2.0 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 Randomized, Open-Label Study Assessing Safety, Tolerability, Efficacy, and Metabolic Effects of a Simplified Lopinavir/Ritonavir-Based Induction/Maintenance Therapy in Antiretroviral-Naïve HIV-Infected Subjects

Coordinating Investigator: [redacted] MD redacted information 30Sep2014

Study Sites: Thirty-three (33) investigators in 5 countries (USA, Canada, United Kingdom, France and Spain)

Publications: Four (4) abstracts

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 12 January 2004 Last Subject Last Visit: 01 June 2006	

Objectives:

The primary objectives of this study were to:

- Assess the safety, tolerability, and antiviral activity of the following treatment strategies:
  - PI Induction/Maintenance: Induction therapy with lopinavir/ritonavir twice daily (BID) + Combivir® (lamivudine [3TC], zidovudine [AZT]) BID followed by maintenance therapy with lopinavir/ritonavir BID monotherapy
  - RTI only regimen: efavirenz (EFV) once daily (QD) + 3TC/AZT BID
- Assess the metabolic effects and morphologic changes associated with the treatment strategies.

The secondary objectives of this study were to:

- Characterize the development of resistance to the antiretroviral (ARV) study drugs.
- Evaluate the effect of demographic and baseline disease characteristics on the duration of antiviral response.

Methodology:

Study M03-613 was a Phase 2, randomized, open-label, multicenter study in ARV-naïve, HIV-infected adults designed to assess the safety, tolerability, antiviral activity, and metabolic effects of a protease inhibitor (PI) induction/maintenance regimen and an RTI only regimen. The planned duration of this study was at least 96 weeks.

Methodology (Continued):

Approximately 150 subjects meeting the selection criteria were to be enrolled in the study at approximately 40 sites across the U.S., Canada, and Europe. Subjects were randomized to either the PI induction/maintenance regimen or the RTI regimen in a 2:1 ratio as follows:

- Induction with lopinavir/ritonavir 400 mg/100 mg BID + 3TC/AZT 150 mg/300 mg BID followed by maintenance with lopinavir/ritonavir 400 mg/100 mg BID monotherapy (N=100)
- EFV 600 mg QD + 3TC/AZT 150 mg/300 mg BID (N=50)

Subjects meeting the selection criteria were randomized on the Day -1 baseline visit and returned for study visits on Day 7, Week 4, every 4 weeks through Week 72, followed by every 8 weeks through Week 96.

Subjects randomized to PI induction/maintenance initiated treatment with the standard dose of lopinavir/ritonavir in combination with the standard dose of 3TC/AZT. During the induction phase, subjects who achieved HIV-1 RNA values below 50 copies/mL on 3 consecutive study visits between Weeks 12 and 44 (inclusive) discontinued taking 3TC/AZT at their next study visit and remained on lopinavir/ritonavir BID monotherapy through study completion/discontinuation. Subjects who failed to achieve 3 consecutive HIV-1 RNA measurements < 50 copies/mL between Weeks 12 and 44 (inclusive) continued treatment with lopinavir/ritonavir plus 3TC/AZT through study completion/discontinuation. Subjects randomized to the RTI regimen remained on EFV in combination with 3TC/AZT throughout the study.

Number of Subjects (Planned and Analyzed):

Approximately 150 subjects were to be enrolled in this study; 100 subjects in lopinavir/ritonavir + 3TC/AZT followed by maintenance with lopinavir/ritonavir monotherapy and 50 subjects in EFV + 3TC/AZT. A total of 104 subjects were randomized and treated in the lopinavir/ritonavir + 3TC/AZT group and a total of 51 subjects were randomized and treated in the EFV + 3TC/AZT group.

Diagnosis and Main Criteria for Inclusion:

HIV-1-positive, antiretroviral-naive adult males and non-pregnant, non-lactating females (< 7 days of any ARV treatment) at least 18-years-old with plasma HIV-1 RNA > 5000 copies/mL at Screening, who were not acutely ill.

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

Lopinavir/ritonavir was provided as co-formulated 133.3 mg lopinavir/33.3 mg ritonavir soft gel capsules. Three capsules of lopinavir/ritonavir (400 mg/100 mg) were taken BID orally with food. Lot Numbers: [redacted]

Duration of Treatment:

96 weeks

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

Efavirenz was provided as 600 mg tablets. One tablet of EFV was taken QD orally on an empty stomach, preferably at bedtime to lessen some side effects. Lot Numbers: [redacted]

Combivir was provided as co-formulated 150 mg lamivudine(3TC)/300 mg zidovudine (AZT) tablets. One tablet of 3TC/AZT was taken BID orally with or without food. Lot Numbers: [redacted] redacted information 30Sep2014

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects with a plasma HIV-1 TNSA lrbrl < 50 copies/mL at Week 96.

Secondary efficacy variables included the time-to-loss of virologic response through Week 96, time-to-loss of virologic response from initiation of maintenance therapy through Week 96, proportion of subjects with HIV-1, RNA levels < 50 copies/mL at each visit, mean change from baseline to each visit in HIV-1 RNA level and CD4 cell count, and emergency of viral resistance.

Safety:

Adverse events, clinical laboratory determinations, vital signs, and DEXA scan data were summarized.

Statistical Methods

Efficacy:

The primary efficacy variable was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96 using an Intent-to-Treat (ITT) previous failure=failure analysis in which subjects with confirmed virologic rebounds > 50 copies/mL were considered nonresponders at all subsequent timepoints. Other analysis methods included an ITT noncompleter=failure method, in which missing values were considered to be > 50 copies/mL unless the immediately preceding and immediately following values were < 50 copies/mL, an ITT missing=failure method, in which all missing values were considered failures, an ITT last observation carried forward method, and an observed data method. In all analyses, discontinuation or switch of the primary drug (lopinavir/ritonavir or EFV) was considered virologic failure. Comparisons between treatment arms were performed using Fisher's exact test.

Loss of virologic response was defined as a confirmed virologic rebound above 50 copies/mL or failure to achieve HIV-1 RNA < 50 copies/mL on 3 consecutive visits. The time-to-loss of virologic response from baseline through Week 96 and from the beginning of maintenance therapy through Week 96 was summarized using a Kaplan-Meier procedure within each treatment arm. The Cox proportional hazards model or log-rank test was used to assess differences between treatment arms.

The mean change from baseline to each visit in CD4 cell count was compared between groups using a one-way analysis of variance.

Resistance to lopinavir was defined as the emergence of any mutation in the protease gene leading to an amino acid substitution at the following loci: 8, 30, 32, 46, 47, 48, 50, 54, 82, 84, or 90, or the emergence of 3 or more mutations, not present at Screening, at the following loci: 10, 20, 24, 36, 53, 63, or 71, and a change in lopinavir phenotypic resistance of > 2.5 fold. Resistance to 3TC, AZT, and EFV was defined by [redacted] TRUGENE™ HIV-1 Guidelines Rules™. redacted information 30Sep2014

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 and HIV-related events were coded and summarized separately. All adverse events were coded according to the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) V dictionary 5th Edition. The proportion of subjects reporting treatment-emergent adverse events was summarized within each treatment arm by severity and relationship to study drug. Fisher's exact test was used to compare the overall incidence rates between the 2 treatment arms.

Safety:

The mean change from baseline to each visit in clinical laboratory determinations, vital signs, and metabolic toxicities (including oral glucose tolerance and DEXA scans) was summarized and compared between treatment arms. A one-way analysis of variance was used to compare treatment arms.

Subjects with extremely high or extremely low clinical laboratory determinations were individually identified. All clinical laboratory and vital sign determinations obtained within 30 days of the last dose of study drug were included in the preceding analyses.

Summary/Conclusions

Efficacy Results:

A majority of subjects in both the lopinavir/ritonavir BID + 3TC/AZT and EFV QD + 3TC/AZT groups achieved plasma HIV-1 RNA levels below the LOQ of 50 copies/mL at every visit after Week 8. Statistically significant differences in the number of subjects achieving HIV-1 RNA < 50 copies/mL in favor of the EFV QD + 3TC/AZT group were observed, primarily in the on-treatment analyses, at various visits. The primary efficacy variable of the study was the proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 96, based on an ITT (PF=F) analysis in which subjects with confirmed virologic rebound at any time during the study were considered non-responders even if they demonstrated plasma HIV-1 RNA < 50 copies/mL at subsequent visits. Based on this analysis, at Week 96, 48% of subjects in the lopinavir/ritonavir BID + 3TC/AZT group and 61% of subjects in the EFV QD + 3TC/AZT group achieved plasma HIV-1 RNA < 50 copies/mL ($p = 0.171$ for the difference between groups). Based on the ITT (NC=F) analysis, in which prior virologic rebounds are ignored, Week 96 response rates were more similar (60% for the lopinavir/ritonavir BID + 3TC/AZT group and 63% for the EFV QD + 3TC/AZT group, $p = 0.730$).

The time-to-loss of virologic response > 50 copies/mL was statistically significantly shorter in the lopinavir/ritonavir BID + 3TC/AZT group compared to the EFV QD + 3TC/AZT group. The Kaplan-Meier estimate of the proportion of subjects still responding at Week 96 was 0.548 in the lopinavir/ritonavir BID + 3TC/AZT group and 0.787 in the EFV QD + 3TC/AZT group. In contrast, a post hoc analysis using a threshold of 500 copies/mL instead of 50 copies/mL, the time-to-loss of virologic response was no longer statistically significantly different between groups.

The time from the beginning of maintenance therapy to loss of virologic response > 50 copies/mL was also statistically significantly shorter in lopinavir/ritonavir BID maintenance subjects compared with EFV QD + 3TC/AZT subjects who had also achieved confirmed HIV-1 RNA < 50 copies/mL. The Kaplan-Meier estimate of the proportion of subjects still responding 72 weeks after the start of maintenance therapy was 0.565 in the lopinavir/ritonavir BID maintenance group. The corresponding estimate for the EFV QD + 3TC/AZT group after 72 weeks was 0.906. However, in a post hoc analysis using a threshold of 500 copies/mL, the time-to-loss of virologic response was no longer statistically significantly different between groups. Overall, these analyses of time-to-loss of virologic response demonstrate that, while a large proportion of subjects in both treatment groups continuously maintained HIV-1 RNA levels < 50 copies/mL, more subjects in the lopinavir/ritonavir BID group (the majority of whom were receiving lopinavir/ritonavir monotherapy) had loss of virologic response characterized by HIV-1 RNA levels between 50 and 500 copies/mL.

Efficacy Results (Continued):

Statistically significant ($p < 0.001$) increases in mean CD4 cell count were observed in both the lopinavir/ritonavir BID + 3TC/AZT and EFV QD + 3TC/AZT groups at all visits. The mean changes from baseline in the lopinavir/ritonavir BID + 3TC/AZT and EFV QD + 3TC/AZT groups were 287 cells/μL and 235 cells/μL, respectively, at Week 96 ($p = 0.093$ for the difference between groups).

Viral isolates from 4 lopinavir/ritonavir BID + 3TC/AZT treated subjects (3 on monotherapy and 1 on triple therapy) who experienced virologic failure demonstrated PI resistance mutations not present at screening. Of note, retrospective analysis of baseline isolates in two of these subjects (both receiving monotherapy), suggested at least some of the PI resistance mutations identified in the rebound isolates were present at study baseline, but not identified in the population sequences performed at that time. Of the 5 EFV QD + 3TC/AZT treated subjects with virologic failure, all of whom had genotype results available, viral isolates from one demonstrated EFV resistance.

In summary, this study demonstrated that a lopinavir/ritonavir deintensification strategy in ARV-naïve subjects provides durable viral suppression in many subjects. However, compared to an EFV-based regimen, there is an increased risk of detectable low-level viremia. Although the number of subjects treated with lopinavir/ritonavir BID maintenance who developed PI resistance mutations in this study was small, rates of occurrence did appear somewhat higher than observed in prior studies of lopinavir/ritonavir administered with NRTIs, and may be directly related to use as monotherapy in treatment of HIV-1 infection.

Safety Results:

A total of 101 (97%) subjects receiving lopinavir/ritonavir BID + 3TC/AZT and 51 (100%) subjects receiving EFV QD + 3TC/AZT reported 1 or more treatment-emergent adverse events during the study.

The majority of the adverse events reported during the study were related to the body as a whole and digestive system. A statistically significantly greater proportion of subjects in the lopinavir/ritonavir BID + 3TC/AZT group compared to the EFV QD + 3TC/AZT group experienced diarrhea, hyperlipemia, and rectal disorder (the majority of these events being hemorrhoids and assessed as not related to lopinavir/ritonavir BID + 3TC/AZT). Conversely, a statistically significantly greater proportion of subjects in the EFV QD + 3TC/AZT group compared to the lopinavir/ritonavir BID + 3TC/AZT group experienced dizziness, rash, abnormal dreams, and neuropathy. A similar pattern was observed among adverse events of moderate or greater severity and possible or probable relationship to study medication.

Serious adverse events were reported with similar frequency in the 2 treatment groups with all serious adverse events considered not related or probably not related to study medication by the investigator. The three deaths occurring in study subjects were attributed to cardiac arrest, complication of ethylene glycol ingestion with renal failure with coma, and Burkett's lymphoma.

Safety Results (Continued):

Several other significant adverse events were reported in this study. These included two adverse events of hepatitis; both events were attributed to the new onset of hepatitis C in previously hepatitis C negative subjects. Five additional subjects (4 lopinavir/ritonavir and one EFV-treated subject) experienced very high hepatitic transaminase levels not reported as adverse events of hepatitis. In all these subjects, hepatic transaminase levels return to baseline or normal levels without study drug discontinuation. In addition, eight subjects (4 lopinavir/ritonavir and 4 EFV-treated subject) experienced very high amylase levels during the study. In all these subjects, values returned to baseline or normal levels without study drug discontinuation. None were associated with adverse events of pancreatitis. Lastly, 1 subject with an abnormal baseline lactate was randomized to lopinavir/ritonavir + 3TC/AZT and experienced a further elevation of lactate. The lactate level decreased to normal after the subject deintensified to lopinavir/ritonavir maintenance therapy.

Overall, the adverse events reported in this study were consistent with the known safety profiles of lopinavir/ritonavir and EFV. While some differences between treatment groups in character of adverse events was observed, therapy was generally well tolerated as reflected in the low rates of study drug related discontinuations; only three (2%) subjects discontinued study drug due to an adverse event.

For each treatment group, statistically significant mean changes from baseline were noted for several hematology variables; however, these changes were either not clinically significant or reflected improved health generally observed in response to successful antiretroviral therapy. With the exception of lipid elevations, statistically significant mean changes from baseline in chemistry variables were also not considered of clinical significance. Statistically significant increases in mean cholesterol, HDL cholesterol, and LDL cholesterol from baseline to Week 96 occurred in both treatment groups. Of note, the magnitude of increase for each of these variables was similar in the two treatment groups with mean cholesterol in the lopinavir/ritonavir BID + 3TC/AZT and EFV QD + 3TC/AZT groups increasing 57.7 mg/dL and 41.53 mg/dL respectively between baseline and Week 96. While the magnitude of change in mean cholesterol was similar in the two treatment groups, more lopinavir/ritonavir- than EFV-treated subjects experienced very high cholesterol values (13% vs. 4%, respectively), suggesting lipid elevations in the lopinavir/ritonavir treatment groups may have been more variable. In addition, the character of LDL elevations was different in the two treatment groups, with lopinavir/ritonavir BID +3TC/AZT-treated subjects having greater increases in small particle LDL. The clinical significance of these observation are unknown. Mean increases in triglycerides between baseline and Week 96 were also statistically significant in both treatment groups, although the magnitude of increase was marginally significantly greater in the lopinavir/ritonavir BID +3TC/AZT vs. EFV QD + 3TC/AZT groups (91.02 mg/dL vs. 42.96 mg/dL, respectively p=0.059). This study was not designed to fully assess use of lipid lowering therapy, but based on an overall assessment of concomitant drug use, more subjects in the lopinavir/ritonavir group were started on a lipid lowering agent compared to the EFV group (p=0.013). There were no adverse events of MI or angina in this study.

Safety Results (Continued):

Several metabolic parameters of interest were analyzed and compared between treatment groups including lipid parameters, oral glucose tolerance tests, and body fat changes as assessed by DEXA scan. As noted above, increases in total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were noted in both treatment groups. These changes were not impacted by discontinuation of NRTIs in those subjects who were maintained on lopinavir/ritonavir BID maintenance therapy, based on a comparison of Week 24 and Week 96 lipid values. Evaluation of the 2 hour average change in glucose and insulin during an oral glucose tolerance test suggested glucose tolerance was not adversely affected by either treatment regimen through 96 weeks of therapy. Body fat changes were assessed by DEXA scan and showed that, although trunk fat increased in both treatment groups through 96 weeks, limb fat loss was significantly spared in the lopinavir/ritonavir BID + 3TC/AZT group compared to the EFV QD + 3TC/AZT group. Thus, although some metabolic abnormalities persisted after withdrawal of NRTIs in the lopinavir/ritonavir group, an induction-maintenance strategy did result in sparing of limb fat loss compared to a regimen of EFV coadministered with 3TC/AZT. It should be noted that these changes in body fat are not reflected in the reporting of adverse events of body fat composition, as there was only one report of lipoatrophy (EFV-treatment group). This may reflect the sensitivity with which DEXA scan can identify body fat composition changes as compared to visual inspection, or the relatively short duration of follow up in this study. In addition, no significant differences between groups were observed in changes from baseline in PBMC mtDNA, a finding consistent with data which indicates that PBMC mtDNA may be a relatively insensitive method for monitoring of peripheral fat loss.

In conclusion, lopinavir/ritonavir BID + 3TC/AZT and EFV QD + 3TC/AZT were both generally well tolerated as reflected by low rates of study drug –related discontinuations. Adverse events and laboratory abnormalities observed with both regimens were fully consistent with prior studies.

Conclusions:

While an induction-maintenance strategy using lopinavir/ritonavir maintains continuous HIV-1 viral load suppression in a large proportion of subjects, the risk of low level viremia appears increased when compared to a standard triple drug HAART regimen. In addition, the emergence of protease mutations in several lopinavir/ritonavir-treated subjects suggests the risk of developing resistance may be increased compared to standard therapy. The lopinavir/ritonavir deintensification strategy did, however result in demonstrable metabolic benefit as reflected in body fat composition when compared to an EFV based standard HAART treatment regimen. These considerations must be carefully considered in assessing the future role of deintensification strategies in treatment of HIV-1 infection.