Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: 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 800/200 mg Once-Daily Versus 400/100 mg Twice-Daily when Coadministered with Nucleoside/Nucleotide Reverse Transcriptase Inhibitors in Antiretroviral-Experienced, HIV-1 Infected Subjects

Coordinating Investigator: Roberto Zajdenverg, MD

Study Sites: 194 investigators in 17 countries (United States [including Puerto Rico], Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Germany, Greece, Ireland, Italy, Mexico, Poland, Portugal, South Africa, Spain, and the United Kingdom). Subjects were enrolled at 120 sites.

Publications: None

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 24 August 2006 Last Subject Last Visit: 12 November 2008	

Objectives: The primary objectives of this study were to compare the safety, tolerability, and antiviral activity of once-daily (QD) and twice-daily (BID) dosing of the lopinavir/ritonavir tablet formulation in subjects with detectable viral load while receiving their current antiretroviral therapy.

The secondary objective of this study was to characterize the development of resistance in QD and BID dosing of the lopinavir/ritonavir tablet in antiretroviral-experienced subjects.

Methodology: This was a Phase 3, randomized, open-label, multicenter, global study designed to demonstrate the safety, tolerability, and antiviral activity of the lopinavir/ritonavir tablet when dosed QD versus BID in combination with investigator-selected nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in the treatment of antiretroviral-experienced, human immunodeficiency virus type 1 (HIV-1) infected subjects.

Approximately 600 subjects meeting inclusion and not meeting exclusion criteria were planned for enrollment in the study at approximately 200 sites. Subjects were randomized in a 1:1 ratio to receive either lopinavir/ritonavir 800/200 mg QD (N = 300) or 400/100 mg BID (N = 300). In addition, all subjects received at least 2 investigator-selected NRTIs optimized for each subject based on prior treatment history and HIV-1 drug resistance genotypic test results at the Screening Visit. The duration of the study was 48 weeks, not including a screening period of up to 30 days.

Subjects meeting the enrollment criteria were randomized on Day –1/Baseline and returned for study visits at Weeks 4, 8, 16, 24, 32, 40, and 48, or premature discontinuation. This report summarizes safety and efficacy data through 48 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 48 weeks.

Number of Subjects (Planned and Analyzed): The planned sample size was 600 subjects, with 300 subjects in each of the lopinavir/ritonavir QD and BID dosing groups. A total of 599 subjects were randomized and received at least 1 dose of lopinavir/ritonavir in combination with at least 2 investigator-selected NRTIs as follows: 300 subjects in the QD group and 299 subjects in the BID group.

Diagnosis and Main Criteria for Inclusion: Subjects were HIV-1 positive, antiretroviral-experienced adults at least 18 years of age. Subjects were currently receiving an antiretroviral regimen that had not changed for at least 12 weeks. Subjects were currently failing their antiretroviral regimen with the most recent 2 consecutive prestudy plasma HIV-1 RNA levels > 400 copies/mL with the most recent being > 1,000 copies/mL, and in the investigator's opinion, should have changed therapy. Female subjects were nonpregnant and nonlactating.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Numbers: Lopinavir/ritonavir was provided as coformulated lopinavir/ritonavir 200/50 mg tablets for oral administration with or without food.

Bulk lot numbers used in the study were 06-007362, 06-007476, 06-008276, 07-010826, and 07-014414.

Duration of Treatment: The duration of treatment was 48 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: None

Criteria for Evaluation

Efficacy: Plasma HIV-1 RNA levels, CD4+ T cell counts

Pharmacokinetic: Lopinavir and ritonavir plasma concentrations

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

Statistical Methods

Efficacy: The efficacy of the QD and BID dosing regimens of the lopinavir/ritonavir tablet was evaluated by assessment of plasma HIV-1 RNA levels and CD4+ T cell counts. The primary efficacy analysis was the proportion of subjects responding at Week 48, based on the FDA time to loss of virologic response (TLOVR) algorithm. The FDA TLOVR algorithm classified a subject as a responder at the first of 2 consecutive plasma HIV-1 RNA levels < 50 copies/mL. The subject continued to be a responder until 2 consecutive values ≥ 50 copies/mL were reached, until the final value if the value was ≥ 50 copies/mL, or until discontinuation or death. Secondary efficacy analyses included the proportion of subjects responding at each visit, the time to loss of virologic response through Week 48, the proportion of subjects with plasma HIV-1 RNA levels < 50 copies/mL at each visit, and the mean change from baseline in HIV-1 RNA level and CD4+ T cell counts at each visit. Additionally, the relationship between baseline genotypic drug resistance and virologic response was assessed and the emergence of new protease mutations was summarized.

Statistical Methods (Continued)

Pharmacokinetic: Exposure-response analyses were conducted to evaluate the relationship between lopinavir pharmacokinetics and antiviral efficacy.

Safety: All randomized subjects who took at least 1 dose of study drug were included in the safety analyses. Adverse events were coded by Abbott personnel using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events were defined as those occurring after study drug initiation and within 30 days after the last dose of study drug.

Treatment-emergent adverse events were summarized for each treatment group with frequencies and percentages by system organ class and preferred term. Each subject was counted no more than once for each preferred term. For analyses by severity, the most severe adverse event for each preferred term was selected for each subject. For analyses by relationship to study drug, the event with the strongest relationship to study drug for each preferred term was selected for each subject.

Fisher's exact test was used to assess the null hypothesis of no difference between the treatment groups for each system organ class and preferred term.

HIV-related treatment-emergent events were coded and summarized separately from other treatment-emergent adverse events.

Clinical laboratory baseline and visit values were summarized with means for each treatment group. At each visit, changes from baseline within treatment groups were summarized with means, standard deviations, and medians. The difference between treatment groups in mean change from baseline was calculated along with the corresponding standard error and 95% confidence interval and was tested for significance using a 1-way analysis of variance (ANOVA) model with treatment group as the only factor. The frequencies and percentages of subjects with very low and with very high hematology and chemistry values were calculated and the percentages were compared between treatment groups using Fisher's exact test.

Analyses of changes from baseline to each visit for each vital sign variable and weight were performed as described for the laboratory data. Very high and very low vital sign and weight criteria were determined, and a listing of values for subjects with very high and very low values was compiled.

Summary/Conclusions

Efficacy Results: The antiviral activity of QD dosing was similar to BID dosing in all analyses. In the primary analysis based on the FDA TLOVR algorithm, the proportions of subjects with plasma HIV-1 RNA levels < 50 copies/mL through Week 48 were 166/300 (55.3%) subjects in the lopinavir/ritonavir QD group and 155/299 (51.8%) subjects in the BID group (intent-to-treat [ITT], TLOVR). The difference (lopinavir/ritonavir QD minus BID) was 3.5% (95% CI: –4.5%, 11.5%). Because the lower limit of the confidence interval is above the prespecified margin of –12%, the lopinavir/ritonavir QD dosing regimen is considered to have noninferior efficacy compared with the BID dosing regimen. Consistent with this observation, the proportion of subjects with plasma HIV-1 RNA levels < 50 copies/mL by other ITT (NC = F, M = F, LOCF) analyses and observed data analysis was similar between groups at each visit.

Efficacy Results (Continued):

The time to loss of virologic response was similar between dosing groups (log-rank $P = 0.673$). The Kaplan-Meier estimate of the percentage of subjects still responding at Day 336 was 64.5% in the lopinavir/ritonavir QD group and 62.6% in the BID group. At Week 48, the mean change from baseline in plasma HIV-1 RNA levels was similar between dosing groups (–2.2 $\log_{10}$ copies/mL for QD and –2.1 $\log_{10}$ copies/mL for BID; $P = 0.606$). The mean increase from baseline in CD4+ T cell counts was also similar between treatment groups (135.3 cells/μL for lopinavir/ritonavir QD and 121.5 cells/μL for BID; $P = 0.281$).

Virologic response rates were lower among subjects with a greater number of protease inhibitor resistance mutations at baseline; however, no meaningful difference between treatment groups was observed in virologic response by number of baseline mutations. Emergence of new primary protease mutations in subjects with inadequate virologic suppression occurred with similar frequency in lopinavir/ritonavir QD- and BID-treated subjects. Virologic response appeared to be less sensitive to the number of prior protease inhibitor-based treatment regimens in subjects receiving lopinavir/ritonavir QD than in subjects receiving lopinavir/ritonavir BID.

Pharmacokinetic Results: Consistent with the Week 48 primary efficacy findings, the exposure-response analysis supports the antiviral efficacy of the lopinavir/ritonavir 800/200 mg QD regimen. The estimated median in vivo drug concentration necessary to inhibit 50% of viral production in vivo (K_{50}) of lopinavir was 0.01 μg/mL (interquartile range: 0.00018 to 0.037 μg/mL), and 90% of the antiretroviral-experienced subjects had in vivo K_{50} values below 0.09 μg/mL. The typical lopinavir C_{trough} values for both QD and BID dosing (3.79 μg/mL and 6.33 μg/mL for QD and BID dosing, respectively, estimated in experienced subjects) are consistently well above the typical in vivo K_{50} values and more than 40-fold above the 90th percentile of K_{50}. Furthermore, prior therapy with protease inhibitor(s) and protease inhibitor mutations at baseline were not predictive of K_{50}. Therefore, based on the exposure-response analysis, lopinavir/ritonavir dosed QD would not likely result in lopinavir concentrations below the K_{50} value and would provide equivalent antiviral efficacy to BID dosing, confirming the primary efficacy analysis.

In addition, based on the logistic regression analysis, lopinavir concentrations do not predict virologic response at Week 48. The proportion of responders was similar above or below a lopinavir C_{trough} cutoff value of 3 μg/mL.

Safety Results: Treatment-emergent adverse events were reported for 86.0% of lopinavir/ritonavir QD-treated subjects (258/300) and 88.6% of BID-treated subjects (265/299) ($P > 0.100$), and, in general, no clinically important differences in the adverse event profile were observed between treatment groups.

Study drug was generally well tolerated with only 34 of the 599 subjects discontinuing therapy due to adverse events: 4.3% (13/300) for the lopinavir/ritonavir QD group and 7.0% (21/299) for the BID group ($P > 0.100$). The most common adverse events leading to discontinuation were gastrointestinal in nature, with diarrhea contributing to discontinuation for 7 (2.3%) lopinavir/ritonavir QD-treated subjects and 6 (2.0%) BID-treated subjects ($P > 0.100$). Discontinuations due to any gastrointestinal adverse events occurred for less than 5.0% of subjects in either treatment group (3.0% lopinavir/ritonavir QD, 4.3% BID) ($P > 0.100$).

The most common adverse events, regardless of severity or relationship to study drug, were gastrointestinal in nature, with diarrhea, nausea, and vomiting being the only adverse events reported by at least 10.0% of subjects in either treatment group. Consistent with the previously described safety profile of lopinavir/ritonavir, the most common adverse event was diarrhea, which was reported with a statistically significantly greater incidence for the lopinavir/ritonavir QD group than the BID group (50.0% QD, 38.8% BID; $P = 0.007$). In contrast, nausea was reported with a greater incidence for the lopinavir/ritonavir BID group (22.4%) than for the QD group (16.3%), although the difference was not statistically significant ($P = 0.063$). The incidence of vomiting was similar between treatment groups (12.3% lopinavir/ritonavir QD, 12.7% BID). All other adverse events were reported for less than 10.0% of subjects in either treatment group, and no statistically significant or clinically important differences between treatment groups were observed in the incidence of these events.

The most common treatment-related adverse events (i.e., considered possibly or probably related to study drug by the investigator) that were at least moderate in severity were diarrhea, which occurred with a similar incidence between treatment groups (14.0% QD, 11.0% BID, $P > 0.100$), and nausea, which occurred with a greater incidence in lopinavir/ritonavir BID- versus QD-treated subjects (2.7% QD, 7.4% BID, $P = 0.009$). The incidence for all other treatment related adverse events that were at least moderate in severity was less than 3.0% for each treatment group, and the differences between treatment groups were not statistically significant.

Serious adverse events were reported for 27 (9.0%) lopinavir/ritonavir QD-treated subjects and 37 (12.4%) BID-treated subjects ($P > 0.100$). Only 5 subjects (3 lopinavir/ritonavir QD, 2 BID) had serious adverse events considered possibly or probably related to study drug by the investigator, including diarrhea for 1 subject (QD), angina pectoris for 1 subject (QD), tricuspid valve incompetence for 1 subject (QD), dehydration for 1 subject (BID), and diarrhea, nausea, and vomiting for 1 subject (BID). Serious adverse events were generally consistent with common comorbidities in HIV-infected subjects and the established safety profile of lopinavir/ritonavir.

Pregnancies were reported for 2 subjects; neither pregnancy went to term. One subject (lopinavir/ritonavir BID) had an elective abortion and 1 subject (lopinavir/ritonavir QD) experienced a spontaneous abortion.

Six subjects (2 lopinavir/ritonavir QD, 4 BID) died during the treatment period or within 30 days after the last dose of study drug. The cause of death was generally attributed to comorbid disease expected in the population studied, with all deaths considered not related or probably not related to study drug per the investigator.

Safety Results (Continued): No clinically important differences between the lopinavir/ritonavir QD and BID groups were observed for clinical laboratory assessments. The mean changes from baseline to Week 48 for these parameters were of similar magnitude to those observed in previous studies of lopinavir/ritonavir in antiretroviral-naïve subjects. Consistent with previous lopinavir/ritonavir studies, very high lipid values (grade 3 or grade 4 elevations) were the most common potentially clinically significant laboratory abnormalities. A similar incidence for the lopinavir/ritonavir QD and BID groups was observed for both cholesterol (6.5% QD, 7.5% BID) and triglycerides (4.8% QD, 6.4% BID). These elevations rarely resulted in study drug discontinuation and none were associated with adverse events of pancreatitis.

The safety and tolerability profile of lopinavir/ritonavir during the 48 weeks of treatment was consistent with that observed in previous studies of lopinavir/ritonavir. The adverse event profile and laboratory abnormalities were similar for both lopinavir/ritonavir treatment groups. Although some differences in rates of specific adverse events were noted in the 2 treatment groups, overall these findings suggest that lopinavir/ritonavir dosed QD or BID is similarly well tolerated.

Conclusions: In summary, the findings from this study show that QD-dosed lopinavir/ritonavir has similar antiviral activity and a similar high genetic barrier to resistance compared with BID-dosed lopinavir/ritonavir in subjects with limited baseline protease resistance. In addition, the study demonstrated both regimens were safe and well tolerated. While some differences in incidence of specific adverse events were noted, the overall character of adverse events and low rates of study drug-related discontinuations, combined with the similar antiviral activity suggest that either QD or BID dosing of lopinavir/ritonavir may be considered for use in antiretroviral-experienced subjects. Lopinavir/ritonavir QD and BID dosing are considered interchangeable in subjects with < 3 protease mutations. In subjects with 3 or more mutations, there is insufficient information to provide guidance on the use of lopinavir/ritonavir dosed QD.

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