Poster #P9

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Improved Tolerability and Quality of Life in Subjects Receiving Lopinavir/Ritonavir

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BACKGROUND

Lopinavir (LPV) is an HIV protease inhibitor that is co-formulated with ritonavir (RTV), which acts as an inhibitor of cytochrome P450 CYP3A. When used in combination, there is a substantial increase in LPV exposure, even at low RTV doses. This pharmacokinetic interaction results in mean LPV pre-dose (trough) concentrations ≥75-fold above the protein binding-adjusted EC_{50} of wild-type HIV when dosed at 400/100 mg twice a day, providing a possible barrier to the emergence of viral resistance.[1] Lopinavir/ritonavir (LPV/r; Kaletra™) has demonstrated potent antiretroviral activity in treatment-naïve patients, single PI-experienced patients, and multiple PI-experienced patients, and has been generally well tolerated in these patient populations.[2-5]

A significant number of virologically stable, HIV-infected subjects experience mild-to-moderate side effects related to the non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) in their antiretroviral (ARV) regimen.[6] Despite the safety and antiretroviral activity demonstrated in previous LPV/r clinical trials, it is unclear whether substituting LPV/r for the NNRTI/PI suspected of causing side effects will alleviate the symptoms and improve quality of life (QOL), while maintaining virologic control.

METHODS

The M00-267 Study (PLATO: Performance of Lopinavir/Ritonavir as an Alternative Treatment Option) is a randomized, open-label, multi-country, multi-center study of 8 weeks duration in HIV-infected subjects. The objective of this study was to evaluate the effect of substituting LPV/r for the NNRTI/PI in the subject's antiretroviral regimen suspected of causing the side effect and the subsequent impact on QOL. Primary outcome measure was the Week 4 results of the validated AIDS Clinical Trials Group (ACTG) Symptoms Distress Module,[7] with two additional questions to evaluate symptoms of nephrolithiasis.[8] In addition, this study was designed to assess whether the side effects experienced while on NNRTI- or PI-based regimens could be improved, and if virologic control could be maintained, after substitution with LPV/r.

Figure 1. Global Enrollment

Key Entry Criteria

Subjects were eligible for participation in this study if they met the following criteria:

- Two consecutive HIV RNA values <400 copies/mL on current ARV regimen, with the most recent within past 3 months.
- Current ARV regimen consists of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus nelfinavir (NFV), indinavir (IDV), IDV/RTV, nevirapine (NVP) or efavirenz (EFV).
- Intolerant to current NNRTI/PI in their ARV regimen as evidenced by an ACTG-defined Grade 2 side effect ("Primary").

Study Design and Analysis

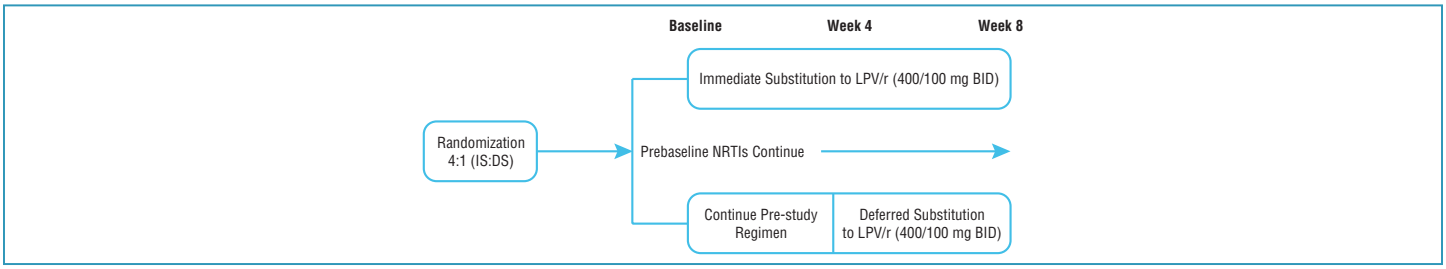
Subjects experiencing a Grade 2 NNRTI/PI – associated side effect were randomized (4:1) to Immediate Substitution at baseline, or Deferred Substitution at Week 4 of the NNRTI/PI with LPV/r. All subjects remained on their baseline NRTIs for the 8-week duration of the study, and all subjects received LPV/r from Week 4 to Week 8. The following QOL instruments were evaluated for this interim analysis:

- ACTG (Augmented) Symptoms Distress Module (ASDM) – measures the presence and bothersomeness of side effects commonly seen with HIV and ARV treatment, with higher scores indicating the presence of more symptoms and/or more distress related to the 22 symptoms.[7]
- Global Condition Improvement Questionnaire – measures the subject's overall tolerability to HIV treatment.
- Therapy Preference Questionnaire – measures the subject's overall therapy preference.

The (Augmented) Symptoms Distress Module was administered at each study visit, while the Global Condition Improvement Questionnaire and the Therapy Preference Questionnaire were administered only at Week 8. Side effects that were present at baseline or developed during the study were assessed at each study visit. Clinical laboratory parameters, including HIV RNA (Roche Amplicor Ultrasensitive 1.5), also were evaluated at each study visit using a central laboratory.

The PLATO database is open and subject to change. Results presented here represent data entered into the clinical database on or before 18 October 2002.

Figure 2. M00-267 Study Design



A total of 809 subjects have data available through 18 October 2002. 17 subjects have been excluded from efficacy analyses as they were not receiving the protocol-specified NNRTI/PI(s) plus 2 NRTIs at study enrollment. Instead these subjects were primarily receiving medication from 3 ARV drug classes.

RESULTS

Table 1. Summary of Demographic Characteristics

	Immediate Substitution	Deferred Substitution	Overall
N	653	156	809
Sex			
Male	521 (80%)	125 (80%)	646 (80%)
Female	131 (20%)	31 (20%)	162 (20%)
Not reported	1 (<1%)	0 (0%)	1 (<1%)
Race			
White	511 (78%)	120 (77%)	631 (78%)
Black	93 (14%)	26 (17%)	119 (15%)
Other	47 (7%)	10 (6%)	57 (7%)
Not reported	2 (<1%)	0 (0%)	2 (<1%)
Ethnicity			
Hispanic	172 (26%)	40 (26%)	212 (26%)
Age			
Mean	42.0	42.4	42.1
Minimum-Maximum	21-82	25-70	21-82

Table 2. Subject Disposition

	Immediate Substitution	Deferred Substitution	Overall
Subjects Enrolled	653	156	809
Discontinuation*	60 (9%)	16 (10%)	76 (9%)
Adverse events/HIV events	33 (5%)	4 (3%)	37 (5%)
Withdrawal of consent	14 (2%)	7 (4%)	21 (3%)
Lost to follow-up	5 (1%)	3 (2%)	8 (1%)
Other	15 (2%)	5 (3%)	20 (2%)

*Multiple reasons for discontinuation were reported.

Table 3. Summary of Pre-study NNRTI/PI Regimen†

	Immediate Substitution	Deferred Substitution	Overall
N	637	155	792
Nelfinavir	215 (34%)	64 (41%)	279 (35%)
Indinavir or Indinavir/Ritonavir	281 (44%)	56 (36%)	337 (43%)
Efavirenz	109 (17%)	21 (14%)	130 (16%)
Nevirapine	21 (3%)	10 (6%)	31 (4%)
Other	9 (1%)	2 (1%)	11 (1%)
Not reported	2 (<1%)	2 (1%)	4 (1%)

† For subjects included in efficacy analyses.

Plasma HIV RNA results determined at baseline and Week 4 are summarized in Tables 4a and 4b for the Immediate and Deferred Substitution arms, respectively. No difference in the proportion of subjects with HIV RNA <400 copies/mL was detected at baseline between the Immediate and Deferred Substitution arms (92% vs. 91%; p=0.716). However, a statistically significant difference was detected between the Immediate and Deferred Substitution arms at Week 4 (96% vs. 85%; p<0.001). At Week 8, after all subjects had substituted LPV/r for their NNRTI/PI, 96% of subjects had HIV RNA <400 copies/mL, with no difference between the Immediate and Deferred Substitution arms (97% vs. 95%; p=0.296).

Table 4a. HIV RNA (copies/mL) – Baseline vs. Week 4* (Immediate Substitution Arm)

	Week 4			Baseline
Baseline	<400	400-10,000	>10,000	Total (N)
<400	512	2	4	518
400-10,000	23	7	0	30
>10,000	7	3	4	14
Week 4 Total (N)	542	12	8	562

*For efficacy evaluable subjects with viral loads at both baseline and Week 4.

Increase Decrease

Table 4b. HIV RNA (copies/mL) – Baseline vs. Week 4* (Deferred Substitution Arm)

	Week 4			Baseline
Baseline	<400	400-10,000	>10,000	Total (N)
<400	104	6	4	114
400-10,000	2	6	0	8
>10,000	0	2	1	3
Week 4 Total (N)	106	14	5	125

*For efficacy evaluable subjects with viral loads at both baseline and Week 4.

Increase Decrease

RESULTS

Results from the (Augmented) Symptoms Distress Module are summarized in Figures 3 and 4. No difference was observed at baseline between the Immediate and Deferred Substitution arms with respect to the total ASDM score. At Week 4, a statistically significant improvement from baseline was noted in the Immediate Substitution arm (-6.13; p<0.001) compared to no change in the Deferred Substitution arm (+0.44; p=0.669). Continued improvement from baseline was observed in the Immediate Substitution arm at Week 8 (-6.96; p<0.001); however, no statistically significant change was detected in the Deferred Substitution arm at Week 8 (-1.95; p=0.075).

Figure 3. Augmented Symptoms Distress Module Total Scores (Baseline vs. Week 4)

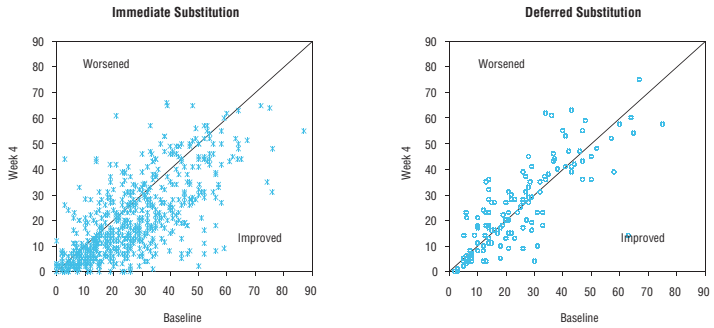
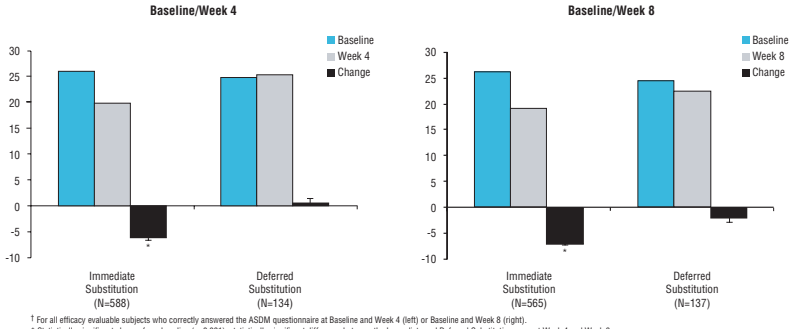


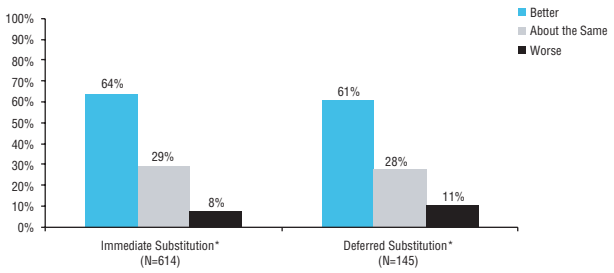
Figure 4. Summary of Augmented Symptoms Distress Module Total Scores†



† For all efficacy evaluable subjects who correctly answered the ASDM questionnaire at Baseline and Week 4 (left) or Baseline and Week 8 (right).
* Statistically significant change from baseline (p<0.001); statistically significant difference between the Immediate and Deferred Substitution arms at Week 4 and Week 8.

Results from question #1 of the Global Condition Improvement Questionnaire (i.e., Has there been any change in your tolerability to HIV treatment since you switched to LPV/r?) are presented in Figure 5. The majority of subjects (>60%) in both the Immediate and Deferred Substitution arms reported that their overall tolerability to HIV treatment had improved from baseline to Week 8.

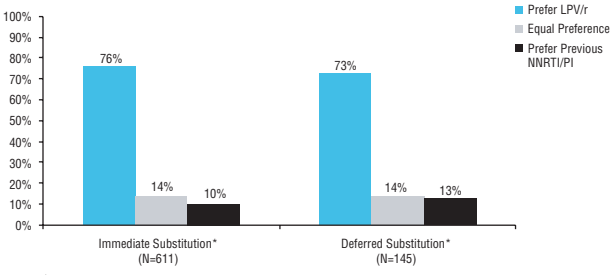
Figure 5. Summary of Global Condition Improvement Questionnaire – Change in Overall Tolerability to HIV Treatment†



† Summarized at Week 8/Premature Discontinuation.
* For all efficacy evaluable subjects who answered Question 1.

Results from the Therapy Preference Questionnaire are presented in Figure 6. The majority of subjects (>70%) in both the Immediate and Deferred Substitution arms preferred LPV/r to the NNRTI/PI they were taking prior to study entry.

Figure 6. Summary of Answers to Therapy Preference Questionnaire†

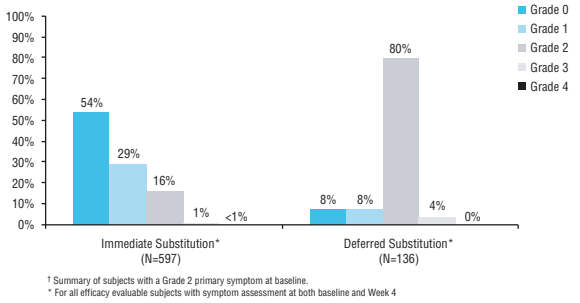


† Summarized at Week 8/Premature Discontinuation.
* For all efficacy evaluable subjects who answered the questionnaire.

RESULTS

Toxicity grades for the "primary" side effects reported at baseline are summarized in Figure 7. 83% of subjects in the Immediate Substitution arm and 16% of subjects in the Deferred Substitution arm reported an improvement of at least one toxicity grade from baseline to Week 4.

Figure 7. Summary of Primary Symptom Grades at Week 4†



† Summary of subjects with a Grade 2 primary symptom at baseline.
* For all efficacy evaluable subjects with symptom assessment at both baseline and Week 4

Of the 809 subjects included in this safety analysis, 4 (<1%) experienced treatment-emergent serious adverse events with possible or probable relationship to LPV/r: diabetes mellitus/hyperglycemia, anaphylactoid reaction, hepatitis, and acute renal failure. No specific adverse event (serious or non-serious) leading to discontinuation of study drug was reported in >2% of subjects.

CONCLUSIONS

Following substitution of LPV/r for their NNRTI/PI, subjects who had experienced mild-to-moderate side effects attributable to the NNRTI/PI in their antiretroviral regimen:

- Demonstrated improved QOL and tolerability to antiretroviral therapy as shown by results from the (Augmented) Symptoms Distress Module and Global Condition Improvement Questionnaire.
- Generally preferred LPV/r to their previous NNRTI/PI.
- Appeared to maintain or improve virologic control.

In addition, substitution of LPV/r for the NNRTI/PI used in the antiretroviral regimen appeared to improve/alleviate the "primary" side effect that caused the subject to enroll in this study.

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