CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020779, S022

MICROBIOLOGY REVIEW(S)

the estimates will decrease as the study proceeds to completion. This does not guarantee that the lower confidence bound will be closer to zero once the study is completed.

Trial 511 showed that Viracept at 750 mg TID plus two NRTI's (3TC + AZT) was, with high confidence, 30-40% better than placebo plus the same two NRTI's. This trial shows that Viracept at 1250 mg BID plus two NRTI's (3TC + d4T) was, with high confidence, no more than 14-19% worse than Viracept at 750 mg TID plus the same two NRTI's. It appears to be a reasonable inference that Viracept at 1250 mg BID would have achieved a higher percent of BLQ subjects than a placebo would have in trial 542. The 1250 mg BID dose appears to have demonstrable efficacy but it is uncertain whether it is better than, comparable to, or inferior to, the 750 mg TID dose.

/S/ (12-9-1999)

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

/S/ (12-9-1999)

Concur: Dr. Aras

cc:
Archival NDA #20-799
HFD-530
HFD-530/Dr. Jolson
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APPEARS THIS WAY
ON ORIGINAL

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA 20-778 SE2-011
NDA 20-779 SE2-022

Reviewer: Lauren C. Iacono-Connors

Date Submitted: 01-26-99
Date assigned: 02-02-99

Date received: 01-28-99
Date reviewed: 08-31-99

Sponsor: Agouron Pharmaceuticals, Inc.
10350 North Torrey Pines Road
La Jolla, CA 92037

Proprietary Name(s): Viracept™
Nonproprietary: Nelfinavir Mesylate
Chemical Name: [3S-[2(2S*,3S*),3α,4aβ-,8aβ-]]-N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3[(3-hydroxy-2-methylbenzoyl) amino]-4-(phenylthio)butyl]-3-isoquinolinecarboxamide monomethanesulfonate (salt).

Molecular Formula: $C_{32}H_{45}N_3O_4S \cdot CH_4O_3S$ **Molecular Weight**: 663.90 (567.79 as free base)

Structural formula: N/A

Indication: Treatment of HIV infection

Dosage Form/route of administration: Tablet and Powder/Oral

Drug Category: HIV Protease Inhibitor

Supporting Documents: IND

Background/Summary

The sponsor has submitted two Supplemental NDAs (SNDA) for VIRACEPT (Tablets and Oral Powder) to support the use of BID dosing instead of the currently approved TID dosing regimen. All supportive technical information is contained in SNDA 20-779 (SE8 022) but is also intended to support SNDA 20-778 (SCR 011).

The sponsor proposes that data they have collected to date, "provides evidence that genotypic changes correlate strongly with phenotypic response to antiretroviral therapy, and demonstrate the benefit of VIRACEPT therapy in patients who have previously failed other protease inhibitors." There are four study reports presented in this supplement that are intended to support this conclusion

four of the Phase IV commitments for Viracept NDA 20-779. As a result of these studies the sponsor has proposed significant changes in the current package insert regarding statements on drug resistance. The study reports are as follows:

1. #AG1343-VI-001: Susceptibility of nevirapine, AZT, or 3TC resistant HIV-1 isolates to nelfinavir. Intended to meet phase IV commitment number 3a.
2. #AG1343-VI-002: Correlation between HIV genotypic resistance and clinical response in patients receiving nelfinavir monotherapy or nelfinavir in combination with 3TC and AZT. Intended to meet phase IV commitment 3d.
3. #AG1343-VI-003: Virologic response to a ritonavir/saquinavir-containing regimen in patients who had previously failed nelfinavir-containing regimens. Intended to meet phase IV commitment 3cii.
4. #AG1343-VI-004: Correlation of virologic response with genotype of plasma HIV-1 variants in patients treated with nelfinavir in the U.S. expanded access program. Intended to meet phase IV commitment 3bi.

Research Report Number AG1343-VI-001: ***Susceptibility of nevirapine, AZT, or 3TC resistant HIV-1 isolates to nelfinavir.***

The purpose of this study was to meet phase IV commitment number 3a, which requested that the sponsor conduct a more thorough analysis of nelfinavir sensitivity to reverse transcriptase inhibitor (RTI)–resistant HIV-1 clinical isolates. Previously the sponsor provided data that demonstrated that a zidovudine-resistant clinical isolate (HIV1-G910-6) retained sensitivity to nelfinavir *in vitro*. Since nelfinavir was to be approved for use in combination with or subsequent to therapy with ZDV, or other RTIs, or selected non-nucleoside (NN) RTIs the sponsor was asked to conduct a more thorough analysis of RTI-resistant HIV-1 clinical isolates for susceptibility to nelfinavir *in vitro*.

The objective of this study was to examine the susceptibility of nucleoside analogue RTI- or NNRTI-resistant HIV-1 isolates to nelfinavir *in vitro*. Four patient's matched-pair clinical isolates, obtained from plasma at two different time points during the course of therapy, were evaluated. For each matched-pair, one isolate remained "susceptible" to the test drugs (ZDV, 3TC, nevirapine) and the other had acquired a phenotypic decrease in susceptibility to one of the test drugs, as measured *in vitro*. The results of this analysis are presented in enclosure 1. Virus isolation and phenotypic analysis of the CALI, JZY, and MDS HIV-1 clinical isolates were conducted in the laboratory of Victoria Johnson (University of Alabama, Birmingham) using methods previously described in Study Report PH-1003-096.A and the ACTG Virology Manual (September 1994). Virus isolation and phenotypic analysis of the MSG HIV-1 clinical isolate were performed using the Antivirogram method (Virco, N.V., Belgium). The data show that the clinical isolates that harbored a measurable shift in phenotypic susceptibility to either ZDV, 3TC, or nevirapine retained susceptibility to nelfinavir *in vitro*.

To date the sponsor has provided phenotypic nelfinavir susceptibility *in vitro* data on a total of 6 clinical isolates, where each isolate had a measurable decrease in susceptibility to an RTI. Two isolates were "resistant" to ZDV, two to nevirapine, and two to 3TC. In all cases these isolates remained sensitive to nelfinavir *in vitro*.

Report Number AG1343-VI-002: ***Correlation between HIV genotypic resistance and clinical response in patients receiving nelfinavir monotherapy or nelfinavir in combination with 3TC and AZT.***

The purpose of this study was to meet phase IV commitment number 3d, which requested that additional analyses of the relationship between the D30N mutation in the viral protease and clinical resistance to VIRACEPT be conducted. The sponsor has evaluated the relationship between treatment associated mutations in viral isolates and treatment response in two different clinical studies; Protocol AG1343-505 and Protocol AG1343-511. It should be noted that the method used in these studies to determine the reverse transcriptase and/or protease nucleotide sequences of viral isolates is investigational and should therefore be viewed with discretion.

In study AG1343-505 thirty two patients were enrolled to receive 750 mg VIRCEPT TID for 12 to 16 weeks. Subjects enrolled in study AG1343-505 had less than one month of prior antiretroviral therapy. The sponsor had previously collected information regarding the frequency of treatment associated mutations in the protease gene of the viral isolates from study participants at certain times during treatment. Here, the sponsor has submitted data that evaluate the relationship between protease-specific genotypic changes in patient viral isolates and clinical response to treatment; the HIV RNA plasma levels at specified time points during treatment. After 12-16 weeks of nelfinavir monotherapy (AG1343-505) viral protease genes were attempted to be amplified for sequencing from all 32 subjects. Of those 32 subjects 28 had nucleic acid material that was recovered and adequate for sequence analysis (enclosure 2). The data show that 18/28 (64%) isolates had the D30N mutation in the viral protease gene. In addition a number of other treatment associated mutations were observed in the viral protease including positions 46, 88 and 90, however the sponsor is focusing simply on the D30N mutation. The sponsor assumes that the 4 nucleic acid negative specimens do not harbor nelfinavir-specific protease gene mutations. It is not logical to conclude that these PCR-negative specimens contain wild-type virus. In addition, the data contained in appendix 1 of report number AG1343-VI-002 show that two of the four patients had detectable HIV RNA plasma levels using an investigational signal amplification method at the time of the PCR-sequencing attempt, therefore, it is not clear why the sponsor wishes to assume that the nucleic acid samples are of a wild-type genotype. These data show that 64% of evaluable patients (n=28) receiving nelfinavir monotherapy for 12 to 16 weeks harbored the predominant nelfinavir treatment associated mutation in the viral protease gene; D30N.

The relationship between the prevalence of the D30N mutation at 12-16 weeks in the population described above and the clinical response was evaluated. The sponsor statistically analyzed the relationship between the acquisition of the D30N mutation with the following clinical parameters; HIV RNA levels at baseline, CD4 cell counts at baseline, HIV RNA levels on treatment, and CD4 cell counts on treatment. According to the sponsor the following conclusions could be drawn from their analysis: baseline HIV RNA was significantly higher in the group that acquired the D30N mutation than the group that did not, baseline CD4 cell counts were not significantly different between the two groups, antiviral response (defined as the mean maximum reductions in HIV-1 RNA and time required to achieve maximum HIV-1 RNA reduction) to treatment was not significantly different between the two groups (enclosure 3). However, the presence of virus containing the D30N mutation was associated

with a significantly greater loss in viral suppression when compared to those patients who did not contain the substitution at position 30.

These analyses were conducted with the inclusion of those 4 patients whose viral protease genes were not sequenced and therefore were scored as wild type virus. It is recommended to the medical reviewer that they along with the statistical reviewer re-analyze these data and in doing so omit the four patients from the analysis who did not have confirmed sequence on their viral isolates.

In study AG1343-511 twenty six randomly selected patients who were receiving nelfinavir 750mg TID in combination with 3TC and zidovudine were evaluated for the incidence at 48 weeks of treatment associated genotypic changes in the viral protease and reverse transcriptase genes; in particular the protease gene D30N mutation. Subjects enrolled in study AG1343-511 had no prior antiretroviral therapy. Further, the sponsor has submitted data that evaluates the relationship between protease/and or reverse transcriptase-specific genotypic changes in patient viral isolates and clinical response to treatment. After 48 weeks of nelfinavir therapy viral gene sequences were attempted to be amplified for sequencing from all 26 subjects. Of those 26 subjects 9 had nucleic acid material that was recovered and adequate for protease gene sequence analysis and 7 had nucleic acid material that was recovered and adequate for reverse transcriptase gene sequence analysis (enclosure 4). The remaining samples were PCR-negative for unknown reasons. Of the 9 samples that were evaluated for sequence changes in the viral protease gene 3/9 (33%) had the D30N mutation (enclosure 4). In addition a number of other treatment associated mutations were observed to include positions 46, and 88, however the sponsor is focusing simply on the D30N mutation (enclosure 4). Of the 7 samples that were evaluated for sequence changes in the viral reverse transcriptase gene 6/7 (86%) had a mutation at position 184 (enclosure 4). A number of other treatment associated mutations were observed to include positions 41 and 219, however the sponsor is focusing on the M184V mutation. Interestingly, all three D30N protease gene mutants also had at least the reverse transcriptase 184 mutation detected at the same time or prior to the detection of the D30N mutation. A total of 6/9 evaluable isolates had mutations in either the protease gene or the reverse transcriptase gene or both (enclosure 4).

The relationship between the presence of the protease gene and reverse transcriptase gene mutations in 48 week virus samples in the population described above (study AG1343-511) and the clinical response was evaluated. The sponsor statistically analyzed the relationship between the acquisition of protease gene and reverse transcriptase gene mutations (PR/RT+) with the following clinical parameters; HIV RNA levels at baseline, CD4 cell counts at baseline, HIV RNA levels on treatment, and CD4 cell counts on treatment. According to the sponsor the following conclusions could be drawn from their analysis: baseline HIV RNA was not significantly different in the group that acquired the mutations than the group that did not, baseline CD4 cell counts were not significantly different between the two groups, antiviral response (defined as the time required to achieve maximum HIV-1 RNA reduction) to treatment was not significantly different between the two groups (enclosure 5). However, the presence in patients of virus containing these mutations was associated with a significantly greater loss in viral suppression when compared to those patients who did not contain the mutations (enclosure 5).

These analyses were conducted with the inclusion of those 17 patients whose viral protease genes were not sequenced and therefore were scored as wild type virus (PR/RT-). It is recommended to the medical reviewer that they, along with the statistical reviewer, analyze these data and in doing so omit the 17 patients from the analysis who did not have confirmed sequence on their viral isolates.

Research Report Number AG1343-VI-003: ***Virologic response to a ritonavir/saquinavir-containing regimen in patients who had previously failed nelfinavir-containing regimens.***

The purpose of this study was to meet phase IV commitment number 3cii. The sponsor committed to following a cohort of patients from clinical trials for at least one additional year. During that follow-up period patients whose viral RNA is not controlled on VIRACEPT would be given the option to change to another protease inhibitor or to a combination of protease inhibitors. These patients would continue to be followed and samples would be collected for *in vitro* assessments of cross-resistance.

The objective of study AG1343-VI-003 was to evaluate the virologic response to a ritonavir/saquinavir containing regimen in patients who had previously failed a nelfinavir-containing regimen as defined by having a minimum of two consecutive plasma HIV-1 RNA levels of >5,000 copies/mL using and experimental signal amplification assay. Additionally, the sponsor evaluated the relationship between virologic response and baseline protease genotype (D30N and/or L90M) or prior reverse transcriptase therapy. It should be noted that the method used in these studies to determine the reverse transcriptase and/or protease nucleotide sequences of viral isolates is investigational and should therefore be viewed with discretion.

A total of 26 patients were initially enrolled into this substudy. Two patients withdrew from the study within the first four weeks of treatment due to gastrointestinal intolerance and were therefore, not included in the analysis. Twenty patients were from study AG1343-506 and had received nelfinavir 500 or 750 mg TID and d4T 40 mg BID. Patients who were enrolled in study AG1343-506 had prior reverse transcriptase experience (mean of 2.1 RTIs) but were protease inhibitor naïve. Four patients were from study AG1343-511 and had received nelfinavir 500 or 750 mg TID in combination with zidovudine and 3TC. Patients who were enrolled in study AG1343-511 were antiretroviral treatment naïve. The mean length of time on nelfinavir therapy for the 24 patients was 59.7 weeks (range 23.3 to 82.4 weeks) and the mean length of time with detectable HIV-1 RNA (based on the assay limit of >500 copies/mL) was 53.4 weeks (range 27.3 to 64.3 weeks). All patients enrolled in the substudy were heavily antiretroviral experienced with a mean of 2.9 (range 1 to 5) reverse transcriptase inhibitors including zidovudine, 3TC, ddC, ddI, and d4T. Substudy subjects were switched to a regimen of ritonavir 400 mg BID/saquinavir 400 mg BID, 3TC 150 mg BID, and d4T 40 mg BID. Subjects remained on therapy for a mean of 48 weeks (range 40 to 56 weeks). Plasma was collected at substudy baseline and at monthly intervals for HIV-1 RNA quantitation using an experimental signal amplification assay with an assay limit of 500 copies/mL. Genotypic analysis of HIV nucleic acid material at substudy baseline revealed that 18/24 (75%) subjects harbored virus containing the protease gene D30N mutation, but was known to be absent prior to nelfinavir therapy. Six of twenty-four (25%) subjects harbored virus containing the protease gene L90M mutation at substudy baseline.

Statistical analyses were used to evaluate whether a specific substudy baseline characteristic correlated with the observed treatment (ritonavir/saquinavir) response. Sixteen of twenty four (67%) subjects were classified as treatment responders; achievement of plasma HIV RNA levels below the assay limit for the last two measurements. Eight (8/24: 33%) subjects were classified as treatment failures for not achieving two consecutive HIV RNA measurements below the assay limit at the last two measurements. Plasma HIV-1 RNA levels at substudy baseline demonstrated a statistically significant higher viral load for those patients classified as treatment failures than those that were treatment responders. Protease gene genotype at substudy baseline, specifically the presence of absence of the D30N mutation, did not correlate with treatment outcome. The D30N mutation was present in 12/16 (75%) treatment responders and was present in 6/8 (75%) treatment failures. Likewise, the presence or absence of the protease gene mutation L90M did not correlate with outcome. In addition, the data showed that prior 3TC experience did not correlate treatment outcome.

The study suggests that some patients who have failed a nelfinavir-containing regimen can be switched to a ritonavir/saquinavir containing regimen and achieve a virologic response. In addition, the data suggest that the D30N or the L90M protease gene mutations at baseline are not predictive of a clinical response when the protease(s) in the current treatment regimen are combined ritonavir/saquinavir. The only correlate of treatment response appears to be viral load at baseline, however, it does not appear that CD4 cell counts were evaluated for their baseline correlation to treatment response.

Research Report Number AG1343-VI-004: ***Correlation of virologic response with genotype of plasma HIV-1 variants in patients treated with nelfinavir in the U.S. expanded access program.***

The purpose of this study was to meet phase IV commitment number 3bi. The sponsor agreed to increase their current efforts to obtain information on cross-resistance between nelfinavir and other protease inhibitors. Towards that end the sponsor initiated a substudy of the VIRACEPT expanded access program to obtain additional virologic information from patients who have failed other protease inhibitors. It should be noted that the method used in these studies to determine the reverse transcriptase and/or protease nucleotide sequences of viral isolates is investigational and should therefore be viewed with discretion. In addition, it is not clear exactly when "baseline" samples were taken for genotyping from participants of this study with respect to their previous treatment history. It is possible that a subject may have been off a previous therapy for an extended period of time prior to baseline genotyping for the nelfinavir expanded access program. Therefore, baseline genotyping results may under-represent the number of actual mutations harbored by a study participant.

A total of 80 patients were initially enrolled in the virologic substudy. These subjects had to have previously failed treatment with ritonavir, indinavir, or saquinavir. Failure was defined as having their HIV-1 RNA concentrations return to within 50% of the baseline value obtained prior to previous protease inhibitor therapy. In addition, CD4 cell counts had to be less than 100 cells/mm3. Nine subjects were excluded from the analysis because they did not satisfy certain entry criteria, and 6 others were excluded because they did not have HIV-1 RNA samples drawn between treatment weeks 0 to 6 or weeks 6 to 12. The remaining 65 subjects were given nelfinavir 750mg TID. Twenty four subjects (37%) initiated therapy with nelfinavir and either an additional new reverse transcriptase inhibitor(s) or

with a previously used antiretroviral added within the first 12 weeks of study. Plasma was collected at baseline and monthly thereafter for genotyping the protease gene of viral isolates and for determination of HIV-1 RNA levels and CD4 cell counts. HIV RNA levels were determined using an investigational signal amplification assay with a proposed limit of 500 copies/mL of plasma. The mean baseline HIV RNA level was 4.6 log10 and the CD4 cell count mean was 110 cell/mm3 (enclosure 6). Patients were heavily pretreated with antiretroviral agents; the mean number of previous protease inhibitors was 2 and the mean number of previous reverse transcriptase inhibitors was 4.4 (most frequently used were 3TC, zidovudine, d4T, and ddI).

Of the 65 patients followed in this substudy the sponsor identified 32/65 (49%) as non-responders; defined as those with a ≤0.5 log10 decrease in plasma HIV-1 RNA on at least two visits between weeks 0 to 6 and weeks 6 to 12 of therapy. The sponsor identified 33/65 (51%) subjects as responders defined as those patients with a >0.5 log10 reduction in plasma HIV-1 RNA or HIV-1 RNA below the assay limit at any one visit within the first 12 weeks of therapy. Of those 33 "responders" 14 were determined to have a sustained virologic response; defined as maintaining a ≥0.5 log10 reduction in plasma HIV-1 RNA or an HIV-1 RNA below the assay limit for the last two visits up to 24 weeks of therapy. Therefore, 14/65 subjects (22%) had a sustained virologic response in this study. The sponsor further categorized the remaining responders as "transient responders." These individuals were defined by not maintaining a ≥0.5 log10 drop in plasma HIV-1 RNA or HIV-1 RNA below the assay limit for the last two visits up to 24 weeks on therapy. Historically the division has classified virologic responders as those individuals who demonstrate a durable (sustained) response to therapy with respect to virologic measurements. Therefore, in this study, 14/65 (22%) of subjects virologically responded to therapy.

Statistical analyses were used to evaluate whether a specific baseline characteristic of study participants correlated with the observed virologic treatment response. Here the sponsor compared the baseline characteristics of the "responders" as defined above (33/65) to the "non-responders" as defined above (32/65). The data show that no statistically significant differences between the response groups for either the baseline HIV-1 RNA levels or CD4 cell counts were observed. Likewise, no statistically significant differences were observed between the response groups for the number of prior protease inhibitors used, and no significant differences were detected for the number or type of reverse transcriptase inhibitors used previously. The possible effects on response of the newly added therapy was unclear.

To determine whether pre-existing specific amino acid substitutions in the viral protease gene had an effect on subsequent treatment response DNA sequence analysis was conducted on the entire HIV protease gene from HIV RNA taken at baseline in a subset of study participants (n=28). The sponsor chose to focus only on specific changes at "critical" amino acid residue positions within the protease; 48, 82, 84 and 90. The results of these analyses are shown in enclosure 7. Briefly, a statistically significant relationship was observed between the number (0,1,2 or 3) of specific genotypic changes present at baseline and the virologic response. Sixteen of nineteen (84%) patients with none or one protease mutation were treatment responders whereas three of nine (33%) patients with two or more protease mutations were treatment responders (enclosure 7). The sponsor suggests that their preliminary results from this study indicate that in this group of pretreated patients, and in the absence of new

antiretroviral reverse transcriptase therapy, the number of specific baseline genotypic changes in the protease gene had a significant impact on the virologic response to nelfinavir.

PROPOSED LABEL INCLUDED IN NDAs #20-778 (SLR-011)/20-779 (SE8-022)
(Sponsor's proposed changes to currently approved labeling indicated)

DRAFT

Labeling

DRAFT

Labeling

PROPOSED MICROBIOLOGY LABEL: as of 31-AUG-99

It is recommended that the label be finalized during the review of SNDAs 20-778 (SE8-012) and 20-779 (SE7-026); the NDAs for traditional approval of nelfinavir.

Conclusions

With respect to microbiology phase IV commitment numbers 3a, 3d, 3cii, and 3bi (NDA 20-778/779) have been satisfied by study reports numbers AG1343-VI-001, AG1343-VI-002, AG1343-VI-003, and AG1343-VI-004. The sponsor has provided additional phenotypic nelfinavir susceptibility *in vitro* data, to date, on a total of 6 clinical isolates, where each isolate had a measurable decrease in susceptibility to an RTI (AG1343-VI-001). Two isolates were "resistant" to zidovudine, two to nevirapine, and two to 3TC. In all cases these isolates remained sensitive to nelfinavir *in vitro*.

The sponsor evaluated the relationship between treatment associated mutations in selected viral isolates and treatment response in two different clinical studies; Protocol AG1343-505 and Protocol AG1343-511. The data from these studies suggest that patients treated with nelfinavir containing regimens who developed nelfinavir-specific, or other treatment associated mutations, were more likely to loose viral suppression than those who did not develop mutations. In addition, in protocol AG1343-505 baseline HIV RNA levels were significantly higher in the group that acquired the D30N mutation. However, these analyses were conducted with the inclusion of patients whose viral protease genes were not sequenced and therefore were scored as wild type virus. It is recommended to the medical reviewer that they along with the statistical reviewer analyze these data and in doing so omit, or reassess how to score, the patients from the analysis who did not have confirmed sequence on their viral isolates.

In study AG1343-VI-003 the virologic response to a ritonavir/saquinavir containing regimen in patients who had previously failed a nelfinavir-containing regimen was evaluated. The results of this study suggest that some patients who have failed a nelfinavir-containing regimen can be switched to a ritonavir/saquinavir containing regimen and achieve a virologic response. In addition, the data suggest

that the D30N or the L90M protease gene mutations at baseline are not predictive of a clinical response when the protease(s) in the current treatment regimen are combined ritonavir/saquinavir.

The sponsor initiated a substudy of the VIRACEPT expanded access program to obtain additional information on cross-resistance between nelfinavir and other protease inhibitors. Patients who had previously failed non-nelfinavir, protease inhibitor therapy were treated with nelfinavir monotherapy or in combination with other antiretrovirals. Using the sponsor's criteria for defining treatment responders the results of this study suggest that 33/65 (51%) of subjects virologically responded to therapy. No statistically significant differences between the response groups for either the baseline HIV-1 RNA levels or CD4 cell counts were observed. Likewise, no statistically significant differences were observed between the response groups for the number of prior protease inhibitors used, and no significant differences were detected for the number or type of reverse transcriptase inhibitors used previously. Results from this study do suggest that for this group of pretreated patients, and in the absence of new antiretroviral reverse transcriptase therapy, the number of specific baseline genotypic changes in the protease gene had a significant impact on the virologic response to nelfinavir. However, it is not clear exactly when "baseline" samples were taken for genotyping from participants of this study with respect to their previous treatment history. It is possible that a subject may have been off a previous therapy for an extended period of time prior to baseline genotyping for the nelfinavir expanded access program. Therefore, baseline genotyping results may under-represent the number of actual mutations harbored by a study participant

RECOMMENDATIONS

/S/

Lauren C. Iacono-Connors, Ph.D.
Microbiology Team Leader

CONCURRENCES:

HFD-530/Div Dir /S/ 9/30/99

HFD-530/TLMicro

CC:

HFD-530/Original NDA 20-778/779
HFD-530/TLMicro/
HFD-530/CSO/S. Lynche

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Reference: NDA 20-778(SLR-001)/20-779(SE8-022): VIRACEPT
Microbiology Section

Table 1

Antiviral Activity of Nelfinavir Against NRTI and NNRTI Resistant HIV-1 Isolates

HIV-1 Isolate[a]	EC_{50} (μM) AZT	3TC	NVP	NFV	IDV
d-14 P1 d10	0.008	<0.04	0.027	<0.008	ND
wk12 P2 d8	0.001	<0.04	>10	<0.008	ND
v00 oc1 d7	0.111	<0.04	0.158	0.09	ND
v12 oc1 d12	0.005	4.3	0.043	0.026	ND
v00 P1 d10	1.787	0.029	ND	0.007	0.015
v12 P1 d10	1.000	23	ND	0.012	0.012
W642990	0.049	4.763	0.093	0.059	0.038
D385291	0.090	3.128	0.351	0.024	0.012

[a]Each virus pair represents virus obtained from plasma HIV-1 RNA at two different time points during the course of a patient's therapy. The [redacted] isolates were evaluated using the HIV Drug Susceptibility Assay described in the ACTG Virology Manual (September 1994) and the MSG isolates were evaluated using the [redacted] method.
(1). ND = Not Determined.

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Reference: NDA 20-778(SLR-001)/20-779(SE8-022): VIRACEPT

Table 1. Summary of nelfinavir-associated genotypic changes at 12 and 16 weeks: Protocol AG1343 -505[a].

Patient	Amino acid residue			
	D30	M46	N88	L90
12-2				
12-9				
18-2				
18-5				
18-1				
18-8				
18-10				
21-2				
23-1				
27-3				
27-4				
27-5				
27-2				
27-6				
27-12				
27-13				
27-15				
27-18				
28-1				
28-2				
28-4				
28-9				
35-2				
35-3				
35-6				
35-8				
35-14				
50-3				
50-5				
50-6				
50-9				
43-3				

[a] Sequence analysis was performed on entire HIV protease genes obtained from plasma samples derived from the entire group of 32 patients after 12 and 16 weeks of nelfinavir 750 mg TID monotherapy. Although entire HIV protease genes were sequenced, only substitutions at residues 30, 46, 88 and 90 are shown.

[b] Patients initially received placebo. After four weeks of treatment, patients were randomized to receive nelfinavir 750 mg TID.

[c] The L90M substitution was detected in two patients following nelfinavir monotherapy. Sequence analysis revealed the L90M substitution in one of these two patients (patient 27-12[illegible]) at baseline, prior to NFV monotherapy.

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Table 2

Plasma HIV-1 RNA and CD4 cell count at baseline and at 16 weeks: Protocol AG1343-505[a].

Time	Parameter	PR+ (n=18)	PR- (n=14) 10 10	p-value[b]
Base-line	Mean HIV RNA (log_{10} bDNA copies/ml)	5.1 (range: 4.3 to 6.1)	4.7 (range: 4.0 to 5.3)	0.03
	Mean CD4 count (cells/mm^3)	265 (range: 55 to 601)	299 (range: 121 to 521)	0.54
16 Weeks	Mean HIV RNA reduction (log_{10} bDNA copies/ml)	-0.5 (range: -1.8 to 0.12)	-0.9 (range: -2.2 to 0)	0.04
	Mean CD4 count increase (cells/mm^3)	97 (range: -14 to 320)	55 (range: -86 to 165)	0.12

[a] Appendix 3A.
[b] ANOVA

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Table 2. Summary of nelfinavir-, 3TC-, and AZT-associated genotypic changes at 48 weeks: Protocol AG1343-511[a].

	Amino Acid Residues						
	Protease				Reverse Transcriptase		
Patient	D30	M46	N88	L90	M41	M184	K219
3-5							
3-18							
4-6							
4-15							
13-5							
19.2-3							
21-1							
26-3							
26-6							
26-22							
27-3							
29-10							
33-24							
36-3							
39-2							
40-6							
41-17							
42-4							
44-12							
51-6							
10-4							
24-2							
41-13							
33-12							
51-1							
43-2							

[a] Sequence analysis was performed on HIV protease and reverse transcriptase genes obtained from plasma samples derived from 26 randomly selected patients receiving NFV 750 mg TID with 3TC and AZT. Although the entire HIV protease gene was sequenced, only substitutions at residues 30, 46, 88, and 90 are shown. Although the first 687 nucleotides (229 amino acid residues) of reverse transcriptase were sequenced, only substitutions at residues 41, 184, and 219 are shown.

Table 4

Plasma HIV-1 RNA and CD4 cell count at baseline and at 48 weeks: Protocol AG1343-511[a].

Time	Parameter	PR/RT+ (n=6)	PR/RT- (n=20)	p-value[b]
Base-line	Mean HIV RNA (log_{10} HIV RNA copies/ml)	5.3 (range: 4.6 to 5.9)	5.2 (range: 4.6 to 5.9)	0.44
	Mean CD4 count (cells/mm^3)	206 (range: 58 to 500)	309 (range: 10 to 662)	0.26
48 Weeks	Mean HIV RNA reduction (log_{10} HIV RNA copies/ml)	-1.7 (range: -2.4 to 1.1)	-2.6 (range: -3.3 to -2.0)	0.001
	Mean CD4 count increase (cells/mm^3)	175 (range: 161 to 196)	194 (range: -155 to 430)	0.77

[a] Appendix 3B.
[b] ANOVA

APPEARS THIS WAY
ON ORIGINAL

Table 3

AG1343-515 Virology Substudy: Mean (Range) Baseline Characteristics

	Responders (n=33)	Nonresponders (n=32)	p-value[a]
HIV RNA (log_{10} bDNA copies/ml)	4.5 (3.2 - 5.7)	4.7 (3.5 - 6.0)	0.242
CD4 count (cells/mm^3)	120 (10 - 480)	100 (10 - 270)	0.480
Weeks of follow up	25 (5 - 40)	24 (8 - 40)	0.801

[a]ANOVA

APPEARS THIS WAY
ON ORIGINAL