2.0 Synopsis

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

Title of Study: A Randomized, Open-label, Study of Lopinavir/ritonavir 400/100 mg Tablet Twice-Daily + Co-formulated Emtricitabine/Tenofovir Disoproxil Fumarate 200/300 mg Once-Daily Versus Lopinavir/ritonavir 400/100 mg Tablet Twice-Daily + Raltegravir 400 mg Twice-Daily in Antiretroviral Naïve, HIV-1 Infected Subjects

Coordinating Investigator: [redacted] MD redacted information 04Sep2014

Study Sites: Thirty-seven study sites in the US, Canada, France, Italy, Poland, Puerto Rico, and Spain participated in the study. Subjects were enrolled at 35 sites.

Publications: None

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 27 June 2008 Last Subject Last Visit: 18 October 2010	

Objectives:

The primary objectives of this study were:

- To compare the safety and tolerability of lopinavir/ritonavir (LPV/r) + emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) with a nucleoside sparing regimen consisting of LPV/r + raltegravir (RAL)
- To compare the antiviral efficacy of LPV/r+FTC/TDF and LPV/r+RAL after 48 weeks of treatment

The secondary objectives of this study were:

- To compare antiviral efficacy of LPV/r+FTC/TDF and LPV/r+RAL at 96 weeks of treatment
- To compare viral decay rates between LPV/r+FTC/TDF and LPV/r+RAL
- To characterize the development of resistance in the 2 treatment groups
- To compare the population pharmacokinetics of lopinavir and ritonavir between the LPV/r+FTC/TDF and LPV/r+RAL regimens
- To compare the effect of LPV/r+FTC/TDF and LPV/r+RAL on metabolic and somatic parameters
- To compare the effect of LPV/r+FTC/TDF and LPV/r+RAL on patient reported outcomes

Methodology:

This was a Phase 3, open-label, randomized, multicenter, multicountry study to evaluate the safety, tolerability, and antiviral activity of LPV/r+RAL compared with LPV/r+FTC/TDF in treatment-naïve, HIV-1 infected subjects.

Approximately 200 subjects meeting inclusion and not meeting exclusion criteria were planned for enrollment in the study at approximately 50 sites. Subjects were randomized in a 1:1 ratio to receive either LPV/r 400/100 mg BID plus a fixed dose combination tablet of FTC/TDF 200/300 mg once daily (QD) (n = 100) or LPV/r 400/100 mg BID plus raltegravir 400 mg BID (n = 100). The duration of the study was planned for 96 weeks, not including a screening period up to 45 days in length.

Subjects meeting the enrollment criteria were randomized on Day –1/Baseline and returned for study visits at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 60, 72, 84, and 96 or at premature discontinuation. This report summarizes safety, efficacy, and patient-reported outcomes data through 96 weeks of treatment. 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 200 subjects, with 100 subjects in each treatment group. A total of 206 subjects were randomized and received at least 1 dose of study drug (LPV/r+RAL [n = 101] or LPV/r+FTC/TDF [n = 105]).

Diagnosis and Main Criteria for Inclusion: Subjects were naïve to antiretroviral (ARV) treatment (< 7 days of any ARV therapy > 30 days prior to study drug administration), had no prior treatment with an HIV-1 integrase inhibitor**,** had plasma HIV-1 RNA level ≥ 1,000 copies/mL at Screening, and in the investigator's opinion required ARV therapy. Female subjects were nonpregnant and nonlactating.

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

LPV/r 200/50 mg tablets + raltegravir 400 mg tablets for oral administration with or without food.

Bulk lot numbers of LPV/r used in the study were [redacted]

Bulk lot numbers of raltegravir used in the study were [redacted]

Duration of Treatment: The duration of treatment was 96 weeks.

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

LPV/r 200/50 mg tablets + FTC/TDF 200/300 mg tablets for oral administration with or without food.

Bulk lot numbers of FTC/TDF used in the study were [redacted]

Criteria for Evaluation

Efficacy: Plasma HIV-1 RNA levels, CD4+ T cell counts, emergence of viral resistance, patient-reported outcomes (Medical Outcomes Study-HIV [MOS-HIV] domain specific total scores, physical component summary [PCS], and mental component summary [MCS]; scale scores of the Treatment Satisfaction Questionnaire for Medication [TSQM]).

Pharmacokinetic: Lopinavir and ritonavir plasma concentrations.

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Criteria for Evaluation (Continued):

Safety: Adverse events, clinical laboratory data, vital signs, somatic toxicity (full-body dual-energy x-ray absorptiometry [DEXA] scan and anthropometric measurements for fat redistribution), and metabolic toxicity (fasted glucose, insulin, total cholesterol, triglycerides, LDL, HDL cholesterol, and exploratory markers [lactate, adiponectin, IL-6, leptin, soluble serum tumor necrosis factor Receptors I and II])

Statistical Methods

Efficacy: The efficacy of the LPV/r+RAL and LPV/r+FTC/TDF treatment regimens 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 < 40 copies/mL. The subject continued to be a responder until 2 consecutive values ≥ 40 copies/mL were reached, or until the final value if the value was ≥ 40 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 and through Week 96, the proportion of subjects with plasma HIV-1 RNA levels < 40 copies/mL at each visit, and the mean change from baseline in CD4+ T-cell counts at each visit. Additionally, the proportion of subjects who developed resistance to each drug in each study regimen and the rate of viral decay in each treatment group were assessed.

Mean change from baseline in each domain score of the MOS-HIV, as well as physical component summary and mental component summary, was analyzed using an analysis of covariance with the change from baseline as the dependent variable and treatment and selected demographic variables as covariates controlling for baseline. For domain specific total scores of the TSQM (Effectiveness, Side Effects, and Global Satisfaction), scores at each visit were analyzed using an analysis of covariance with score as the dependent variable and treatment and selected demographic variables as covariates.

Pharmacokinetic: Individual lopinavir and ritonavir plasma concentrations were tabulated. Population pharmacokinetic analyses were to be performed; however, these analyses were not performed.

Safety: Adverse events (AEs) were coded by Abbott personnel using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.1. Treatment-emergent adverse events were defined as those occurring after study drug initiation and within 30 days after the last dose of study drug. HIV-related treatment-emergent events were coded and summarized separately from other treatment-emergent adverse events. Treatment-emergent adverse events and HIV-related events were summarized through the first 48 weeks and through the entire 96 weeks of the study for each treatment group by System Organ Class (SOC) and Preferred Term (PT). In these analyses, each subject was counted no more than once for each PT and no more than once for each SOC for analyses by SOC. Fisher's exact test was used to assess the null hypothesis of no difference between the treatment groups for each SOC and PT.

Safety (Continued):

Clinical laboratory baseline and visit values were summarized for each treatment group. At each visit, changes from baseline within treatment groups were also summarized. 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 one-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 occurring during the first 48 weeks and during the 96 weeks of the study were both 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 established, and frequencies and percentages of subjects with very low and with very high values occurring during the first 48 weeks and during the 96 weeks of the study were both calculated. Percentages were compared between treatment groups using Fisher's exact test.

Dual-energy x-ray absorptiometry and anthropometric baseline and visit values were summarized for each treatment group. At each visit, percent changes from baseline within treatment groups were also summarized. The differences between treatment groups in mean percent change were calculated along with the corresponding standard error; treatment groups were compared using one-way ANOVA.

Summary/Conclusions:

Efficacy Results: The antiviral activity of the LPV/r+RAL regimen was non-inferior to the antiviral activity of LPV/r+FTC/TDF at Week 48. In the primary analysis based on the FDA TLOVR algorithm, the proportions of subjects with plasma HIV-1 RNA levels < 40 copies/mL through Week 48 were 83.2% and 84.8% in the LPV/r+RAL and LPV/r+FTC/TDF treatment groups, respectively (difference between groups: –1.6%; 95% confidence interval for the difference: -12.08%, 8.8%). The LPV/r+RAL regimen was non-inferior to the LPV/r+FTC/TDF regimen according to the non-inferiority margin of –20%, as well as according to the more stringent margin of –12%, both of which were specified in the protocol. At Week 96, similar proportions of subjects in the 2 treatment groups were categorized as responders based on the FDA TLOVR algorithm: 66.3% and 68.6% in the LPV/r+RAL and LPV/r+FTC/TDF treatment groups, respectively.

Consistent with this observation, the proportions of subjects with plasma HIV-1 RNA levels < 40 copies/mL by other ITT analyses (Noncompleter = Failure, Missing = Failure, last observation carried forward [LOCF]) and observed data analysis were similar between groups at Weeks 48 and 96.

The LPV/r+RAL treatment group exhibited a rapid virologic response; 33.7% of subjects were responders at Week 2 compared with 7.6% of subjects in the LPV/r+FTC/TDF treatment group. Differences between the treatment groups in proportions of responders were statistically significant at Weeks 2, 4, 8, and 16; the proportion of responders was greater in the LPV/r+RAL treatment group at each of those time points.

The time to loss of virologic response was similar between treatment groups (log rank $P = 0.916$). The Kaplan-Meier estimate of the percentage of subjects still responding at Day 672 was 77.8% in the LPV/r+RAL group and 79.1% in the LPV/r+FTC/TDF group.

Summary/Conclusions:

Efficacy Results (Continued):

Mean increases in baseline in CD4+ T-cell counts within both treatment groups were statistically significant ($P < 0.001$) at all measurement time points, and mean increases were similar for both treatment groups throughout the 96-week treatment period. At Week 48, the mean change from baseline in CD4+ T-cell counts was +241.9 cells/µL for the LPV/r+RAL group and +245.0 cells/µL for the LPV/r+TDF/FTC group ($P = 0.237$). At Week 96, the mean change from baseline in CD4+ T-cell counts was +281.0 cells/µL for the LPV/r+RAL group and +296.4 cells/µL for the LPV/r+TDF/FTC group ($P = 0.598$).

Through Week 96 (starting at Week 12), 13 subjects (8 in the LPV/r+RAL and 5 in the LPV/r+FTC/TDF treatment groups, respectively) met the protocol-defined criteria for resistance testing. Of these subjects, no subject in either treatment group developed lopinavir resistance using the IAS-USA panel criteria. Using the more conservative criteria, 1 of 8 subjects in the LPV/r+RAL treatment group developed lopinavir resistance. Three of 8 subjects in the LPV/r+RAL treatment group developed resistance to raltegravir, and 1 of 5 subjects in the LPV/r+FTC/TDF treatment group developed resistance to emtricitabine, using the IAS USA Panel criteria. The subject who developed lopinavir resistance using the more conservative method also developed resistance to raltegravir and is included in the 3 of 8 noted above; in this instance, RAL resistance emerged at Week 16 followed by an extended period of low-level viremia (HIV RNA ≤ 533 copies/mL). A lopinavir-associated resistance mutation (M46I) emerged at Week 72, and lopinavir resistance emerged at Week 96.

The rates of viral decay from Week 2 through Week 16 were similar between treatment groups ($P = 0.108$).

Results of the MOS-HIV quality of life and TQSM analysis showed that although improvement in a number of quality of life attributes was observed at Week 48 and continued to Week 96, there were no statistically significant differences between the treatment groups.

Pharmacokinetic Results: Exposure-response analyses were not conducted, based on the results obtained in this study, which showed similar safety and efficacy of the LPV/r+RAL regimen relative to the LPV/r+FTC/TDF regimen.

Safety Results:

Through Week 48, 95% of subjects in each treatment group experienced 1 or more treatment-emergent AEs; through Week 96, 2 additional subjects in the LPV/r+RAL treatment group and no additional subjects in the LPV/r+FTC/TDF treatment group experienced AEs. Study drug was generally well tolerated; only 5 subjects (5.0%) in the LPV/r+RAL treatment group, and 4 subjects (3.8%) in the LPV/r+FTC/TDF treatment group discontinued due to AEs.

Similar proportions of subjects in the 2 treatment groups experienced any AE at least possibly drug-related (as assessed by the investigator), any moderate or severe AE at least possibly drug-related (as assessed by the investigator), any severe AE, any SAE, any AE leading to interruption of study drug, and any AE leading to antiretroviral dose change.

Safety Results (Continued):

Gastrointestinal disorders were the most frequently reported treatment-emergent AEs through 96 weeks of treatment, particularly diarrhoea (LPV/r+RAL, 62 subjects [61.4%]; LPV/r+FTC/TDF, 64 subjects [61.0%]) and nausea (LPV/r+RAL, 13 subjects [12.9%]; LPV/r+FTC/TDF, 20 subjects [19.0%]). Other gastrointestinal events reported for ≥ 10% of subjects were vomiting, flatulence, and abdominal pain. Bronchitis, nasopharyngitis, upper respiratory tract infection, hypercholesterolaemia, headache, and depression also were reported for ≥ 10% of subjects in one or both groups. A statistically significantly greater proportion of subjects in the LPV/r+RAL treatment group (15.8%; 16 subjects) experienced hypertriglyceridaemia compared with subjects in the LPV/r+FTC/TDF treatment group (5.7%; 6 subjects).

Moderate or severe treatment-related adverse events were reported for 30.7% and 34.3% of subjects in the LPV/r+RAL and LPV/r+FTC/TDF treatment groups, respectively. Diarrhoea was reported more frequently for subjects in the LPV/r+FTC/TDF treatment group (17 subjects; 16.2%) compared with the LPV/r+RAL treatment group (8 subjects; 7.9%), although the difference was not statistically significant. A statistically significantly greater proportion of subjects in the LPV/r+FTC/TDF treatment group (22 subjects; 21.0%) experienced 1 or more treatment-related moderate or severe gastrointestinal AEs (primarily diarrhoea, and also regurgitation, and abdominal distension) compared with subjects in the LPV/r+RAL treatment group (10 subjects; 9.9%).

HIV-related events were reported for similar proportions of subjects in the LPV/r+RAL (10.9%) and LPV/r+FTC/TDF (9.5%) treatment groups.

Two subjects died during the study or within the 30-day follow-up. One subject in the LPV/r+RAL treatment group experienced a series of AEs that culminated in sepsis and death. The sepsis was attributed to Klebsiella infection and was assessed by the investigator as not related to study drug. The other subject, also in the LPV/r+RAL treatment group, died of a subarachnoid haemorrhage attributed to an AE of viral encephalitis; these AEs were assessed by the investigator as not related to study drug.

Through Week 96, treatment-emergent SAEs were reported for 12 subjects (11.9%) in the LPV/r+RAL treatment group and 14 subjects (13.3%) in the LPV/r+FTC/TDF treatment group. Serious infections were reported for 8 subjects (7.9%) in the LPV/r+RAL treatment group and 9 subjects (8.6%) in the LPV/r+FTC/TDF treatment group. In addition, 2 serious HIV-related events were reported: herpes zoster in a subject in the LPV/r+RAL treatment group and cervical dysplasia in a subject in the LPV/r+FTC/TDF treatment group.

Safety Results (Continued):

No AEs of non-infectious hepatitis or acute pancreatitis were identified using the Standardized MedDRA Queries (SMQs). One subject in the LPV/r+RAL treatment group and 1 subject in the LPV/r+FTC/TDF treatment group were identified by the SMQ for hyperglycaemia or new onset diabetes mellitus AEs that were considered relevant with regard to study drug, i.e., these subjects did not have a history of diabetes or hyperglycaemia. Three subjects in the LPV/r+RAL treatment group and 2 subjects in the LPV/r+FTC/TDF treatment group were identified by the SMQ for lipodystrophy; all were considered relevant. Four of the subjects were reported to have the PT: acquired lipodystrophy, and 1 subject was reported to have the PT: facial wasting. Four events were assessed by the investigator as mild in severity, and one was assessed as moderate.

Analyses of changes from baseline in clinical laboratory measurements demonstrated statistically significant differences between treatment groups for alkaline phosphatase at all measurement time points, with larger mean increases in the LPV/r+FTC/TDF treatment group. Statistically significant differences between treatment groups in mean changes from baseline were observed for creatinine at Weeks 4, 8, 16, 32, 84, and 96 and in calculated creatinine clearance at Weeks 72, 84, and 96; the LPV/r+FTC/TDF treatment group had larger mean increases in creatinine and larger mean decreases in calculated creatinine clearance values compared with the LPV/r+RAL treatment group. These differences were not reflected in differences between groups in renal and urinary disorders AEs. Nine (8.9%) and 11 (10.5%) subjects in the LPV/r+RAL and LPV/r+FTC/TDF treatment groups, respectively, experienced renal and urinary disorders events. One subject in each treatment group experienced renal failure.

Statistically significant differences between treatment groups in mean changes from baseline were observed for cholesterol at all time points from Week 4 to Week 84; mean increases for the LPV/r+RAL treatment group were larger than those for the LPV/r+FTC/TDF treatment group. Statistically significant differences between treatment groups in mean changes from baseline were observed for HDL cholesterol at Weeks 4, 8, 40, 48, 72, and 84 and for triglycerides at Weeks 8, 24, 32, 40, and 48.

The mean changes in vital signs from baseline were generally small and similar between the treatment groups for all parameters.

No statistically significant differences between groups were observed in mean percent changes from baseline for any anthropometric measurement. At Week 96, the LPV/r+RAL treatment group exhibited statistically significant within-group mean percent increases in chest, waist, hip, mid-arm, and mid-thigh measurements. Through Week 96, the LPV/r+RAL treatment group exhibited statistically significantly greater mean percent increases in upper extremity fat and lower extremity fat compared with the mean percent changes from baseline in the LPV/r+FTC/TDF treatment group.

At Week 96, the LPV/r+RAL treatment group exhibited a mean percent increase from baseline in bone mineral content compared with a mean percent decrease in the LPV/r+FTC/TDF treatment group. At Weeks 48 and 96, the LPV/r+RAL treatment group exhibited mean percent increases from baseline in bone mineral density compared with mean percent decreases in the LPV/r+FTC/TDF treatment group; these differences were statistically significant.

One pregnancy was reported in the study in a subject in the LPV/r+FTC/TDF treatment group; it resulted in a live birth. No medically significant complications occurred during pregnancy or labor and delivery, and no birth defects were noted.

Conclusions:

This study shows that an LPV/r+RAL treatment regimen has similar antiviral efficacy to a regimen of LPV/r+FTC/TDF. One subject in the LPV/r+RAL treatment group developed resistance to LPV/r after an extended period of functional monotherapy. In addition, the study demonstrated that an LPV/r+RAL treatment regimen was safe and well tolerated. The LPV/r+RAL regimen was associated with more frequent mean increases from baseline in lipid parameters. However, the regimen also resulted in improved bone mineral density/content on average compared with LPV/r + FTC/TDF.