In multiple stepwise logistic regression analysis, CD4 cell count (most recent), prior number of PIs and prior number of NRTIs were found to be independent predictors of viral load response (<0.5 log10 reduction). The results of this analysis are presented in Table 5.

Table 5. Multiple Stepwise Logistic Regression Analysis of Plasma Viral Load (Subjects with Viral Load ≤500 copies/mL or ≥1.0 log10 Decrease from Baseline)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odd Ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count</td>
<td>0.839</td>
<td>0.769, 0.914</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PIs number</td>
<td>0.879</td>
<td>0.845, 0.915</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NRTIs number</td>
<td>0.895</td>
<td>0.865, 0.927</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Only SAEs were to be collected per protocol. A summary of SAEs that were reported by two or more LPV/r dosed subjects and of possible, probable or unknown relationship to LPV/r are summarized in Table 6.

Table 6. Serious Adverse Events Reported by Two or More LPV/r Dosed Subjects and of Possible, Probable, or Unknown Relationship to LPV/r

<table>
<thead>
<tr>
<th>Body System</th>
<th>Subjects Dosed (N=1772)</th>
<th>2 (0.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy Reaction</td>
<td></td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td>7 (4.2%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
<td>3 (1.7%)</td>
</tr>
<tr>
<td>Hepatitis Failure</td>
<td></td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Endocrine System</td>
<td></td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td>2 (1.0%)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Spanish subjects are a representative population of this worldwide early access program, with 2077 subjects enrolled. This represents the largest EAP-clinical trial managed to date in Spain.

Subjects enrolled in this EAP represented a heavily pretreated population with the mean number of prior PIs, NRTIs and NRTIs of 2.8, 4.3 and 1.1, respectively. In addition, 44.3% of subjects had CDC Class C events prior to enrollment, with the most common inactive AIDS-defining illnesses reported to be esophageal candidiasis (12.1%) and inactive pulmonary (6.0%), extrapulmonary (5.7%).

In a multiple stepwise logistic regression analysis, CD4 cell count (most recent), prior number of PIs and prior number of NRTIs were found to be independent predictors of viral load response (<0.5 log10 reduction). The results of this analysis are presented in Table 5.

The main inclusion criteria prior to dosing were:

- CD4 count <50 cells/mm3 or a history of an AIDS-defining opportunistic infection while on highly active antiretroviral therapy (HAART)
- HIV RNA ≥100,000 copies/mL and failure on at least 2 prior protease inhibitors; however, these specific criteria were removed after approximately 5 months of enrollment in the global EAP and were no longer applicable by the time most Spanish sites started to enroll subjects in the study.

The majority of the subjects had a vinpocetine response, with significantly higher response rates in subjects who initiated therapy with baseline CD4 cell count and less antiretroviral experience.

Kaletra appeared to be well-tolerated with only 3.1% of subjects discontinuing due to adverse events/HAIRelated events. Further, no specific SAEs was reported for greater than 1% of subjects.

ACKNOWLEDGMENTS

Abbott Spain would like to acknowledge all of the subjects who enrolled in Spanish sites who participated (see below as the Spain EAP Study Group), mainly the co-investigators, study nurses and pharmacists; to study CRAs (B. Box, P. de la Iglesia, J.A. Palacios and E. Salmerón) and to A. Meints, R. (Reitmayer) Heuser and R. Retamay and Spain for their constant support during the study.

REFERENCES

### Table 1. Summary of Demographic and Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Demographic or Disease Characteristic</th>
<th>LPV/Dosed Subjects (N=1772)</th>
<th>Demographic or Disease Characteristic</th>
<th>LPV Dosed Subjects (N=1772)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td>Kendall's Score</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74.2%</td>
<td>Mean (SD)</td>
<td>94.2 ± 7.8</td>
</tr>
<tr>
<td>Female</td>
<td>25.8%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>2.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>98.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Specified</td>
<td>2.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>Mean (SD)</td>
<td>39.2 ± 7.7</td>
</tr>
<tr>
<td>History of Hepatitis Influenza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Renal Influenza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC Classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Asymptomatic, Acute (primary) HIV</td>
<td>22.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or persistent generalized lymphadenopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Symptomatic, Not A or C conditions</td>
<td>23.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: AIDS – Indicator Conditions</td>
<td>44.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Specified</td>
<td>9.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Summary of Most Commonly Reported “Active/Inactive” AIDS-Defining Illnesses at Screening

<table>
<thead>
<tr>
<th>Disease</th>
<th>Subjects (N=1605)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active (≥6.0% of subjects)</td>
<td>0.9%</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>0.9%</td>
</tr>
<tr>
<td>HIV related wasting syndrome</td>
<td>0.9%</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>0.6%</td>
</tr>
<tr>
<td>Inactive (&lt;12% of subjects)</td>
<td>12.1%</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>12.1%</td>
</tr>
<tr>
<td>Pulmonary M. tuberculosis</td>
<td>6.0%</td>
</tr>
<tr>
<td>Extrapulmonary M. tuberculosis</td>
<td>1.7%</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>4.4%</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>2.1%</td>
</tr>
<tr>
<td>CD4 reactivation</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

### Table 3. Summary of Antiretroviral Medication Use*  

<table>
<thead>
<tr>
<th>Antiretroviral Medication</th>
<th>Baseline ARV Use (N=1772)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitors</td>
<td>3.3%</td>
</tr>
<tr>
<td>Indinavir</td>
<td>0.3%</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>0.3%</td>
</tr>
<tr>
<td>Abacavir</td>
<td>3.1%</td>
</tr>
<tr>
<td>Nucleoside Reverse Transcriptase Inhibitors</td>
<td>55.2%</td>
</tr>
<tr>
<td>Stavudine (ddI)</td>
<td>15.1%</td>
</tr>
<tr>
<td>Zidovudine (AZT, ddC)</td>
<td>11.1%</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>54.1%</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>51.7%</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>33.5%</td>
</tr>
<tr>
<td>Non-Nucleoside Reverse Transcriptase Inhibitors</td>
<td>5.6%</td>
</tr>
<tr>
<td>Tenofovir (PMPA)</td>
<td>21.2%</td>
</tr>
<tr>
<td>Other Drugs</td>
<td>21.2%</td>
</tr>
<tr>
<td>Other Agents</td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>2.2%</td>
</tr>
<tr>
<td>Tenofovir (PMPA)</td>
<td>0.9%</td>
</tr>
<tr>
<td>T-20</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

*Includes use of more than one ARV at subjects are reported.
* Includes use of Tenofovir or T310 and Lamivudine or Combivir, respectively.

### Summary of Demographic and Baseline Disease Characteristics

Demographic and disease characteristics for all subjects who initiated dosing with LPV/r are summarized in Table 1. The mean baseline HIV RNA and CD4 count for these subjects were 4.37 log copies/mL and 277.1 cells/mm³, respectively. In addition, 44.3% of these subjects had experienced at least 1 CDC Class C (AIDS-defining) event.

### Efficacy and Safety

As of August 7, 2001, a total of 356 (20.1%) of the 1772 subjects dosed with LPV/r have been discontinued from the study. The disposition of those subjects who initiated dosing with LPV/r is summarized in Table 4. The majority of the subjects that discontinued have done so due to the availability of Kaletra by other means.

### Table 4. Summary of Documented Subject Disposition

<table>
<thead>
<tr>
<th>Subject Disposition</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Discontinued</td>
<td>1772</td>
</tr>
<tr>
<td>Subjects Prematurely Discontinued*</td>
<td>20.1%</td>
</tr>
<tr>
<td>Withdrawn Consent</td>
<td>0.9%</td>
</tr>
<tr>
<td>Adverse Event/HIV-related Event</td>
<td>3.1%</td>
</tr>
<tr>
<td>Subject Death</td>
<td>1.5%</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>1.0%</td>
</tr>
<tr>
<td>Administrative (commercial availability)</td>
<td>10.9%</td>
</tr>
<tr>
<td>Other</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

*More than 1 reason for discontinuation may have been selected.

Virologic response (defined as either a plasma HIV RNA measurement at or below 500 copies/mL or at least a 1.0 log reduction, decrease from baseline) was further evaluated as a function of baseline HIV RNA (<100,000, =100,000 copies/mL), baseline CD4 count (<50 cells/mm³, 50-200 cells/mm³, >200 cells/mm³), prior protease inhibitor use (0-2, 3, 4), prior NRTI use (0, 2-3, 4, 5) and prior NNRTI use (0, 5). Also, the use of NNRTI as a new class was evaluated. Results are summarized in Figures 4-6.

### Figure 4. Percent of Subjects with Viral Load

**Nadir ≤500 copies/mL or ≥1.0 log reduction Below Baseline Stratified by Baseline HIV RNA**

### Figure 5. Percent of Subjects with Viral Load

**Nadir ≤500 copies/mL or ≥1.0 log reduction Below Baseline Stratified by Baseline CD4 Cell Count**

### Figure 6. Percent of Subjects with Viral Load

**Nadir ≤500 copies/mL or ≥1.0 log reduction Below Baseline Stratified by Prior PI Use**

### Figure 7. Percent of Subjects with Viral Load

**Nadir ≤500 copies/mL or ≥1.0 log reduction Below Baseline Stratified by Prior NNRTI Use**

### Figure 8. Percent of Subjects with Viral Load

**Nadir ≤500 copies/mL or ≥1.0 log reduction Below Baseline Stratified by Prior NNRTI Use**

### Figure 9. Percent of Subjects with Viral Load

**Nadir ≤500 copies/mL or ≥1.0 log reduction Below Baseline Stratified by the Use of NNRTI as a New Class**