Seven Year Follow-up of a Lopinavir/ritonavir (LPV/r)-Based Regimen in Antiretroviral (ARV)-Naïve Subjects

Background

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir, which functions as an inhibitor of cytochrome P450 3A. Even at low ritonavir doses, there is a substantial increase in LPV exposure. At a dosage of 400 mg of LPV/100 mg ritonavir twice daily (3 co-formulated capsules BID), ritonavir concentrations are below those required for antiviral activity. By contrast, the mean LPV Cmax/IC50 (ratio Inhibitory Quotient or IQ for wild-type HIV type 1 (HIV-1)) is ≥70 when lopinavir/ritonavir is dosed at 400/100 mg twice a day, potentially serving as a barrier to the emergence of drug resistance and providing activity against drug resistant virus.

Lopinavir/ritonavir (LPV/r, marketed as Kaletra™) has been studied in both antiretroviral-naive and experienced HIV-1-infected subjects. The M97-720 study was a phase II trial of LPV/r in combination with stavudine (d4T) and lamivudine (3TC) in antiretroviral-naive HIV-1-infected subjects. This study began in 1997 and was closed in 2005. This was the first trial of LPV/r in HIV-1-infected subjects and hence provides the longest duration of follow-up for subjects treated with LPV/r. This poster presents data on antiviral activity, immunological parameters, and safety through 7 years (360 weeks).

Methods

Entry Criteria

- Antiretroviral-naive subjects with confirmed HIV-1 infection.
- Plasma HIV-1 RNA ≤500 copies/mL with no CD4 count cell restriction.
- Exclusion criteria included ALT or AST >2.5x Upper Limit Normal (ULN) and creatinine >1.5x ULN.

Study Design and Analysis

- One hundred antiretroviral-naive HIV-1-infected subjects were randomized to receive one of three dosage levels of LPV/r (200/100 mg BID, 400/100 mg BID or 400/200 mg BID), together with d4T (40 mg BID) and 3TC (150 mg BID) given either after 3 weeks of monotherapy (Group I) or from study entry (Group II) (Figure 1).
- Enrollment into Group II began following an evaluation of preliminary efficacy and safety of LPV/r in Group I.
- After 48 weeks, all subjects converted to open-label LPV/r 400/100 mg BID dosing.
- Subjects were evaluated every 2–4 weeks for the first 24 weeks and every 12 weeks thereafter.
- At Year 6, 37 subjects treated with LPV/r + stavudine + lamivudine substituted stavudine with tenofovir disoproxil fumarate (tenofovir DF).

Figure 1. M97-720 Study Design

Efficacy

- Proportion of subjects with HIV-1 RNA either ≤<0.05 copies/mL or <50 copies/mL was measured using an on-treatment method (missing values and values obtained during treatment interruptions excluded) and an intent-to-treat, noncompleter-failure method (ITT NC=F method).
- Immunologic response was assessed by the mean change in CD4 cell count from baseline to each study visit.

ViroLogic Evaluation

- Samples from any subject with HIV-1 RNA >500 copies/mL any time at or after Week 24 were submitted for genotypic and phenotypic drug resistance analyses. Genotype (GeneScan™) and phenotype (PhenoSense™) analyses were performed by ViroLogic, Inc.

Conclusions

- Through 7 years (360 weeks) of follow-up, antiretroviral-naive subjects receiving LPV/r-based therapy exhibited sustained virologic responses, with 61% of subjects demonstrating HIV-1 RNA <50 copies/mL, and 59% demonstrating HIV-1 RNA <50 copies/mL by intent-to-treat (NC=P) analysis. Corresponding on-treatment response rates were 98% and 96%, respectively.
- Mean CD4 cell count increased 501 cells/mm3 over 360 weeks of follow-up with consistent CD4 cell count increases regardless of baseline CD4 cell count.
- Through 360 weeks of follow-up, no primary protease inhibitor resistance mutations have been observed in subjects with HIV-1 RNA >500 copies/mL any time at or after Week 24.
- LPV/r was safe and well tolerated on 7 years of therapy, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events.
- This is the longest duration of follow-up for any study of an antiretroviral regimen, and clearly demonstrates the potency and durability of a LPV/r-based regimen in antiretroviral-naive HIV-1-infected patients.

References

• Genotypic resistance to LPV was defined as the development of any primary or active site mutation in protease (amino acids 8, 30, 32, 46, 47, 48, 50, 54, 82, 84, and 90) confirmed by phenotypic analysis (≥2.5 fold increase in IC\textsubscript{50} to LPV relative to wild type HIV-1).
• Resistance to lamivudine (3TC) was defined as the presence of an M184V and/or M184I mutation in reverse transcriptase.
• Resistance to stavudine (d4T) was defined as any thymidine analog mutation in reverse transcriptase (amino acids 41, 67, 70, 210, 215, 219).

Safety
• Cumulative incidence through Week 360 for adverse events and grade 3/4 laboratory values was summarized, as was the prevalence at Week 360, or the final visit.
• Laboratory measurements were obtained without regard to fasting, through year 6, after which all measurements were obtained in fasted state.
• Events of fat distribution changes/lipodystrophy were based on subject reports and investigator assessment of symptoms.

Results

Baseline Characteristics
1. Ninety-six male and 4 female subjects: 65% White, 29% Black, 6% Hispanic.
2. Mean age: 35 years (range 21–69).
3. Among all 100 subjects enrolled, the median baseline HIV-1 RNA and CD4 cell count were 4.8 log\textsubscript{10} copies/mL and 326 cells/mm\textsuperscript{3}, respectively.

Efficacy

Viral Load Suppression Below the LOQ
• Based on the ITT NC=F analysis through Week 360, 61% of subjects had HIV-1 RNA <400 copies/mL (on-treatment analysis: 98%) (Figure 2) and 59% of subjects had HIV-1 RNA <50 copies/mL (on-treatment analysis: 95%) (Figure 3).

Analysis of Genotypic and Phenotypic Drug Resistance
• A total of 33 samples from 29 subjects were submitted for resistance testing (Figure 4).
• 18 subjects met criteria for loss of virologic response, and 11 patients had at least 1 "blip" (single HIV-1 RNA value >500 copies/mL bracketed by HIV-1 RNA values <400 copies/mL) after Week 24.
• Genotypic drug resistance testing failed for 10 subjects whose median HIV-1 RNA was 575 copies/mL.
• In 19 subjects with available results, no lopinavir or stavudine resistance was observed, and 4 subjects demonstrated lamivudine resistance. Correspondingly, no evidence of phenotypic resistance to any PI was observed (Figure 5).
• 6 subjects demonstrated a substitution at a new position in protease during viral rebound (1 each at amino acids 15, 36, 43, 57, 63, 70). However, as demonstrated previously, none of these substitutions are primary protease inhibitor mutations, no impact on protease inhibitor phenotypic resistance was observed, and all 3 of these subjects who completed the study demonstrated HIV-1 RNA <50 copies/mL at the final visit.

CD4 Cell Count Response
• Among subjects with values at both baseline and Week 360 (N=60), the mean CD4 cell count increased from 275 cells/mm\textsuperscript{3} at baseline to 776 cells/mm\textsuperscript{3} at Week 360, an increase of 501 cells/mm\textsuperscript{3} (Figure 6).
• CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count (Table 1). Among subjects with baseline CD4 cell count <50 cells/mm\textsuperscript{3}, mean CD4 cell count increased from 23 cells/mm\textsuperscript{3} at baseline to 556 cells/mm\textsuperscript{3} at Week 360, an increase of 533 cells/mm\textsuperscript{3}.

Table 1. CD4 Cell Count Increase at Week 360 by Baseline CD4 Cell Count

<table>
<thead>
<tr>
<th>Baseline CD4 Cell Count in cells/mm\textsuperscript{3}</th>
<th>Mean CD4 Cell Count Increase from Baseline to Week 360 (cells/mm\textsuperscript{3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 (n=15)</td>
<td>533</td>
</tr>
<tr>
<td>50–199 (n=12)</td>
<td>476</td>
</tr>
<tr>
<td>200–349 (n=11)</td>
<td>374</td>
</tr>
<tr>
<td>350–499 (n=11)</td>
<td>652</td>
</tr>
<tr>
<td>≥500 (n=11)</td>
<td>410</td>
</tr>
</tbody>
</table>

Safety

Table 2. Subject Disposition Through Week 360

<table>
<thead>
<tr>
<th>Subjects Enrolled</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuations prior to Week 360</td>
<td>38</td>
</tr>
<tr>
<td>Discontinuations probably or possibly related to study drugs</td>
<td>2</td>
</tr>
<tr>
<td>AEs</td>
<td>1</td>
</tr>
<tr>
<td>Lopinavir, enalapril, furosemide</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal lipids</td>
<td>2</td>
</tr>
<tr>
<td>Fat distribution changes</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
</tr>
</tbody>
</table>

Other reasons for discontinuation
• Adverse Event unrelated to study drugs (symptoms like reaction, hyperglycemia in diabetic patient, alcohol dehydrogenase)
•Lost to follow-up
•Noncompliance
•Personal/other reasons

Subjects completing study at Week 360 | 62 |

Table 3. Most Common Adverse Events occurring in ≥10% of subjects Through Week 360

<table>
<thead>
<tr>
<th>Moderate/Severe Drug-related AE</th>
<th>Incidence Through Week 360 (n=100)</th>
<th>Prevalence at Week 360 (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>≥10%</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11%</td>
<td>0%</td>
</tr>
</tbody>
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Safety

Table 2. Subject Disposition Through Week 360

CD4 Cell Count Increase at Week 360 by Baseline CD4 Cell Count

<table>
<thead>
<tr>
<th>Baseline CD4 Cell Count in cells/mm³</th>
<th>N</th>
<th>HIV-1 RNA &lt;50 copies/mL at Week 360</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 (n=15)</td>
<td>533</td>
<td></td>
</tr>
<tr>
<td>50–199 (n=12)</td>
<td>476</td>
<td></td>
</tr>
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<td>200–349 (n=11)</td>
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<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Drug-related AEs</th>
<th>Incidence Through Week 360</th>
<th>Prevalence at Week 360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>28%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>6%</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
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<td>11%</td>
<td>4%</td>
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