



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:	
Name of Active Ingredient: Lopinavir/ritonavir	Page:	
Title of Study: A Randomized Open-Label Study of 800 mg Lopinavir/200 mg Ritonavir QD in Combination with Tenofovir DF and Emtricitabine vs. 400 mg Lopinavir/100 mg Ritonavir BID in Combination with Tenofovir DF and Emtricitabine in HIV-Infected Antiretroviral-Naïve Subjects		
Investigators: 47 investigators		
Study Sites: Multicenter		
<p>Publications: Gathe J, Podzamczar D, Johnson M, <i>et al.</i> Once-daily vs. twice-daily lopinavir/ritonavir in antiretroviral-naïve patients: 48-week results. 11th Conference on Retrovirus and Opportunistic Infections 2004;Poster 570.</p> <p>Podzamczar D, Gathe J, Johnson M, <i>et al.</i> Study 418: Efficacy and safety of once-daily lopinavir/ritonavir vs. twice-daily lopinavir/ritonavir in antiretroviral-naïve patients: 24-week results. 9th European AIDS Conference, Warsaw, Poland, 26-29 October 2003 (Oral #F1/3).</p> <p>Chiu Y-L, Foit C, Gathe J, <i>et al.</i> Multiple-dose pharmacokinetics and initial antiviral effect of once daily lopinavir/ritonavir (LPV/r) in combination with tenofovir (TDF) and emtricitabine (FTC) in HIV-infected antiretroviral-naïve subjects (Study 418). 2nd IAS Conference on HIV Pathogenesis and Treatment 2003;Abstract 839.</p> <p>Molina JM, Gathe J, Lim PL, <i>et al.</i> Comprehensive resistance testing in antiretroviral-naïve patients treated with once-daily lopinavir/ritonavir plus tenofovir DF and emtricitabine: 48-week results from Study 418. XV International AIDS Conference 2004;Poster WePeB5701.</p> <p>Yeh V, Barros C, Easterbrook P, <i>et al.</i> Virologic response to a once-daily lopinavir/ritonavir (LPV/r) based regimen in ARV-naïve patients is not associated with trough lopinavir concentrations or baseline HIV RNA and CD4 count. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy 2004;Poster H-570.</p> <p>Easterbrook P, Green S, Wilkin A, <i>et al.</i> Antiretroviral therapy in special populations: response to lopinavir/ritonavir, tenofovir DF, and emtricitabine in antiretroviral-naïve patients by gender, race/ethnicity, and hepatitis co-infection status. 7th International Congress on Drug Therapy in HIV Infection 2004;Abstract P15.</p> <p>Bertz R, Chiu Y-L, Naylor C, Luff K, Brun SC. Lack of effect of gastric acid reducing agents on lopinavir/ritonavir plasma concentrations in HIV-infected patients. 7th International Congress on Drug Therapy in HIV Infection 2004;Poster 201.</p>		



Studied Period (Years): Initiation Date: 7 Aug 2002 (first subject dosed) Completion Date: 10 Oct 2004 (last subject dosed)	Phase of Development: 3
Objectives: To compare the safety, tolerability and antiviral activity between once-daily (QD) and twice-daily (BID) dosing of lopinavir/ritonavir and to further characterize the pharmacokinetics of QD dosing of lopinavir/ritonavir.	
Methodology: Study M02-418 a Phase 3, open-label, randomized, multiple-center study designed to demonstrate the safety, tolerability, pharmacokinetic and antiviral activity of QD dosing of lopinavir/ritonavir (LPV/r) in combination with tenofovir DF (TDF) and emtricitabine (FTC) in the treatment of ARV-naïve, HIV-infected subjects. Approximately 200 subjects meeting inclusion and exclusion criteria were to be enrolled in the study at approximately 50 sites. Subjects were randomized in a 3:2 ratio to receive either lopinavir/ritonavir 800 mg/200 mg QD (N = 120) or lopinavir/ritonavir 400 mg/100 mg BID (N = 80). All subjects also received tenofovir DF 300 mg and emtricitabine 200 mg QD. At the Screening Visit, subjects underwent a complete physical examination, review of concomitant medications and clinical laboratory assessments. Subjects who met enrollment criteria during the Screening Period were eligible to be enrolled in the study. At the Randomization/Placebo Lead-in Visit, subjects underwent a symptom-directed physical examination (including vital signs and body weight) and were randomized to either the QD or BID dosing group. In order to monitor the subject's adherence with the assigned regimen, the placebo bottle was fitted with a Medication Event Monitoring System (MEMS) Monitor. Subjects received instructions regarding their dosing schedule and the use of the MEMS Monitors. Subjects in the QD group were instructed to take 6 capsules once daily in the morning; subjects in the BID group were instructed to take 3 capsules in the morning and 3 capsules in the evening. The adherence information obtained from the Lead-In Period was used to counsel subjects on their adherence patterns and the potential impact of their adherence on their response to antiretroviral (ARV) therapy. Subjects returned to clinic for the Study Day -1/Baseline Visit. At this visit, subjects underwent a complete physical examination, review of concomitant medications and clinical laboratory assessments. Adherence during the Placebo Lead-in Period was reviewed and discussed with the subject. During the Study Day -1/Baseline study visit, subjects were dispensed their study drug. The MEMS Monitor used on the bottle of placebo was transferred to the bottle of lopinavir/ritonavir prior to the drug being dispensed to the subject. Subjects underwent the Study Day -1/Baseline Visit procedures and were to begin taking their study medications following the Study Day -1/Baseline Visit.	



Methodology (continued):

Subjects returned to the clinic every 4 weeks through Week 8, every 8 weeks until Week 48 and then quarterly until their final/discontinuation visit. Procedures at these visits included symptom-directed physical examinations, vital sign measurements, clinical laboratory tests, download and review of the MEMS data and determinations of antiviral and immunologic activity. For selected sites, serial blood samples were drawn at the Week 4 visit for 24 subjects in the QD dosing group and 16 subjects in the BID dosing group. At all sites, a blood sample for pharmacokinetic evaluation was drawn just prior to morning dosing at Weeks 4, 8, 16, 24, and 48 and every 12 weeks after Week 48.

Subjects returned for study procedures at the Final or Discontinuation Visit after their final study drug dose. Procedures at this visit included physical examination, ECG, vital sign measurements, laboratory analysis and the recording of any adverse events and concomitant medication use since the previous visit. All adverse events noted at this visit were to be followed until they resolved.

Number of Subjects (Planned and Analyzed):

Approximately 200 subjects were planned to be enrolled. A total of 196 subjects were randomized into the study; 6 subjects were never dosed, 115 subjects received 800 mg/200 mg lopinavir/ritonavir QD with tenofovir DF 300 mg QD and emtricitabine 200 mg QD and 75 subjects received 400 mg/100 mg lopinavir/ritonavir BID with tenofovir DF 300 mg QD and emtricitabine 200 mg QD. All 190 subjects who received at least 1 dose of lopinavir/ritonavir are included in this analysis.

Diagnosis and Main Criteria for Inclusion:

- HIV positive male or female at least 18 years of age.
- Antiretroviral (ARV) naïve (< 7 days of any ARV treatment).
- Plasma HIV RNA level > 1,000 copies/mL at Screening.

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

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Duration of Treatment: at least 96 weeks

Reference Therapy, Dose and Mode of Administration, Lot Number:

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Criteria for Evaluation:

Efficacy: Plasma HIV RNA levels and CD4 cell counts.

Pharmacokinetic: The Week 4 pharmacokinetic parameter values of lopinavir and ritonavir were estimated using noncompartmental methods. These included: the maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}), the minimum plasma concentration (C_{min}), the pre-dose concentrations (C_{trough}), and the area under the plasma concentration-time curve from time 0 to 24 hours after dosing (AUC_{24}). The lopinavir inhibitory quotient (IQ) was calculated as the ratio of C_{trough} to protein binding-adjusted IC_{50} for wild-type HIV (0.07 μ g/mL).

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Pharmacodynamic: Subjects with plasma HIV RNA levels below 50 copies/mL at Week 48 were considered successes and those with levels above 50 copies/mL at Week 48 were considered failures. The composite value of trough concentration for a subject was calculated from the available data obtained during Weeks 4 through 48 in two ways:

1. Median over Week 4 through Week 48;
2. Average defined by the area under the trough concentration *vs.* time curve divided by the time interval over which the measurements were obtained.

Two lopinavir and ritonavir C_{trough} datasets were used for the pharmacokinetic and pharmacokinetic/pharmacodynamic analyses. Dataset A included all collected trough data, except those samples that were obtained after a missed dose, ≥ 20 hours post-dose for the BID regimen and ≥ 40 hours post-dose for the QD regimen. Dataset B excluded trough data if samples were obtained outside the window of 12 ± 3.5 hours from the previous dose for the BID regimen and 24 ± 3.5 hours from the previous dose for the QD regimen.

Safety: HIV-related events/adverse events and changes from baseline in laboratory determinations.

Statistical Methods:

Efficacy:

The primary efficacy variable was the proportion of subjects with a plasma HIV RNA level below 50 copies/mL at Week 48 based on an intent-to-treat analysis in which noncompleters were considered non-responders (ITT NC = F). This estimate was provided for each treatment group, along with the corresponding 95% confidence interval for the difference in proportions (QD group minus BID group), based on the normal approximation to the binomial distribution. If the lower limit of the confidence interval was above -20%, the QD group would be considered noninferior to the BID group. Secondary efficacy analyses included the following: time to loss of virologic response through Week 96; proportion of subjects with plasma HIV RNA level below 50 copies/mL at each visit; and mean change from baseline to each visit in plasma HIV RNA level and CD4 cell count.

Additionally, the incidence of lopinavir resistance, emtricitabine resistance, and tenofovir DF resistance was summarized and compared between treatment groups.

Pharmacokinetic:

Analysis of covariance (ANCOVA) with effects for regimen and covariates of weight, gender and hepatitis B/C status was performed for lopinavir and ritonavir T_{max} , and the natural logarithms of C_{max} , AUC_{24} , C_{min} and C_{trough} determined at Week 4. Within the ANCOVA framework, the QD regimen was compared to the BID regimen with a significance level of 0.05. Point estimates and 90% confidence intervals for the ratio of central values were obtained for the natural logarithms of C_{max} , AUC_{24} , C_{min} and C_{trough} . A repeated measure analysis was performed for the natural logarithm of C_{trough} for lopinavir and ritonavir over Weeks 4, 8, 16, 24 and 48. An across study comparison with Study M99-056 pharmacokinetic parameters for each of the dosing regimens (QD and BID) to investigate a potential interaction with tenofovir DF was also performed for lopinavir and ritonavir.



Pharmacodynamic:

The relationship between lopinavir drug exposure and the primary efficacy variable was evaluated utilizing a logistic regression analysis. The efficacy response variable was binary, as indicated by 1 if a subject had plasma HIV RNA levels below 50 copies/mL at Week 48, or 0 if the level was not less than 50. Subject to the restriction, an analysis was performed using both the intent-to-treat (ITT) approach and a dropouts-as-censored (DAC) approach that excluded subjects who did not have a measurement of plasma HIV RNA level at Week 48. The initial model included terms for intercept, treatment arm, a composite value of lopinavir trough concentration over Weeks 4, 8, 16, 24 and 48, and interaction of treatment with the composite value of trough concentration.

Safety:

Safety was assessed using reports of adverse events and HIV-related events and changes from baseline in laboratory determinations and vital signs. Adverse events were summarized using Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) V.

Summary/Conclusions:**Efficacy Results:**

Through 96 weeks, 37% of subjects in the QD group and 39% in the BID group prematurely discontinued the study. Using the ITT (NC = F) analysis, 70% of subjects in the QD group and 63% of subjects in the BID group achieved plasma HIV RNA < 50 copies/mL at Week 48. The difference between the groups was not statistically significant and the 95% confidence interval (-6.9%, 20.7%) for the difference (QD minus BID) between groups for the proportions of subjects achieving plasma HIV RNA < 50 copies/mL confirmed the noninferiority of the QD group compared to the BID group, since the lower limit of the confidence interval remained above the study-defined threshold of -20% and the commonly used threshold of -12%. In the observed data analysis, 90% in the QD group and 87% in the BID group had plasma HIV RNA < 50 copies/mL at Week 48. At Week 96, 57% of subjects in the QD group and 53% of subjects in the BID group achieved plasma HIV RNA < 50 copies/mL. The difference between the groups was not statistically significant and the 95% confidence interval (-10.4%, 18.5%) for the difference (QD minus BID) between groups for the proportions of subjects achieving plasma HIV RNA < 50 copies/mL confirmed the noninferiority of the QD group compared to the BID group, since the lower limit of the confidence interval remained above the study-defined threshold of -20% and the commonly used threshold of -12%. In the observed data analysis, 89% in the QD group and 91% in the BID group had plasma HIV RNA < 50 copies/mL at Week 96. At both Week 48 and Week 96, no statistically significant differences were observed between the QD and BID groups for the proportions of subjects achieving plasma HIV RNA < 50 copies/mL using the observed data, ITT (LOCF), or ITT (M = F) analyses.

Results were similar when analyzed based on the FDA TLOVR algorithm. Through 96 weeks, 57% of subjects in the QD group and 55% of subjects in the BID group achieved and maintained plasma HIV RNA levels < 50 copies/mL. The 95% confidence interval for the difference (-11.7%, 17.2%) confirmed the noninferiority of the QD group compared to the BID group.

In both groups, statistically significant decreases in mean plasma HIV RNA levels were seen as early as the first visit following the baseline evaluation and were maintained at all subsequent visits through Week 96. There was no statistically significant difference between the groups in the mean change from baseline to Week 96 in plasma HIV RNA levels. The mean decrease from baseline to Week 96 was 3.09 log₁₀ copies/mL in the QD group and 3.09 log₁₀ copies/mL in the BID group.



Efficacy Results: (Continued)

Statistically significant increases in mean CD4 cell counts were observed in both groups at all visits, with no statistically significant differences observed between groups at any time point. The mean change from baseline to Week 96 was 244 cells/mL in the QD group and 264 cells/mL in the BID group.

From Weeks 12 to 96, genotypic resistance testing was conducted on all available samples for which plasma HIV RNA was above 500 copies/mL. In 23 subjects with available genotypic resistance data, no confirmed PI resistance was observed. Similarly, no development of tenofovir DF resistance (K65R mutation in reverse transcriptase) was observed. Four subjects (3 QD, 1 BID) demonstrated the emergence of emtricitabine resistance (M184V/I mutation in reverse transcriptase). An M46M/I mixture in protease observed in 1 subject is of unknown significance. The M46I mutation has been shown to contribute to resistance to various PIs, but the phenotypic susceptibility to lopinavir for this subject remained below the wild-type level and below the baseline level. Further, this subject did not demonstrate emtricitabine resistance. If the changes in protease were a manifestation of PI resistance development, emtricitabine resistance would also be expected, since resistance generally develops first to the most fragile component of a regimen.

Thus, consistent with several previous trials of lopinavir/ritonavir in ARV-naïve subjects, these resistance data indicate that loss of viral suppression or incomplete viral suppression is unlikely to lead to viral resistance that may limit the subsequent use of PI-based treatment. No clinically relevant changes in phenotypic resistance to lopinavir or other PIs were observed compared to baseline values.

Pharmacokinetic Results:

Lopinavir C_{trough} and C_{min} were 64% and 74%, respectively, lower after QD dosing compared to BID. Although not statistically significant, based on central values, lopinavir C_{max} was slightly (21%) higher and AUC was slightly (18%) lower for the QD regimen relative to BID.

The overall median lopinavir IQ from Weeks 4 through 48 (Dataset A) was 86.5 for the BID regimen (N = 71) and 48.1 for QD dosing (N = 106) ($p \leq 0.0001$ for C_{trough} differences between regimens over Weeks 4 through 48). These median IQ values are similar to those observed in the subjects in the pharmacokinetic subgroup at Week 4 (IQ median of 97 and 47 for BID (N = 13) and QD (N = 24), regimens, respectively). The 25th percentile for IQ was 20 for QD compared to 60 for the BID regimen. For the overall mean, C_{trough} displayed more variability for the QD (CV = 87%) compared to the BID regimen (CV = 52%).

Lopinavir concentrations are very similar between the current study and previous study M99-056. Based on point estimates, AUC and C_{max} values were within 10% and C_{min} within 15% of each other across studies for both the QD and BID regimens. These cross-study comparisons suggest that the change in background NRTI regimen to one including tenofovir does not negatively impact lopinavir exposures.



Pharmacokinetic/Pharmacodynamic Results:

Although comparable clinical activity and resistance profiles were observed between the QD and BID dosing arms, a pharmacokinetic/pharmacodynamic evaluation was conducted to explore the relationship between lopinavir concentrations and virologic outcome. Results from the ITT (NC=F) analyses of virologic outcome with time-averaged and median lopinavir C_{trough} using Dataset A are the most data inclusive. Results from the DAC analysis of virologic outcome, using Dataset B, includes only true virologic successes and failures at 48 weeks and lopinavir concentrations collected within a given time window.

A relationship between either the time-averaged or median lopinavir C_{trough} and the efficacy measure as defined by the ITT (Dataset A) or DAC (Dataset B) analysis is not evident ($p \geq 0.330$ for final models). Hence, there appeared to be little evidence within this sample of data that the composite lopinavir trough values had a significant effect on determining the probability of an HIV RNA level below 50 copies/mL at 48 weeks.

Safety Results:

The safety and tolerability of QD and BID dosing of lopinavir/ritonavir were evaluated and compared in this study. Overall, the proportion of subjects reporting treatment-emergent adverse events of any severity and of any relationship to study drug was 95% in the QD group and 92% in the BID group. The most common adverse events noted were related to the digestive system, in particular diarrhea and nausea. Among individual adverse events, diarrhea occurred in a statistically significantly higher proportion of subjects in the QD group than in the BID group (64% vs. 39%, respectively; $p < 0.001$). The prevalence of treatment-emergent diarrhea decreased over time in both groups. The incidence of treatment-emergent nausea was similar in the QD and BID groups (31% and 29%, respectively).

The overall incidence of adverse events of at least moderate severity and possible, probable or unknown relationship to study medications was greater in the QD group compared to the BID group (33% vs. 20%, respectively; $p = 0.068$). However, of specific adverse events of moderate or greater severity and possible, probable or unknown relationship to study medications, only diarrhea was reported statistically significantly more frequently in the QD group than in the BID group (17% vs. 5%, respectively; $p = 0.014$). Nausea of at least moderate severity and probable, possible, or unknown relationship to study drugs occurred in a similar proportion of subjects in the QD and BID groups (9% and 8%, respectively). Adverse events of any severity and relationship to study drug associated with the digestive system were most common and occurred in a statistically significantly greater proportion of subjects in the QD group than in the BID group (81% vs. 61%, respectively; $p = 0.004$).

Treatment-emergent serious adverse events were reported by 10% of subjects in the QD group and 17% of subjects in the BID group. Of these, the events for 4 subjects in the QD group (liver damage, diarrhea, nephritis, and bronchitis and pharyngitis) and 1 subject in the BID group (hepatitis and immune system disorder) were considered by the investigator to be possibly or probably related to lopinavir/ritonavir. All other serious adverse events were considered to be probably not or not related to lopinavir/ritonavir.



Safety Results: (Continued)

Two deaths, both in the BID group, were reported during the 96-week treatment period of the study. Each of the events leading to death (lymphoma-like reaction and AIDS) was considered by the investigator to be not related to study drug.

Study drug related adverse events resulting in study drug discontinuation were more frequent in the QD group than in the BID group. Eighteen (16%) subjects in the QD group and 4 (5%) subjects in the BID group experienced study drug related adverse events leading to discontinuation. Discontinuation for adverse events of nausea and diarrhea occurred in \leq 8% of subjects in either group.

Laboratory abnormality profiles were similar between groups and consistent with observations from prior studies. Lipid elevations were the most common laboratory abnormalities observed. The mean increases from baseline to Week 96 for total cholesterol were similar in the QD and BID groups (29.3 mg/dL and 33.5 mg/dL, respectively). Triglycerides also increased from baseline to Week 96 in both groups, with similar mean increases from baseline to Week 96 in the QD and BID groups (51.9 mg/dL and 61.0 mg/dL, respectively). Very high cholesterol and/or triglyceride levels were reported in 9% of subjects in the QD group and 10% of subjects in the BID group through 96 weeks. There were no discontinuations or dose interruptions related to these very high lipid values.

No subjects reported adverse events of lipid elevations that resulted in premature discontinuation. Interestingly, effects on LDL cholesterol were modest in both groups. At baseline, LDL cholesterol $<$ 130 mg/dL was observed in 90% and 80% of subjects in the QD and BID groups, respectively. At Week 48, 75% and 67% of subjects in the QD and BID groups, respectively, maintained LDL cholesterol $<$ 130 mg/dL. Similarly, HDL cholesterol increases were observed in both groups, resulting in a greater percentage of the study population demonstrating favorable HDL cholesterol profiles on lopinavir/ritonavir therapy relative to baseline.

Mean SGOT/AST and SGPT/ALT values at Week 96 were lower than baseline values in both the QD and BID groups. Very high SGOT/AST and/or SGPT/ALT elevations were reported for 9 subjects in the QD group and 3 subjects in the BID group. Five of the 12 subjects had improvements in SGOT/AST and SGPT/ALT levels without interruption of study drug and 1 subject prematurely discontinued from study drug due to abnormal liver function tests.

Since renal toxicity, including cases of acute renal failure, has been reported in association with the use of tenofovir DF, an analysis of renal function parameters was performed. Only 4 (2%) subjects in the study experienced a creatinine value $>$ 1.5 mg/dL during the 96-week treatment period of the study, 2 in the QD group and 2 in the BID group. Two subjects were hospitalized and interrupted study drug for acute renal failure during the 96-week treatment period of the study. As the clinical presentation and pathophysiologic mechanism leading to renal failure appeared to differ between these 2 subjects, these cases did not appear to represent an aggregate signal for synergistic renal toxicity attributable to coadministration of lopinavir/ritonavir and tenofovir DF.



Safety Results (continued):

In this study, low precision ECG capture methodologies utilizing paper tracings were employed since ECGs were performed to detect gross changes from baseline for purposes of individual subject safety and management as opposed to allowing for precise quantification of ECG interval changes. Consequently, a minority of enrolled subjects had baseline and on study ECGs of sufficient quality to allow for digitization and interval measurement. PR interval changes were similar to those observed in previous studies of lopinavir/ritonavir dosed BID. Similar mean changes in QTc interval were observed in both the BID and QD dosing arms, consistent with the similar overall lopinavir exposures achieved in both arms as reflected by AUC. These mean changes were of larger magnitude than observed in multiple prior studies of lopinavir/ritonavir in antiretroviral-naïve subjects and may be artifactual, given the ECG capture methodology employed and the resulting restricted sample size.

In summary, adverse event profiles were similar in character between groups, although diarrhea occurred at a higher rate in the QD group. Overall, both treatments were well tolerated, with a higher proportion of subjects discontinuing the study for study drug related adverse events in the QD group than in the BID group (16% vs. 5%, respectively). Fasting lipid profiles were similar between groups, with elevated triglycerides representing the predominant effect.

Conclusions:

The antiviral activity of lopinavir/ritonavir QD treatment at 96 weeks appears comparable to that of lopinavir/ritonavir BID treatment. The lack of compelling evidence of selection of PI resistance in viral isolates from subjects with plasma HIV RNA above 500 copies/mL suggests that the subsequent use of PI-based regimens would not be limited through the use of either lopinavir/ritonavir dosing schedule as initial therapy for HIV. Detailed pharmacokinetic/pharmacodynamic analysis did not indicate an association of lower lopinavir trough exposures with reduced virologic response, suggesting that the lopinavir/ritonavir QD group does not rest on the steep portion of the dose/response curve. Adverse event profiles were similar in character between groups, although diarrhea occurred at higher rates in the QD group. Future formulation improvements with more limited excipients may theoretically attenuate gastrointestinal irritability. Lastly, fasting lipid profiles were similar between groups, with elevated triglycerides representing the predominant effect. HDL cholesterol profiles improved for the study population across both groups at Week 48 and for the BID group at Week 96. Through 96 weeks, the pattern of creatinine increases was similar to what has been reported in prior clinical trials evaluating tenofovir DF therapy.

The safety and efficacy results from this study indicate that lopinavir/ritonavir, tenofovir DF and emtricitabine would provide an entirely QD treatment regimen for patients initiating HIV therapy, with clinically comparable efficacy to a lopinavir/ritonavir BID regimen.