the 750 mg BID and 1000 mg BID regimens switch to the 1250 mg BID regimen (highest daily dose) in response to results from study 511 which showed that 750 mg TID was superior to 500 mg TID. Thus many patients in the 1250 mg BID arm had actually received lower daily doses for several months. In this respect, the study was actually biased against the 1250 mg BID regimen. This adds further reassurance that the 1250 mg BID regimen should produce treatment responses that are comparable to the currently approved regimen.

The safety profiles of the two regimens were similar, with only a slightly greater frequency of diarrhea reported among patients receiving the BID regimen vs. the TID regimen. Also a slightly greater percentage of patients receiving BID VIRACEPT had marked transaminase elevations; however, the incidence in both groups was no more than 3%.

Overall, VIRACEPT 1250 mg BID appeared equivalently effective and safe as the approved TID regimen, with the additional benefit of less frequent dosing. The sponsor states that fewer doses were missed on the BID treatment arm in study 542. BID dosing may help with patient adherence in the treatment of a disease that has become increasingly complex.

VIRACEPT 1250 mg should be approved with the labeling changes negotiated by DAVDP and Agrouron. Agouron has agreed to submit the final study 542 report after all patients have received 48 weeks of dosing. In addition they have agreed to study BID dosing of VIRACEPT in pediatric patients.

/S/

Jeffrey S. Murray, M.D., M.P.H.
Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL