2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Item of the Submission:**	**(For National Authority Use Only)**
Name of Study Drug: Kaletra®	**Volume: N/A**	
Name of Active Ingredient: Lopinavir/ritonavir	**Page: N/A**	

Title of Study: A Phase 2 Study of Lopinavir/ritonavir in Combination with Saquinavir Mesylate or Lamivudine/Zidovudine to Explore Metabolic Toxicities in Antiretroviral HIV-1 Infected Subjects

Coordinating Investigator: [redacted] M.D. redacted information 30Sep2014

Study Sites: Multi-center; 1 site in Canada and 5 sites in the U.S.

Publications: 2 posters

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 07 January 2003 Last Subject Last Visit: 08 April 2005	

Objectives:

- Explored the metabolic toxicities associated with lopinavir/ritonavir (Kaletra® or LPV/r) plus saquinavir mesylate (Invirase® or SQV) *vs.* LPV/r plus lamivudine/zidovudine (Combivir® or 3TC/ZDV) in antiretroviral-naïve subjects.
- Assessed the overall safety, tolerability and efficacy of LPV/r plus SQV *vs.* LPV/r plus 3TC/ZDV in antiretroviral-naïve subjects.
- Assessed the pharmacokinetics of 400 mg SQV BID, 600 mg SQV BID and 800 mg SQV BID in combination with LPV/r 400/100 mg plus 3TC/ZDV 150/300 mg BID.

Methodology:

This was a Phase 2, open-label, randomized, multiple-center study design to explore the metabolic toxicities, overall safety, tolerability and efficacy associated with LPV/r plus SQV *vs.* LPV/r plus 3TC/ZDV in antiretroviral-naïve subjects.

Thirty (30) subjects meeting the inclusion and exclusion criteria were enrolled in the study at six sites. Subjects were randomized (1:1) to receive LPV/r 400/100 mg BID plus 800 mg SQV BID or LPV/r 400/100 mg BID plus 3TC/ZDV 150/300 mg BID.

Number of Subjects (Planned and Analyzed): Approximately 30 subjects planned; 35 subjects were screened; 30 subjects received study drug and were included in the analyses. A total of 10 subjects prematurely discontinued from the study.

Diagnosis and Main Criteria for Inclusion: HIV-1 infected males who were at least 18 years of age, had less than 7 days of antiretroviral treatment and met all other selection criteria specified in the protocol were eligible for study participation.

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

Test Product: Lopinavir/ritonavir (Kaletra)
Dose: 133.3 mg lopinavir/33.3 mg ritonavir soft gel capsules
Mode of Administration: Oral

Test Product: Lopinavir/ritonavir placebo
Dose: Not applicable
Mode of Administration: Oral

Test Product: Saquinavir mesylate (Invirase)
Dose: 200 mg capsules
Mode of administration: Oral

Test Product: Lamivudine/zidovudine (Combivir)
Dose: 150 mg lamivudine/300 mg zidovudine tablets
Mode of Administration: Oral

Duration of Treatment: 96 weeks planned; however, study was closed after the last subject reached Week 48.

Reference Therapy, Dose and Mode of Administration, Lot Number: The reference therapy for this study was LPV/r 400/100 mg BID plus 3TC/ZDV 150/300 mg BID.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the proportion of subjects with plasma HIV-1 RNA levels below 50 copies/mL at Week 48.

Secondary efficacy variables included:

- Time to loss of virologic response through Week 48.
- Proportion of subjects with HIV-1 RNA levels below 50 copies/mL at each visit.
- Mean change from baseline to each visit in HIV-1 RNA level and CD4 cell count.

The analysis of the primary efficacy variable is discussed, but only clinically meaningful secondary analyses were discussed in this abbreviated report.

Safety:

Medical history, physical exam, vital signs, electrocardiogram (ECG), clinical laboratory testing and adverse event monitoring were assessed throughout the study. Exploratory tests were performed including assays for mitochondrial DNA levels and insulin resistance to monitor the development of metabolic toxicities and dual-energy x-ray absorptiometry (DEXA) scans to evaluate the changes in body fat composition. Only the relevant exploratory tests were discussed in detail in this abbreviated report.

Summary/Conclusions:

Efficacy Results: This study was conducted as a pilot study and was not powered to detect a difference in efficacy between treatment groups. No statistically significant differences in the intent-to-treat (ITT) analyses or the observed data analysis were observed for the proportion of subjects with HIV-1 RNA levels < 50 copies/mL at Weeks 24 or 48. In the ITT (M=F) analysis at Week 48, 10/16 (63%) SQV-treated subjects and 7/14 (50%) 3TC/ZDV-treated subjects achieved HIV-1 RNA < 50 copies/mL ($p = 0.713$). In analysis of observed data, at Week 48, 10/13 (77%) SQV-treated subjects and 7/9 (78%) 3TC/ZDV-treated subjects achieved HIV-1 RNA < 50 copies/mL ($p > 0.999$). In addition, a Kaplan-Meier analysis of the time to loss of virologic response indicated no statistically significant differences between treatment groups using the Cox proportional hazards model.

Analysis of CD4 cell counts indicated that subjects in both treatment groups demonstrated statistically significant increases from baseline detected at all visits after Week 4. No statistically significant difference was observed between treatment groups for the mean change from baseline in CD4 cell count. Through Week 48, mean change from baseline in the SQV and 3TC/ZDV treatment groups of 141 cells/μL and 187 cells/μL, respectively, were noted.

Safety Results: All subjects experienced at least one adverse event while on study. The majority of these adverse events were considered by the investigator to be mild in severity and did not result in study discontinuation or dose interruptions of study medications. No statistically significant differences between treatment groups in frequency of specific adverse events of any severity or relationship to study drug was noted. Similarly, no statistically significant difference in the overall incidence of adverse events or specific adverse events of at least moderate severity and possible or probable relationship to any study medication was observed between the two treatment groups.

The most common adverse events were digestive system events with 28 of 30 subjects experiencing at least one such event. The most frequent digestive system adverse events of any severity or relationship to study drug in the SQV and 3TC/ZDV treatment groups were, respectively, diarrhea (8/16 [50%] and 9/14 [64%]) nausea (5/16 [31%] and 7/14 [50%]) and vomiting (4/16 [25%] and 5/14 [36%]). Although these adverse events were relatively common, only four subjects (two in each treatment group) discontinued therapy due to adverse events of the digestive system. No statistically significant differences between treatment groups in the overall incidence of these adverse events, or specific adverse events of the digestive system were noted.

Four subjects, all in the SQV treatment group, experienced serious adverse events during the study. In one of these reports, all events were considered not related by the investigator. Two additional subjects experienced serious adverse events primarily of the digestive system that were considered by the investigator to be probably not related or possibly related to study drug. The remaining subject experienced a serious adverse event of syncope in the setting of alcohol ingestion and dehydration that was considered by the investigator to be not related to study drug.

Overall, five subjects experienced adverse events leading to permanent discontinuation of study medications. Four (two SQV and two 3TC/ZDV) of these five noted a variety of adverse events of the digestive system as noted above. The remaining subject, treated with 3TC/ZDV, discontinued study medications in the setting of Grade 4 AST and ALT elevations and positive hepatitis C antibody.

Safety Results: (Continued)

No difference between treatment groups in the frequency of adverse events meeting protocol-defined body fat composition changes was noted, with one such event occurring in each treatment group. One SQV-treated subject noted weight gain of the midsection and one 3TC/ZDV-treated subject experienced asymmetric bilateral gynecomastia. Both events were considered by the investigator to be mild in severity and possibly or probably related to LPV/r. Metabolic and nutritional disorders adverse events were noted more frequently in the SQV *vs.* 3TC/ZDV treatment groups (7/16 [44%] *vs.* 2/14 [14%], respectively, p = 0.118). However, no pattern to these adverse events was identified. Of the metabolic and nutritional disorder adverse events, weight loss and hypokalemia occurred most frequently in the SQV treatment group, noted in three and two subjects, respectively. In contrast, weight gain was the most common adverse metabolic and nutritional disorder adverse event in the 3TC/ZDV treatment group, noted in two subjects.

One subject died 31 days after discontinuation of study medication. Death was considered not related to study medication and attributed to an HIV-related event of progressive multifocal leukoencephalopathy (PML).

Laboratory abnormalities were generally mild and with the exception of hematologic abnormalities attributable to ZDV therapy, occurred with similar frequency in the two treatment groups. Other sporadic changes in hematologic parameters were generally felt to be consistent with virologic control of HIV-1 infection and overall improvement in subject health.

Similar statistically significant increases in total cholesterol were observed in both treatment groups at all visits after Week 8. Mean total cholesterol increased from 166 mg/dL at baseline to 226 mg/dL at Week 48 in the SQV treatment group and from 171 mg/dL at baseline to 231 mg/dL at Week 48 in the 3TC/ZDV treatment group. Coincident with increases in total cholesterol, increases from baseline in HDL were also observed at both Week 24 and Week 48 in both treatment groups. The mean HDL level increase from baseline through Week 48 was 9.42 mg/dL in SQV-treated subjects and 9.79 mg/dL in 3TC/ZDV-treated subjects. No statistically significant change in baseline total cholesterol/HDL ratio *vs.* Week 48 total cholesterol/HDL ratio was observed in either the SQV or 3TC/ZDV treatment groups (5.33 *vs.* 5.68 [p = 0.511] and 4.53 *vs.* 5.49 [p = 0.164], respectively).

Statistically significant mean increases from baseline in triglycerides were noted at Weeks 16, 24 and 48 in the SQV treatment group, but did not occur at any visit in the 3TC/ZDV treatment group. At Week 48, mean increases of triglycerides in the SQV *vs.* 3TC/ZDV treatment groups were 85.30 mg/dL *vs.* 63.78 mg/dL (p = 0.724).

With the exception of lipids determinations, statistically significant mean changes from baseline in chemistries were generally sporadic and not felt to be clinically significant.

Very high clinical chemistry values occurred in four SQV and five 3TC/ZDV-treated subjects. Only total cholesterol, triglycerides, SGOT and SGPT reached very high values in more than one subject in either treatment group. All of the very high SGOT and SGPT determinations occurred in subjects with underlying hepatitis B or C. Only one subject [redacted] discontinued treatment due to very high SGOT and/or SGPT levels. One subject in each treatment group experienced very high total cholesterol values with both subjects subsequently treated with statins. In addition, one subject in each treatment group experienced very high triglyceride levels. Neither of these subjects were treated with lipid lowering agents, and none of the subjects with very high lipid values required study drug interruption or discontinuation.

Safety Results: (Continued)

Changes in mtDNA:nDNA ratios between Baseline and Weeks 8, 16, 32 and 48 were assessed in both treatment groups. No statistically significant changes from Baseline were observed at any visit in either treatment group.

In summary, both treatment regimens appeared relatively well tolerated with only three 3TC/ZDV-treated and two SQV-treated subjects discontinuing study medications due to adverse events. Laboratory abnormalities were also noted with similar frequency in both treatment groups. The occurrences of metabolic abnormalities, including both adverse events and laboratory parameters did not suggest clinically significant differences between the two treatment groups.

Conclusions:

The safety profile observed in prior clinical trials of LPV/r reflect the combination therapies employed, and include potential toxicities from both LPV/r and the nucleoside reverse transcriptase inhibitors used. However, several studies have suggested that select toxicities may be attributable to specific antiretroviral drug classes. In particular, mitochondrial toxicity associated with nucleoside reverse transcriptase inhibitors has been well described. Reduction in mitochondrial DNA has also been associated with symptomatic hyperlactatemia, an effect noted to resolve when therapy is discontinued.

Based on these observations, this study was initiated to examine the metabolic toxicities, overall safety, tolerability and efficacy associated with a nucleoside reverse transcriptase inhibitor-sparing regimen containing LPV/r plus SQV *vs.* a nucleoside containing "standard" regimen of LPV/r plus 3TC/ZDV in antiretroviral-naïve subjects infected with HIV-1. The selection of LPV/r plus SQV as the nucleoside-sparing regimen was based on prior observations from the M96-462 study of ritonavir plus SQV, which suggest that mono-class protease inhibitor regimens may have sustained antiviral activity while avoiding toxicities associated with nucleoside reverse transcriptase inhibitors.

This study demonstrated similar antiviral activity of the SQV and 3TC/ZDV-containing regimens. Analysis of the proportion of subjects with HIV-1 RNA < 50 copies/mL at each visit indicated no statistically significant differences between treatment groups for either ITT or on-treatment evaluations. In the ITT (NC = F) analysis at Week 48, 10/16 (63%) SQV-treated subjects and 7/14 (50%) 3TC/ZDV-treated subjects achieved HIV-1 RNA < 50 copies/mL ($p = 0.713$). A robust CD4 response was also noted with a mean increase from baseline in the SQV and 3TC/ZDV treatment groups of 141 cells/μL and 187 cells/μL, respectively. Overall, the results of these efficacy analyses are consistent with observations from the M96-462 study demonstrating the antiviral activity of nucleoside reverse transcriptase inhibitor-sparing regimens.

In general, the safety profile of the two regimens was similar, as reflected in both adverse events and laboratory abnormalities. Adverse events of the digestive system were reported most frequently, occurring in 28 of the 30 study subjects, most commonly with diarrhea, nausea and vomiting. Despite the frequency of digestive system adverse events, only four subjects (two in each treatment group) discontinued study medications due to an adverse event of the digestive system. No statistically or clinically significant differences between treatment groups, in the incidence or severity of these adverse events was noted.

Conclusions: (Continued)

Laboratory abnormalities were generally mild and with the exception of hematologic abnormalities attributable to ZDV, occurred with similar frequency in the two treatment groups. Changes in hematologic parameters in both treatment groups, such as increases in mean platelet count or white blood cell count, were felt to be consistent with virologic control of HIV-1 infection and overall improvement in subject health. With the exception of total cholesterol and triglycerides, discussed below, no clinically significant mean changes from baseline in chemistry values were observed.

Overall metabolic abnormalities, including adverse events, body fat composition changes and laboratory abnormalities occurred with similar frequency in the SQV and 3TC/ZDV treatment groups. No pattern to these adverse events was noted in either treatment group. No specific adverse events of the metabolic or nutritional disorders body system occurred in more than two subjects.

Similar statistically significant increases in total cholesterol were observed in both treatment groups. Increases in total cholesterol were accompanied by increases in HDL with total cholesterol/HDL ratios similar at Week 48, compared to Baseline, in both treatment groups. The clinical significance of these observations, especially as they relate to risk of cardiovascular disease, is unclear, given the small sample size. Sporadic increases in triglyceride levels, compared to Baseline were also observed in both treatment groups. These changes from baseline only achieved statistical significance in the SQV treatment group, and at Week 48 were also similar across the two treatment groups.

Statistically significant reductions in mtDNA:nDNA ratio were not observed in either treatment group at any visit over the course of this study. The lack of identified changes in this ratio with the nucleoside reverse transcriptase inhibitor-containing treatment group may reflect, in part, the small sample size (Baseline and Week 48 samples were obtained in only 7 subjects in this treatment group), and the relatively short duration of follow-up. No conclusions regarding potential mitochondrial toxicity of nucleoside reverse transcriptase inhibitor therapy can be drawn from this limited data set.

In conclusion, this pilot study demonstrated the antiviral activity of a nucleoside reverse transcriptase inhibitor-sparing regimen, with efficacy similar to that observed in a standard nucleoside reverse transcriptase inhibitor-containing regimen. While adverse events of the digestive system were frequent with both regimens, there were few study drug related discontinuations. The occurrences of metabolic abnormalities, including both adverse events and laboratory parameters did not suggest clinically significant differences between the two treatment groups. However, interpretation of the latter finding is limited by the relatively short duration of observation and small sample size.