Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Kaletra®, lopinavir/ritonavir, ABT-378	**Volume:**	
Name of Active Ingredient: Lopinavir/ritonavir	**Page:**	

Title of Study: A Phase 3, Randomized, Open-label, Study of Lopinavir/ritonavir Tablets Versus Soft Gel Capsules and Once Daily Versus Twice Daily Administration, when Co-administered with NRTIs in Antiretroviral Naïve HIV-1 Infected Subjects

Coordinating Investigator: Dr. Juan Gonzalez-Garcia, MD

Study Sites: 131 investigators in 19 countries (United States, Australia, Belgium, Canada, Czech Republic, France, Germany, Greece, Ireland, Italy, Netherlands, Poland, Puerto Rico, Russia, Singapore, Spain, Switzerland, Taiwan, and United Kingdom)

Publications: 1

Studied Period (Years):	**Phase of Development:** 3
First Subject First Dose: 03 January 2006 Last Subject Last Dose: 09 July 2008 (Week 96 Visit/End of Study)	

Objectives:

The primary objectives of this study were to:

- Compare the safety and tolerability of the to-be-marketed lopinavir/ritonavir tablet formulation with the marketed SGC formulation.
- Compare the safety, tolerability, and antiviral activity of QD and BID dosing of the lopinavir/ritonavir tablet formulation.

The secondary objectives of this study were to:

- Characterize the development of resistance in QD and BID dosing of the lopinavir/ritonavir tablet.
- Characterize the pharmacokinetics of the lopinavir/ritonavir tablet in human immunodeficiency virus type 1 (HIV-1) infected subjects following multiple dose administration.

Results of the comparison of safety and tolerability of the to-be-marketed lopinavir/ritonavir tablet formulation with the marketed SGC formulation and characterization of the pharmacokinetics of the lopinavir/ritonavir tablet in HIV-1 infected subjects following multiple dose administration have been presented in a prior Week 8 clinical study report.

Objectives (Continued): Analyses comparing the QD and BID dosing regimens of the lopinavir/ritonavir tablet formulation through Week 48 have been presented in a prior Week 48 clinical study report. The same analyses through Week 96 (end of study) were conducted for this report.

Methodology: This was a Phase 3, open-label, randomized, multicenter, multicountry study designed to demonstrate the safety, tolerability, pharmacokinetics, and antiviral activity of the lopinavir/ritonavir tablet formulation when dosed QD vs. BID in combination with nucleoside reverse transcriptase inhibitors (NRTIs) in the treatment of antiretroviral naïve, HIV-1 infected subjects.

Approximately 600 subjects meeting inclusion and exclusion criteria were planned for enrollment in the study at approximately 160 sites. Subjects were randomized in a 1:1 ratio to receive either lopinavir/ritonavir 800/200 mg QD (n = 300) or lopinavir/ritonavir 400/100 mg BID (n = 300). Further stratification within each group was 1:1 (tablet vs. SGC).

Subjects were administered either the tablet or the SGC formulation for 8 weeks, after which all subjects were administered the tablet formulation QD or BID for the remainder of the study. Subjects were administered emtricitabine 200 mg QD and tenofovir disoproxil fumarate 300 mg QD, either as separate tablets/capsules or a fixed dose combination tablet of emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg QD. Until emtricitabine or the fixed combination tablet of emtricitabine and tenofovir disoproxil fumarate were locally available, subjects were administered lamivudine 300 mg QD and tenofovir disoproxil fumarate 300 mg QD.

Subjects meeting the enrollment criteria were randomized on Day –1/Baseline and returned for study visits at Weeks 1, 2, 4, 8, 10 (pharmacokinetic data only), 12, 16, 24, 32, 40, 48, and every 12 weeks thereafter through Week 96 or premature discontinuation. An initial Week 8 report summarized data through 8 weeks of treatment including data from Day –1/Baseline and Weeks 1, 2, 4, 8, and 10 (pharmacokinetic analysis only). A subsequent Week 48 report summarized data through 48 weeks of treatment including data from Day –1/Baseline and Weeks 1, 2, 4, 8, 10 (pharmacokinetic analysis only), 12, 16, 24, 32, 40, and 48. The present Week 96 report summarizes safety and efficacy data through 96 weeks of treatment (the end of the study). In addition, data from the Discontinuation Visit are also included, as applicable, for subjects who prematurely discontinued during the 96 weeks.

Number of Subjects (Planned and Analyzed): The planned sample size was 600 subjects, with 300 subjects in each of the QD and BID dosing groups and 300 subjects in each of the SGC and tablet formulation groups for a total of 150 subjects in each of the 4 lopinavir/ritonavir treatment groups. A total of 664 subjects were randomized and received at least 1 dose of lopinavir/ritonavir in combination with once-daily tenofovir disoproxil fumarate and emtricitabine, as follows: 333 subjects in the QD group and 331 subjects in the BID group.

Diagnosis and Main Criteria for Inclusion: Subjects were HIV-1 positive, antiretroviral-naïve adults at least 18 years of age with < 7 days of prior antiretroviral therapy. Subjects had plasma HIV-1 ribonucleic acid (RNA) levels ≥ 1,000 copies/mL at screening and were not acutely ill. Female subjects were nonpregnant and nonlactating.

Test Product, Dose/Strength/Concentration, and Mode of Administration:

Lopinavir/ritonavir was provided as follows: coformulated lopinavir/ritonavir 200/50 mg tablets for oral administration with or without food; coformulated lopinavir/ritonavir 133.3/33.3 mg SGCs for oral administration with food.

Duration of Treatment: 96 weeks. This report includes data through 96 weeks of treatment.

Reference Therapy, Dose/Strength/Concentration, and Mode of Administration:

Emtricitabine 200 mg (tablet) and tenofovir disoproxil fumarate 300 mg (capsule), separately or as coformulated tablets, were taken orally once a day with or without food.

For sites in countries where emtricitabine was not available, lamivudine 300 mg was taken orally once a day with or without food.

Criteria for Evaluation

Efficacy: Plasma HIV-1 RNA, CD4+ T cell levels, and subject questionnaire data. Analyses of subject questionnaire data were presented in a Week 48 report.

Pharmacokinetic: Noncompartmental pharmacokinetic analysis for the first 8 weeks of the study was presented in a prior Week 8 clinical study report and population pharmacokinetic analysis for the first 48 weeks was presented separately in a Week 48 population pharmacokinetic report. Pharmacokinetic samples were not collected after Week 48.

Safety: Adverse events, clinical laboratory data, and vital signs

Statistical Methods

Efficacy:

The efficacy of the QD and BID dosing regimens of the tablet formulation of lopinavir/ritonavir was evaluated by assessment of plasma HIV-1 RNA levels and CD4+ T cell counts. The primary efficacy analysis for this study was the proportion of subjects with plasma HIV-1 RNA levels < 50 copies/mL at Week 48. An intent-to-treat approach was used for this analysis, in which subjects with missing values at Week 48 were considered nonresponders (noncompleter = failure analysis). Differences between QD and BID dosing groups were assessed using Fisher's exact test. Secondary analyses of data collected throughout the 96-week study included time to loss of virologic response, proportion of subjects with plasma HIV-1 RNA levels < 50 copies/mL at each visit, mean change from baseline to each visit in CD4+ T cell counts, emergence of viral resistance, and response by FDA time to loss of virologic response algorithm.

Pharmacokinetics:

Noncompartmental pharmacokinetic analysis for the first 8 weeks of the study was presented in a prior Week 8 clinical study report and population pharmacokinetic analysis for the first 48 weeks was presented separately in a Week 48 population pharmacokinetic report. Pharmacokinetic samples were not collected after Week 48.

Safety:

For the Week 96 (end of study) analysis, the lopinavir/ritonavir QD dosing regimen was compared to the BID dosing regimen as follows:

Treatment-emergent adverse events were defined as those occurring after study drug initiation and within 30 days after the last dose of study drug. All adverse events were coded according to the Medical Dictionary for Regulatory Affairs (MedDRA). Treatment-emergent adverse events and HIV-1-related events were coded and summarized separately.

Safety (Continued):

The proportion of subjects reporting treatment-emergent adverse events during the study was summarized by severity and relationship to study drug (lopinavir/ritonavir) and comparisons were made between the QD and BID dosing regimens of lopinavir/ritonavir. Differences between the QD and BID dosing regimens were assessed using Fisher's exact test. Additionally, the following types of treatment-emergent adverse events were analyzed: serious adverse events; events resulting in death; events leading to interruption of study drug; events leading to NRTI substitution/dose change; events treated with medication; and events leading to study discontinuation.

The proportion of subjects with potentially clinically significant (Grade 3–4) laboratory abnormalities or vital signs parameters was calculated and differences between the dosing regimens were assessed using Fisher's exact test.

Mean changes from baseline in laboratory and vital signs determinations to each study visit were compared between the QD and BID dosing regimens using a 1-way analysis of variance (ANOVA).

Summary/Conclusions

Efficacy Results:

During the study, there was no loss of efficacy with QD dosing relative to BID dosing. The primary efficacy analysis was the proportion of subjects with plasma HIV-1 RNA levels < 50 copies/mL at Week 48. At Week 48, response rates between QD and BID dosing were similar in all analyses. By ITT NC=F analysis, the proportion of subjects with plasma HIV-1 RNA levels < 50 copies/mL at Week 48 were 77.2% in the QD group and 75.8% in the BID group, with a difference of 1.3% (95% CI: –5.1%, 7.8%). Because the lower limit of the confidence interval was above the prespecified margin of –12%, the QD dosing regimen is considered to have noninferior efficacy compared to the BID dosing regimen. At Week 96, the proportion of subjects with plasma HIV-1 RNA levels < 50 copies/mL were 64.9% in the QD group and 69.2% in the BID group. The difference in proportions of subjects responding between treatment groups was –4.3% (95% CI: –11.5%, 2.8%), supporting the noninferiority of the QD dosing regimen compared to the BID dosing regimen. These results were generally consistent in subgroup analyses defined by age, gender, race, baseline CD4+ T cell count, and baseline plasma HIV-1 RNA level.

Efficacy Results (Continued):

A number of additional analyses were performed to fully assess the relative antiviral activity of lopinavir/ritonavir QD and BID dosing. Numerical differences in response rates between treatment groups were observed at all time points in this study. There was a statistically nonsignificant numerical advantage with lopinavir/ritonavir BID dosing compared to QD dosing at Week 96. However, at most time points prior to Week 96, including the 5 time points immediately preceding Week 96, the proportion of subjects responding by ITT NC=F analysis favored QD dosing. This change from numerical advantage favoring QD dosing to BID dosing at the Week 96 time point was due, in part, to low-level viremia occurring more frequently in lopinavir/ritonavir QD compared to BID subjects at the Week 96 time point. In order to investigate whether this observation was related to the lopinavir/ritonavir QD dosing interval, rates of viral rebound were assessed at all time points after Week 24. If the disproportionate number of low-level plasma HIV-1 RNA elevations in QD subjects at Week 96 was indicative of a true difference in efficacy, loss of virologic suppression would be expected to occur more frequently in QD-treated subjects at other time points as well. In this analysis, no differences in rates of viral rebound were observed when QD and BID treatment groups were compared. These findings strongly suggest that the changes in response rates observed between Week 84 and Week 96 were not due to lopinavir/ritonavir QD dosing, but represent the variability in response inherent in antiretroviral therapy as reflected in rates of virologic suppression at various time points in this study.

Other analyses also support the conclusion that lopinavir/ritonavir QD and BID dosing are similarly efficacious. Differences between QD and BID response rates were similar across all baseline plasma HIV-1 RNA or CD4+ T cell strata. If 1 regimen were less potent than the other, differences in response rates would likely be magnified in the more difficult to treat populations (e.g., higher baseline plasma HIV-1 RNA or lower baseline CD4+ T cell count). However, this was not observed when lopinavir/ritonavir QD and BID response rates were compared across various strata. Lastly, differences in rates of viral suppression might be expected to result in differences in rates of viral resistance. However, in this study, the rates of emergence of resistance were virtually identical in the 2 treatment regimens.

Pharmacokinetic Results:

Noncompartmental pharmacokinetic analysis for the first 8 weeks of the study was presented in a prior Week 8 clinical study report and population pharmacokinetic analysis for the first 48 weeks was presented separately in a Week 48 population pharmacokinetic report. Pharmacokinetic samples were not collected after Week 48.

Safety Results:

A total of 314 (94.3%) QD-treated subjects and 313 (94.6%) BID-treated subjects experienced 1 or more treatment-emergent adverse events. Adverse events were generally reported with similar frequency and character between the QD and BID dosing regimens with no clinically significant differences noted.

Safety Results (Continued):

Study drug was generally well tolerated with only 36 of the 664 subjects discontinuing therapy due to an adverse event and/or HIV-related event. The discontinuations occurred with similar frequency in the 2 treatment groups (20 QD-treated subjects and 16 BID-treated subjects), with diarrhea listed as an adverse event contributing to discontinuation in 10 (3.0%) QD-treated subjects and 6 (1.8%) BID-treated subjects. There were no statistically significant differences observed between the dosing groups in the proportion of subjects discontinuing for adverse events. HIV-related adverse events leading to premature discontinuation from the study occurred in 2 BID-treated subjects and no QD-treated subjects.

The most frequently reported adverse events, regardless of severity or relationship to study drug, were gastrointestinal in nature. Consistent with the previously described safety profile of lopinavir/ritonavir, the most common of these adverse events was diarrhea, which was reported with similar frequency in both treatment groups. Nausea and vomiting were the only other gastrointestinal adverse events reported by at least 10.0% of subjects in either treatment group, and these events also occurred with a similar incidence between the 2 groups. Other gastrointestinal adverse events were reported in fewer than 10.0% of subjects in either treatment group, and, with the exception of dyspepsia, were noted with similar frequency in QD vs. BID-treated subjects.

When all other adverse events regardless of severity or association with study drug were evaluated, all occurred with similar frequency in the 2 treatment groups except for hypersensitivity, seasonal allergy, syphilis, and poor quality sleep. Because of the small numbers of these events and the lack of consistent pattern or plausible causative pathophysiologic mechanism, the differences in rates of these events are not felt to be clinically significant.

Among adverse events considered by the investigator to be at least moderate in severity and possibly or probably related to study drug, there were no statistically significant differences between the QD and BID dosing regimens when comparing incidence of specific events. Diarrhea and nausea were the only events of moderate or greater severity and possibly or probably related to study drug occurring in more than 5.0% of subjects in either treatment group.

A total of 37 (11.1%) QD-treated subjects and 50 (15.1%) BID-treated subjects experienced 1 or more treatment-emergent serious adverse events during the study. There were no statistically significant differences between the QD and BID treatment groups observed for any of these adverse events.

Four subjects died within 30 days after the last dose of study drug: Subjects 7336 and 7608 in the QD group and Subjects 7033 and 7174 in the BID group. None of these deaths were considered by the investigator as possibly or probably related to study drug. Two subjects (Subjects 7325 and 7244, both BID) died more than 30 days after the last dose of study drug. Serious adverse events were generally consistent with common comorbidities in HIV-infected subjects or the established safety profile of lopinavir/ritonavir.

Among other adverse events of interest, hepatitis was noted in 2 QD-treated subjects. One of the events was an episode of transaminase elevations which occurred on Study Day 57 and resolved on Study Day 142 without study drug interruption; the subject had a past history of chronic hepatitis C. The other event of hepatitis occurred in the setting of fluconazole use and also improved in the setting of ongoing study drug therapy. There were 12 reports of body fat composition change noted and 4 reports of hyperglycemia or elevated blood glucose. No events of pancreatitis were reported.

Safety Results (Continued):

Among other laboratory parameters, only a few sporadic differences between the QD and BID treatment groups in mean change from baseline (i.e., small increase vs. small decrease) were observed. Of these noted differences, a statistically significant difference between the QD and BID treatment groups in mean change from baseline was observed at Week 96 and at some other visits during the study for sodium, LDL:HDL ratio, and triglycerides. The difference in change from baseline in sodium was small and not clinically meaningful. While the differences in change from baseline tended to favor the QD treatment group, the significance of these differences is unclear.

There were no statistically significant differences in the mean change from baseline to Week 96 between the QD and BID treatment groups for chloride, total cholesterol, LDL, HDL, and calculated creatinine clearance. Mean change from baseline to Week 96 for these parameters were of similar magnitude to that observed in previous studies of lopinavir/ritonavir in antiretroviral-naïve subjects.

Consistent with previous lopinavir/ritonavir studies, very high lipid values (Grade 3–4 elevations) were among the most common potentially clinically significant laboratory abnormalities observed. These were noted with similar frequency in the 2 treatment groups and resulted in study drug discontinuation in only 1 QD and 1 BID-treated subjects. Other laboratory abnormalities meeting very high criteria included elevated fasting glucose in 1 QD and 1 BID-treated subject and lipase elevations in 15 QD and 18 BID-treated subjects, none of which were associated with adverse events of pancreatitis. Reduced creatinine clearance of < 50 mL/min was noted in 8 QD and 13 BID-treated subjects, the majority of whom either experienced only a transient decrease or had an underlying risk factor for renal impairment.

Overall, the safety and tolerability profile of lopinavir/ritonavir during the 96 weeks of treatment was consistent with that reported in the Week 48 report and with that observed in previous studies of lopinavir/ritonavir in antiretroviral-naïve subjects. Although the rate of a few adverse events was different in QD-treated and BID-treated subjects, these events were all uncommon and no pattern to these differences was observed. In addition, these differences largely disappeared when only events considered possibly or probably related to study drug were compared. Finally, laboratory abnormalities observed with both dosing regimens were similar and fully consistent with those reported in previous lopinavir/ritonavir studies. These findings suggest that there is no clinically meaningful difference in the safety or tolerability of lopinavir/ritonavir dosed QD or BID.

Conclusions:

In summary, the findings from this Week 96 analysis are consistent with the results of the Week 48 analysis, showing that there are no clinically significant differences between the lopinavir/ritonavir QD and BID dosing regimens with regard to safety, tolerability, or antiviral activity. These results support the conclusion that lopinavir/ritonavir dosed QD can be considered a safe and effective treatment option for antiretroviral-naïve patients.

Date of Report: 31Mar2009