Factors associated with adherence in a cohort of HIV positive subjects on a first time PI containing HAART regimen: Observational study of the impact of adherence on viral load for a HAART regimen containing Kaletra vs. other selected PI containing HAART regimen

ABBOTT LABORATORIES (Abbott)

Synoptic Clinical Study Report R&D
ABT-378/Protocol PUER-01-001

Development Phase: IV
Rationale for Synoptic Clinical Study Report: Study Close to Enrollment due to Low Enrollment Rate
Coordinating Investigator: Multicenter Study
Date First Subject First Visit: 21/AUG/2002
Date Last Subject Last Visit: 13/FEB/2007
Sponsor Signatory: Carlos R. Rivera-Vázquez, MD Medical Director Abbott Laboratories (Puerto Rico), Inc Montehiedra Office Centre 9615 Ave. Los Romero, Suite 700 San Juan, Puerto Rico 00926-7038

Phone: (787) 257-4402 Fax: (787) 257-4453

This study was conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements including the archiving of essential documents.

Confidential Information
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.
## 2.0 Synopsis

<table>
<thead>
<tr>
<th>Abbott Laboratories</th>
<th>Individual Study Table Referring to Part of Dossier:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of Study Drug:</strong> Kaletra</td>
<td><strong>Volume:</strong></td>
</tr>
<tr>
<td><strong>Name of Active Ingredient:</strong> Lopinavir/ritonavir</td>
<td><strong>Page:</strong></td>
</tr>
</tbody>
</table>

| **Title of Study:** Factors associated with adherence in a cohort of HIV positive subjects on a first time PI containing HAART regimen: Observational study of the impact of adherence on viral load for a HAART regimen containing Kaletra vs. other selected PI containing HAART regimen |
|**Investigator:** Multicenter study |

**Study Sites:** Victor Palmer, MD; Gladys Sepulveda, MD; Ruth Soto, MD; Carlos Dominguez, MD; Ivan Melendez, MD; Morgan Cordero, MD; Ramon Ramirez-Ronda, MD; Lizette Santiago, MD; Bernard Christenson, MD; Milton Garland, MD; Jacobo Quinones, MD

**Publications:** N/A

<table>
<thead>
<tr>
<th><strong>Studied Period (Years):</strong></th>
<th><strong>Phase of Development:</strong> IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Subject First Visit: 21/AUG/2002</td>
<td></td>
</tr>
</tbody>
</table>
Objectives:
Primary: To evaluate clinical outcomes related to adherence in subjects on a HAART regimen containing Kaletra vs. other selected PI-containing HAART regimens

Secondary:
To determine factors associated with adherence in a cohort of HIV positive patients

To evaluate the safety, tolerability, adherence patterns and antiviral activity of Kaletra tablet formulation, and compare these outcomes with comparable group of subjects who received Kaletra Soft-gel capsules

To analyze the development of HIV resistance to antiretroviral agents and the resistance patterns of a subgroup of subjects and compare differences among protease inhibitors

Assessment of clinical outcomes will include:

Time to virological failure based on adherence rates

Proportion of subjects with viral load below non-detectable levels by weeks 24, 36 and 48

Rebound episodes (episodes of detectable VL after initial response)

Discontinuation from treatment due to drug related adverse events and toxicity

Proportion of subjects with adequate adherence equal to or greater than 95% (based on Patterson reference)
Methodology:
PUER-01-001 was a randomized (two arms), open-label, multicenter trial. Subjects were randomized in a 1:1 rate to receive either Kaletra or Any Other PI plus two NRTIs chosen by the investigators.

After the baseline visit, subjects returned to the sites every four weeks up to the end of the study. Laboratories were drawn at baseline and weeks 4, 8, 16, 24, 36 and 48. Questionnaires were answered on baseline and weeks 8, 24, 36 and 48. Kaletra, ritonavir and other PIs PK levels were drawn on weeks 4, 16, 24, 36 and 48. Adverse events assessment and concomitant medications record were performed at all study visits.

Number of Subjects (Planned and Analyzed): The planned enrollment was 200 subjects (100 in each arm). The final enrollment was 169 subjects.
Diagnosis and Main Criteria for Inclusion:

**Diagnosis:** HIV positive subjects

**Inclusion criteria:**

HIV infected male and female subjects ≥18 years of age who are required to begin for the first time a PI containing HAART regimen. Subject eligible for enrollment are:

- Subject has confirmed his or her willingness to participate in this study after being informed of all aspects of the trial that are relevant to his or her decision to participate, by signing and dating the IRB/IEC approved informed consent form.

- Subject is documented HIV positive.

- Subject is ≥18 years of age.

- Subject does not exhibit evidence of acute illness.

- Subject has not been treated for an active opportunistic infection within 30 days of the baseline visit.

- Subject has a Karnofsky Score ≥70.

- Subjects currently on a regimen of either an NNRTI + 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs), two or three NRTIs who have failed regimen as evidenced by 2 consecutive viral loads with values over 1,000 copies within the last three months.

- Subjects who have become intolerant to their current antiretroviral regimen as evidenced by a grade 2 adverse event as defined in appendix C and Appendix I which the investigator suspects is related to its current ARV regimen and are required to be changed to PI containing HAART regimen

- Naïve subjects to ARV regimen who are required to begin in a HAART regimen containing regimen

- Subject does not require and agrees not to take, for the duration of the study, any of the following medications that are contraindicated with Kaletra: astemizole, terfenadine, midazolam, triazolam, cisapride, certain ergot derivatives (ergotamine, dihydroergotamine, ergonovine, and methylergonovine), pimozide, propafenone and flecainide. Rifampin, a potent enzyme inducer, should not be administered with the study medication, because of the possibility of significant decreases in Kaletra concentrations during concurrent administration.

- The subject agrees not to take any medication, including over-the-counter medicine, alcohol, recreational drugs or herbal preparations without the knowledge and permission of the principal investigator. Subject had laboratory testing within the previous three months and the most recent testing demonstrates all of the following:
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Kaletra Capsules 400/100 mg BID (up to 01/NOV/05) or Kaletra Tablets 400/100 mg BID (up to the end of the study); or any other PI chosen by the investigators using the dosing and scheduled as per the label.

Duration of Treatment: 108 weeks (up to 01/NOV/05) and 48 weeks (up to the end of the study)

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: All HIV drugs used were prescribed as per each product’s label.

Criteria for Evaluation
Efficacy: The primary endpoint was a comparison between the two open label arms in terms of clinical outcomes such as: time to virological failure, proportion of subjects with viral load below non-detectable levels by weeks 24, 36 and 48, rebound episodes, discontinuation from treatment due to drug related adverse events and toxicity based on adherence rates (based on pill counting).

Pharmacokinetic: Pharmacokinetic tests for the different Protease Inhibitors were performed at study weeks 4, 16, 24, 36, and 48; and 60, 72, 84, 96 and 108 (if applicable).

Safety: Laboratory evaluations (hematology, chemistries (SMA-24), amylase, CD4 count, HIV viral load) were performed at Baseline, weeks 4, 8, 16, 24, 36, and 48; and 60, 72, 84, 96 and 108 (if applicable). Adverse events assessment was performed at each study visit (every four weeks). Serious adverse events assessment was performed since the subjects signed the Informed Consent and throughout the study; and 30 days after completing the study (or prematurely discontinued).
**Statistical Methods**

**Efficacy:** The primary endpoints will be a comparison between the two open label arms in terms of clinical outcomes such as: time to virological failure, proportion of subjects with viral load below non-detectable levels by weeks 24, 36 and 48, rebound episodes, discontinuation from treatment due to drug related adverse events and toxicity based on adherence rates (based on pill counting). Adherence rates will be correlated with MEMS Caps analysis, plasma drug levels and ACTG Questionnaire responses.

**Pharmacokinetic:** Drug plasma levels were used to correlate with suboptimal adherence and subtherapeutic levels of medication in each study group.

**Safety:** Serious adverse events and serious HIV-related events that began after the informed consent process and within 30 days after the last dose of study medication were considered.

Grade III and IV laboratory determinations (i.e., clinical chemistry, hematology and amylase), vital signs, and physical examination determinations were summarized by treatment arm. Subjects with extremely high or extremely low clinical laboratory determinations were individually identified and summarized by treatment arm.
Summary/Conclusions

Efficacy Results: A total of 163 subjects were dosed. The percent of subjects with HIV viral load <400 copies/mL was 40.3%, 71.2%, 87.5%, 87.1%, 87.0%, 92.5%, 95.6%, 93.0%, 95.1%, 97.3% and 94.3% respectively for the Kaletra arm in each study visit in which laboratory tests were drawn. For the Any Other PI arm, the percent of subjects with HIV viral load <400 copies/mL was 42.0%, 67.7%, 73.7%, 78.0%, 78.7%, 80.4%, 75.7%, 85.3%, 83.3%, 89.3% and 86.2% respectively.

The mean CD4 count by study visit in Kaletra vs Any Other PI arms respectively are as follow: 219 vs 228, 323 vs 351, 364 vs 374, 346 vs 373, 369 vs 368, 402 vs 399, 457 vs 457, 486 vs 511, 493 vs 461, 476 vs 486, 532 vs 497, 572 vs 507.

Seven subjects experienced virological failure during the study. Four of them were using nelfinavir, two were using fosamprenavir, and one was using atazanavir.

Pharmacokinetic Results: PK results were in accordance with adherence data and the date and time reported by study subjects as the date and time of last PI dose.

Safety Results: No different safety issues noted compared with each product's label.

Conclusions: There were not statistically significant differences in clinical outcomes related to adherence between subjects in both arms, according % of subjects with viral load <400 copies/mL across the time. The seven subjects who experienced virological failure during the study, developed primary resistance genotypic mutations to the respective PIs that were exposed to. None of the subjects in the Kaletra arm showed detectable resistance mutations.