2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Kaletra	**Volume:**	
Name of Active Ingredient: Lopinavir/ritonavir	**Page:**	
Title of Study: Evaluation of clinical response and safety in HIV positive subjects co-infected with Hepatitis C treated with a Kaletra containing HAART regimen.		
Investigator: Multicenter study		
Study Sites: [redacted] redacted information 08Aug2014		
Publications: N/A		
Studied Period (Years): First Subject First Visit: 09/OCT/2002 Last Subject Last Visit: 02/JAN/2008	**Phase of Development: IV**	

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Objectives:

- **Primary**: To evaluate changes in liver functions enzymes from baseline throughout time in patients treated with Lopinavir/ritonavir who are Hepatitis C positive vs. those that are negative to Hepatitis C.
    - **Secondary**: To evaluate changes in HIV viral load in patients treated with Lopinavir/ritonavir who are HIV positive co-infected with Hepatitis C vs. those Hepatitis C negative.
    - To evaluate changes in CD4/CD8 cell count in patients treated with Lopinavir/ritonavir who are HIV positive co-infected with Hepatitis C vs. those negative for Hepatitis C.
    - To evaluate the safety, tolerability and antiviral activity of Kaletra tablet formulation among HIV/HCV infected subjects and compare these outcomes with comparable group of subjects who received Kaletra Soft-gel capsules.
    - To evaluate the safety, tolerability and antiviral activity of Kaletra tablet formulation among HIV infected subjects and compare these outcomes with comparable group of subjects who received Kaletra Soft-gel capsules.
    - To evaluate changes in Hepatitis C viral load in patients treated with Lopinavir /ritonavir who are HIV positive co-infected with Hepatitis C.

Methodology:

PUER-02-003 was an open-label, multicenter trial. Subjects were classified as HIV/HCV positive or HIV/HCV negative. All subjects received Kaletra plus two NRTIs chosen by the investigators.

Subjects went to a screening visit, in which laboratory tests were drawn, and a Medical History was documented. Between screening and baseline, Hepatitis C positive subjects underwent a liver biopsy to determine their METAVIR Score.

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 and 24.

Kaletra PK levels were drawn on week 4.

Adverse events assessment and concomitant medications record were performed at all study visits.

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Number of Subjects (Planned and Analyzed): The planned enrollment was 133 subjects (100 HIV/HCV positive and 33 HIV/HCV negative). The final enrollment was 86 subjects, 54 HIV/HCV+ and 32 HIV/HCV-. Sixty-one percent of subjects in the HCV+ group vs eighty-one percent in the HCV – group completed the study period (24 weeks).

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Diagnosis and Main Criteria for Inclusion:

Diagnosis: HIV positive subjects with or without Hepatitis C

Subjects must meet all the following criteria 30 days prior to the initial dosing (except where otherwise stated):

- Subjects that required to be started on a PI containing HAART regimen and physician in charge has chosen to start patient on a lopinavir/ritonavir containing HAART regimen.
- Subject who will not require the use of an NNRTI in addition to the selected lopinavir/ritonavir containing HAART regimen.
- Subjects who are HIV positive co-infected with Hepatitis C as confirmed by a Hepatitis C antibody test.
- Control arm only: Subjects who are HIV positive and negative to Hepatitis C.
- 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 (specially any acute liver disease, except Hepatitis C).
- Subject has not been treated for an active opportunistic infection within 30 days of the baseline visit.
- Subject has a Karnofsky Score ≥70.
- 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.

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- Subject had laboratory testing within the previous three months and the most recent testing demonstrates all of the following:
  - ✓ Hemoglobin >8.0 g/dL
  - ✓ Absolute neutrophil count >750 cells/μL
  - ✓ Platelet count >20,000/μL
  - ✓ ALT or AST </=10 x Upper Limit of Normal (ULN)
  - ✓ Creatinine <1.5 x ULN
  - ✓ Triglycerides </=750 mg/dL
- Subjects have no have evidence of grade III or IV adverse event or laboratory abnormality. (except for LFTs)

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); plus two NRTIs using the dosing and scheduled as per the label.

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Duration of Treatment: 24 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: N/A

Criteria for Evaluation

Efficacy: The primary endpoint was to evaluate changes in lever function tests among subjects treated with Lopinavir/ritonavir who are HIV positive co-infected with Hepatitis C vs those that are negative to Hepatitis C.

Pharmacokinetic: Pharmacokinetic test for Lopinavir/ritonavir was performed at study week 4.

Safety: Laboratory evaluations (hematology, PT/PTT, HIV genotype, HIV viral load, HCV serology and HbsAg) were performed at screening. Hematology, chemistries (SMA-24), amylase, CD4 count, HIV viral load, HCV viral load and HCV genotype were performed at Baseline. Hematology, chemistries (SMA-24), amylase, CD4 count, HIV viral load, HCV viral load and Lopinavir/r PK levels were performed at week 4. Hematology, chemistries (SMA-24), amylase, CD4 count, HIV viral load and HCV viral load were performed at weeks 8, 16 and 24. 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).

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Statistical Methods

Efficacy: Descriptive analysis will be done for each study group. Continuous variables will be summarized with n, arithmetic mean, median, standard error of the mean, maximum, and minimum values. Categorical variables will be summarized with count, percents and the data should be compared in the form of a frequency table.
All subjects who receive at least one dose of study drug will be included in the efficacy analyses.
The proportion of subjects with plasma HIV RNA levels below the limit of quantification (50 copies/ml) will be summarized in both arms at each visit. Two approaches will be used for this analysis, the first of which is an intent-to-treat approach in which all missing values will be considered above 50 copies/ml. All measurements obtained more than one day after study drug discontinuation will be considered above 50 copies/ml. The second approach will involve observed results only, and will exclude any missing values from the analysis.

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.

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Summary/Conclusions

Efficacy Results: Median ALT value (U/L) for HIV/HCV+ subjects was 53 at baseline, 41.5 at week 4, 53 at week 8, 64.5 at week 16 and 67 at week 24. Median AST value (U/L) for HIV/HCV+ subjects was 61.5 at baseline, 51 at week 4, 56.5 at week 8, 60.5 at week 16 and 66 at week 24. Median ALT value (U/L) for HIV/HCV- subjects was 42 at baseline, 24 at week 4, 21 at week 8, 21.5 at week 16 and 22 at week 24. Median AST value (U/L) for HIV/HCV- subjects was 40.5 at baseline, 29 at weeks 4 and 8, 27 at week 16 and 26 at week 24.

Proportion of subjects with undetectable HIV viral load (<400 copies/mL) on baseline, weeks 4, 8, 16 and 24 in the HIV/HCV+ cohort was 13%, 37.5%, 51.2%, 72.2% and 61.5% respectively.

Proportion of subjects with undetectable HIV viral load (<400 copies/mL) on baseline, weeks 4, 8, 16 and 24 among the HIV/HCV- cohort was 6.3%, 25.8%, 50%, 69.2% and 77.8% respectively.

Mean CD4 counts among the HIV/HCV+ group were 312.5, 398.3, 384.6, 376.6 and 479.4 cells/mL at baseline, week 4, week 8, week 16 and week 24 respectively.

Mean CD4 counts among the HIV/HCV- group were 273.3, 303.7, 335.0, 344.7 and 393.6 cells/mL at baseline, week 4, week 8, week 16 and week 24 respectively.

Pharmacokinetic Results: There was a direct relationship among the Lopinavir PK result on week 4 and the adherence rate based on pill counting.

Safety Results: There were no safety concerns during the study. Only one SAE probably related to study drug was reported. This was a grade III AST and grade IV ALT elevation in a Hepatitis C positive subject.

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Conclusions: 94 subjects were screened, 8 of those subjects (8.5%) were screening failures. Sixty-one percent of subjects in the HCV+ group vs eighty-one percent in the HCV – group completed the study period (24 weeks). There were a statistically significant difference in the number of subjects who were prematurely discontinued among both study groups [redacted]. Most of the subjects who discontinued treatment prematurely were secondary to lost to follow-up in both groups.

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There were a total of 133 adverse events reported in the HCV+ group vs 100 in the HCV – group. Most of the adverse events in both groups were considered not related to study drug. The proportion of subjects with adverse events probably related to study drug was similar in both groups.

There were a total of twelve SAEs in the HCV+ group vs two in the HCV- group. Of the total of fourteen SAEs, thirteen were considered by the investigators as not-related to study drug, and only one SAE was classified as probably related (in the HCV+ group). [redacted]

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