2.0 Protocol Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Kaletra®	**Volume:**	
Name of Active Ingredient: Lopinavir/ritonavir	**Page:**	
Title of Study: Phase I/II Study of ABT-378/Ritonavir in Combination with Reverse Transcriptase Inhibitors in Antiretroviral Naive HIV-1 Infected Subjects		
Coordinator Investigator: [redacted] M.D. redacted information 26Sep2014		
Study Site(s): 10 Sites in United States		
Publications: 2 Articles, 31 Abstracts, 27 Posters, 4 Oral Presentations		
Studied Period (Years): Date First Subject Dosed: 18 November 1997 Date Last Subject Completed Dosing: 30 April 2005	**Phase of Development:** 1/2	

Objectives: Primary: To assess the safety, tolerability and antiviral activity of lopinavir/ritonavir when administered orally in antiretroviral-naive HIV type 1 (HIV-1)-infected subjects

Secondary:

1) To determine the steady-state pharmacokinetic profile of lopinavir/ritonavir in antiretroviral-naive HIV-1-infected subjects
2) To characterize the HIV-1 ribonucleic acid (RNA) decay profile of lopinavir/ritonavir in antiretroviral-naive HIV-1-infected subjects
3) To assess the relationship between lopinavir/ritonavir pharmacokinetics and HIV-1 RNA decay profile in antiretroviral-naive HIV-1-infected subjects.

Methodology: Study M97-720 is a Phase 1/2, randomized, multicenter study of lopinavir/ritonavir in combination with stavudine and lamivudine in HIV-1-infected males and females. The study consisted of a double-blind study period and an open-label study period. Subjects were enrolled in 2 cohorts (Group I or Group II).

Approximately 32 subjects were planned to participate in Group I of Study M97-720. In Group I, subjects were equally randomized to 1 of 2 blinded treatment arms according to a previously generated randomization schedule. Sixteen (16) subjects were planned to receive lopinavir 200 mg/ritonavir 100 mg every 12 hours (q12h) and 16 subjects were planned to receive lopinavir 400 mg/ritonavir 100 mg q12h. Open-label stavudine and lamivudine were added to each Group I subject's lopinavir/ritonavir regimen on Day 22.

Methodology (continued):

Following a safety review of 4 weeks of dosing by the first 16 subjects enrolled in Group I, a second cohort of approximately 70 subjects was to be enrolled into Group II. Group II subjects were equally randomized to 1 of 2 blinded treatment arms according to a previously generated randomization schedule. Approximately 35 subjects were planned to receive lopinavir 400 mg/ritonavir 100 mg q12h and approximately 35 subjects were planned to receive lopinavir 400 mg/ritonavir 200 mg q12h. All Group II subjects also received stavudine and lamivudine as open label study drug beginning on Day 1.

For subjects enrolled in Group I, study drug administration began with lopinavir/ritonavir on Day 1. Study drug dosing was directly observed for Days 1-14. After Day 14, follow up visits were planned for Day 16, Day 21 (Week 3), and Day 28 (Week 4). Following Day 28, visits were scheduled every two weeks until Week 12 (Month 3), monthly until Week 24 (Month 6), and every 3 months thereafter for the duration of the study.

For subjects enrolled in Group II, study drug administration began with lopinavir/ritonavir, stavudine, and lamivudine dosing on Day 1. Subjects were scheduled to return to the clinic on Day 14, Day 28 (Week 4), monthly until Week 24 (Month 6), and every 3 months thereafter for the duration of the study.

Based on the acceptable accumulation of safety, tolerability, and antiviral efficacy data from Group II through 31 December 1998, the study was extended to allow subjects to continue to receive open-label lopinavir/ritonavir therapy with ongoing study follow-up.

All study subjects who entered the open label period received lopinavir 400 mg/ritonavir 100 mg twice daily (BID). Study subjects continued to take stavudine 30 or 40 mg (depending on subject's weight) BID and lamivudine 150 mg BID. After approval of Amendment 9, at approximately Week 312 (6 years) of the study, all subjects, with investigator consultation, may have substituted stavudine (or zidovudine) in the subject's regimen with tenofovir disoproxil fumarate (if not already part of the subject's regimen). Study visits in the open label period continued according to the established schedule.

Measurements of vital signs, physical examinations, electrocardiograms (ECGs), routine clinical laboratory evaluations, and determinations of antiviral activity were repeated at regularly scheduled intervals. Blood samples for determination of plasma levels of lopinavir and ritonavir were obtained for Group I subjects and a subset of Group II subjects. Blood samples for the determination of plasma levels of stavudine and lamivudine were obtained and archived for Group I subjects. Blood samples for determination of lopinavir protein binding were obtained and archived for Group I subjects.

Any subject who discontinued lopinavir/ritonavir was followed for at least 30 days after the last dose.

Number of Subjects (Planned and Analyzed): Approximately 32 subjects were to be enrolled in Group I, and a second cohort of approximately 70 subjects were to be enrolled in Group II. Thirty-two (32) subjects in Group I and 68 subjects in Group II who were randomized and received at least 1 dose of study drug are included in the analyses.

Diagnosis and Main Criteria for Inclusion: HIV-1-positive, antiretroviral-naive adult males and non-pregnant, non-lactating females at least 18-years-old with plasma HIV-1 RNA > 5000 copies/mL, who were not acutely ill.

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

ABT-378, Formulation A, 100 mg/Soft Elastic Capsules; Lot Numbers: [redacted] Ritonavir Formulation T-1B 100 mg, Lot Number: [redacted] Norvir Soft Gelatin Capsules, 100 mg, Ritonavir Formulation, T-1B 100 mg, Lot Number: [redacted] ABT-378, 200 mg capsules Formulation B, Lot Numbers: [redacted] ABT-378, [redacted] ABT- 378/ritonavir 133.33/33.3 mg capsules, Formulation B2HM, Lot Number: [redacted] ABT-378/ritonavir 133.33/ 33.3 mg capsules, Formulation B2, Lot Numbers: [redacted] ABT-378 ritonavir 133.3/33.3 mg Soft Gelatin capsules, Lot Numbers: [redacted] ABT-378/ritonavir capsules, 133.3/33.3 mg, 180/bottle, Lot Number: [redacted] Kaletra Capsules, 133.3 mg, Lopinavir/33.3 mg ritonavir Soft Gelatin Capsules, Lot Numbers: [redacted] redacted information 26Sep2014

Duration of Treatment: This study was originally designed to last for at least 48 weeks. Based on the accumulation of safety, tolerability, and antiviral efficacy data, the study was extended to allow subjects to continue to receive lopinavir/ritonavir therapy with ongoing study follow-up.

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

None.

Criteria for Evaluation:

Efficacy: Plasma HIV-1 RNA levels and CD4 and CD8 cell counts.

Pharmacokinetic: Blood samples for determination of plasma levels of lopinavir and ritonavir were collected for subjects in Group I and for a subset of subjects in Group II.

Safety: HIV/adverse events, vital signs, physical examination, ECG evaluation, and clinical laboratory determinations.

Statistical Methods

Efficacy: The primary efficacy variable was the proportion of subjects with viral load below the limit of quantitation (LOQ) at Week 24 and the time to loss of virologic response through Week 48. Analyses of the proportion of subjects with viral load below the LOQ were performed at Weeks 48, 72, 204, and 360 as well; statistical significance was determined using Fisher's exact test. The primary analysis was performed after all eligible subjects had completed 48 weeks of study therapy. Time to loss of virologic response was determined using Kaplan Meier methodology. Secondary efficacy variables included:

1. Proportion of subjects with viral load below the LOQ at each visit.
2. Proportion of subjects who did not experience loss of virologic response by Week 24.
3. Change from baseline to each visit in HIV-1 RNA, CD4 cell count, and CD8 cell count.
4. Area under the curve minus baseline (AUCMBL) through Weeks 16, 24, and 48 for HIV-1 RNA level, CD4 cell count, and CD8 cell count.

The change from baseline and the AUCMB analyses were performed using a one way analysis of variance (ANOVA). Baseline was defined as the mean of the last 2 measurements prior to the first dose of study drug. The effect of subject immunization on HIV-1 RNA was also explored.

Pharmacokinetic: For the 12 hour dosing intervals in which pharmacokinetic plasma samples were obtained, maximum observed plasma concentration (C_{max}), minimum observed plasma concentration (C_{min}), plasma concentration at time 0 (C_0), time to maximum observed plasma concentration (T_{max}), and area under the curve (AUC_{12}) for lopinavir and ritonavir were determined by standard noncompartmental methods and subjected to statistical analyses. Additionally, a peak to trough half life was calculated from time of C_{max} to C_{12} and the apparent oral clearance (CL/F) was also determined. The natural log transformed C_{max}, C_{min}, C_0, and AUC were used for statistical analyses of pharmacokinetic parameters, except where noted. Analyses of covariance with effect for regimen and using weight as a covariate were performed to examine the effect of lopinavir on ritonavir pharmacokinetic parameters as well as to examine the effect of ritonavir on lopinavir pharmacokinetic parameters, to compare pharmacokinetic parameters among regimens, and to investigate the dose proportionality of lopinavir and ritonavir pharmacokinetic parameters. Repeated measures analyses using a mixed linear model with effects of regimen, week, and their interaction were performed to examine if the pharmacokinetic parameters changed over time and to assess diurnal effect using the untransformed 0 and 12 hour concentrations in Group I and II. Linear correlation analysis was used to examine the relationship between the lopinavir and ritonavir C_{max}, C_{min}, and AUC (untransformed).

Safety: Safety was assessed using reports of HIV/adverse events and changes from baseline in physical condition and laboratory determinations. Adverse events were summarized using Coding Symbols for Thesaurus of Adverse Reaction Terms, 5th edition (COSTART V) dictionary. Mean changes in laboratory values from baseline to each visit were assessed using a paired t test. The proportion of subjects with Grade 3 elevations was summarized and listed.

Summary/Conclusions

Efficacy Results: The proportions of subjects with HIV-1 RNA levels < 400 copies/mL at Week 360 for the on-treatment and intent-to-treat (ITT) analyses are presented in the table below.

	Proportion of Subjects with HIV RNA Levels < 400 Copies/mL			
Week	**On-treatment**	**ITT (LOCF)**	**ITT (NC=F)**	**ITT (M=F)**
24	87/92 (95%)	94/100 (94%)	90/100 (90%)	87/100 (87%)
48	85/94 (90%)	89/100 (89%)	85/100 (85%)	85/100 (85%)
72	82/84 (98%)	94/100 (94%)	87/100 (87%)	82/100 (82%)
204	71/72 (99%)	92/100 (92%)	71/100 (71%)	71/100 (71%)
360	61/62 (98%)	91/100 (91%)	61/100 (61%)	61/100 (61%)

LOCF: last observation carried forward, NC=F: non-completer = failure, and M=F: missing equals failure

The proportion of subjects with HIV-1 RNA levels < 50 copies/mL at Week 360 for the on-treatment and intent to treat (ITT) analyses are presented in the table below.

Week	Proportion of Subjects with HIV RNA Levels < 50 Copies/mL			
	On-treatment	**ITT (LOCF)**	**ITT (NC=F)**	**ITT (M=F)**
24	71/90 (79%)	74/100 (74%)	74/100 (74%)	71/100 (71%)
48	76/94 (81%)	77/100 (77%)	76/100 (76%)	76/100 (76%)
72	76/84 (91%)	82/100 (82%)	79/100 (79%)	76/100 (76%)
204	70/72 (97%)	88/100 (88%)	70/100 (70%)	70/100 (70%)
360	59/62 (95%)	87/100 (87%)	59/100 (59%)	59/100 (59%)

LOCF: last observation carried forward, NC=F: non-completer = failure, and M=F: missing equals failure

Results of drug resistance testing during the study were available from 19 subjects. No subject demonstrated genotypic or phenotypic evidence of protease inhibitor resistance and 4 of the 19 demonstrated lamivudine resistance. The largest change in the 50% inhibitory concentration of lopinavir relative to wild type HIV-1 was 1.45-fold for any of these subjects.

Statistically significant increases in CD4 cell counts were evident for all subjects at all visits ($p < 0.001$). The mean change from baseline in CD4 cell counts at Week 360 was 501 cells/μL. The mean change in CD4 cell count from baseline to Week 360 was consistent regardless of baseline CD4 cell count value.

Pharmacokinetic Results: During administration of lopinavir/ritonavir 200/100 mg, 400/100 mg, and 400/200 mg q12h dosing regimens to antiretroviral naïve HIV-1-infected subjects, lopinavir and ritonavir concentrations reached steady state by Day 14 and did not differ from Weeks 3 to 24. Lopinavir plasma concentrations were increased when the lopinavir dose was increased from 200 to 400 mg at a fixed 100 mg ritonavir dose, and when the ritonavir dose was increased from 100 to 200 mg at a fixed 400 mg lopinavir dose. Dose proportionality in lopinavir pharmacokinetics was observed when both the lopinavir and ritonavir doses were increased proportionally, but less than proportional increases occurred when the lopinavir dose was increased at a fixed 100 mg ritonavir dose.

The pharmacokinetics of lopinavir are correlated to those of ritonavir. The lopinavir peak to trough $t_{1/2}$ (C_{max} to C_{12}) averaged 5-6 hours and the mean oral clearance was 6-7 L/h at the dosing regimen of 400/100 mg lopinavir/ritonavir q12h. For all dosing regimens, lopinavir concentrations fluctuated ≤ 2.5-fold throughout a 12-hour dosing interval. As noted in healthy subjects, plasma protein binding of lopinavir in HIV-1-positive subjects is 98-99% and does not appear to be concentration dependent within the therapeutic range. Ritonavir plasma concentrations achieved with 100 mg q12h when combined with 200-400 mg lopinavir are < 10% of those achieved with the clinical dose of ritonavir 600 mg q12h.

In antiretroviral naïve subjects, lopinavir C_{min}/EC_{50} (protein binding corrected for wild type HIV-1) ratios averaged > 50 for 400/100 mg q12h and > 30 for all regimens. No correlations between antiviral efficacy and lopinavir concentrations were evident, probably due to the observed high lopinavir plasma concentrations relative to the EC_{50} for wild type HIV-1 throughout a dosing interval. At the dose selected for Phase 3 trials of 400/100 mg q12h, ritonavir plasma concentrations are generally below the EC_{50} for wild type HIV-1 throughout a dosing interval, and are therefore likely to contribute minimally to antiviral activity.

Safety Results: All 100 subjects who received study drug reported at least 1 treatment-emergent adverse event. Overall, the most commonly reported adverse events were related to the digestive system, body as a whole, or skin and appendages. The majority of the treatment-emergent adverse events were reported by the investigator as mild in severity and probably not or not related to study drug. Among adverse events that were judged by the investigator to be at least moderate in severity and at least possibly related to study drug, the most commonly reported were diarrhea, hypercholesterolemia, hyperlipemia, nausea, lipodystrophy, abdominal pain, asthenia, abnormal stools, dyspepsia, headache, and vomiting. These adverse events were consistent in profile to those observed in other studies of lopinavir/ritonavir.

One death occurred during the study. The subject was found to have a spinal cord mass on computed tomography (CT) scan. The subject underwent surgery for stabilization of the spinal column (T6-7 vertebral fusion) and a biopsy of a paraspinal mass. The subject experienced a perioperative myocardial infarction. An autopsy was not performed. Both the investigator and the sponsor considered the death possibly related to study drug, although the alternative etiology of cardiac arrhythmia was provided.

Serious adverse events were reported for 31% (31/100) of all subjects. Serious adverse events for 3 subjects were assessed by the investigator as possibly or probably related to study drug (fatal cardiac arrest, diarrhea/dehydration, and enterocolitis). Fifteen subjects were prematurely discontinued from the study due to adverse events during the 360-week treatment period. Of these, the events for 2 subjects (alcohol intolerance and lymphoma-like reaction) were considered by the investigator not related to study drug and the events for 2 subjects (elevated glucose and depression) were considered probably not related to study drug. All remaining events were considered possibly or probably related to study drug. Body fat composition changes were noted for 55 subjects. The majority of the events occurred after more than 9 months of treatment with study drug. Most subjects remained on study drugs. All subjects were exposed to stavudine, a nucleoside reverse transcriptase inhibitor that is associated with body fat composition changes, most notably lipoatrophy. The relative contribution of stavudine to body fat composition changes, compared to the other study drugs, could not be assessed in this study. Grade 3 or higher elevations in triglycerides and total cholesterol were observed in 41 subjects overall; however, lipid elevations did not generally result in study drug interruption or discontinuation. After a switch from stavudine (or zidovudine) to tenofovir disoproxil fumarate was allowed at year 6, statistically significant improvements were noted in total cholesterol and triglyceride levels. At Week 360, the median total cholesterol and triglyceride values were 196 and 214 mg/dL, respectively. Subjects with positive baseline serologies for viral hepatitis were found to be at increased risk for Grade 3/4 elevations of hepatic transaminases during the study.

Conclusions: At 7 years of therapy, lopinavir/ritonavir was safe, well tolerated, and exhibited both potent and durable antiretroviral activity with no genotypic or phenotypic protease inhibitor resistance development.