2.0 Synopsis

<table>
<tr><td>Abbott Italy Medical Department</td><td>Individual Study Table Referring to Part of Dossier:</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Kaletra®</td><td>Volume:</td><td rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient:
Lopinavir/ritonavir – LPV/r</td><td>Page:</td></tr>
<tr><td colspan="3">Title of Study:
KALEAD 1 – A phase III, open- label, randomized, comparative study of the antiviral efficacy of ARV therapy with Lopinavir/Ritonavir (LPV/r – Kaletra®) in combination with Tenofovir versus SOC (Kaletra® in combination with 2 nucleoside RTIs) in naïve HIV-1 positive patients</td></tr>
<tr><td colspan="3">Investigators: 16 Investigators</td></tr>
<tr><td colspan="3">Study Sites:
Multi-center, Italy. Investigator & Site information is on file at Abbott Italy</td></tr>
<tr><td colspan="3">Publications:
Pinola M., Carosi G., Di Perri G., Lazzarin A., Moroni M., Vullo V., Mazzotta F., Leoncini F., Pastore G., Norton M., Di Luzio Paparatti U., for the Kalead1 Study Group: LPV/r-based 2-drug HAART vs LPV/r-based 3-drug HAART: Comparable virological efficacy and tolerability in HIV-1-infected naïve subjects (Kalead1 study) – 48-Week results. Poster WEPEB035, 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, July 2007, Sydney, Australia</td></tr>
<tr><td colspan="2">Studied Period (Years):
Initiation Date: 18 Jan 2005 (First Subject First Visit)
Completion Date: 29 Jun 2007 (Last Subject Last Visit)</td><td>Phase of Development:
III</td></tr>
<tr><td colspan="3">Objectives:
The primary objectives of the present study were:
To compare in naïve subjects the antiviral activity of the two-drug regimen Lopinavir/Ritonavir (LPV/r; Kaletra®) BID in combination with Tenofovir QD versus the standard-of-care HAART three-drug regimen of LPV/r in combination with 2 nucleoside analogs.
To evaluate the safety of the two regimens, the two-drug regimen LPV/r BID with Tenofovir QD versus a HAART standard-of-care three-drug regimen of LPV/r in combination with 2 nucleoside analogs.
The secondary objectives of the study were:
to compare the two arms (LPV/r BID/Tenofovir QD versus LPV/r + 2 NsRTIs) in terms of immunological efficacy and patients' adherence, satisfaction and quality of life.</td></tr>
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Methodology:

The Kalead1 study was a phase III, open-label, randomized, comparative, multi-center study of the antiviral efficacy of antiretroviral two-drug therapy with Lopinavir/Ritonavir in combination with Tenofovir versus the SOC three-drug therapy (Kaletra® in combination with 2 nucleoside reverse transcriptase inhibitors, NsRTI's) in antiretroviral naïve, HIV-positive patients. At randomization, the subjects were stratified according to their Baseline HIV-1 RNA value >100.000 or ≤100.000 copies/mL.

The study consisted of a run-in phase of 24 weeks (Phase A) and a treatment phase of 48 weeks (Phase B). The run-in phase was deemed appropriate for safety reasons, in order to exclude patients who were not responding to the two-drug regimen LPV/r BID + Tenofovir QD.

Approximately 150 subjects meeting the inclusion and exclusion criteria were to be enrolled in the study at 16 sites. The subjects were randomized in a 1:1 ratio to receive either a two-drug regimen: LPV/r in combination with Tenofovir QD; Arm A, or a three-drug regimen: LPV/r in combination with 2 nucleoside analogs, NsRTIs, prescribed according to the applicable international guidelines and the investigator's judgement; Arm B. After 24 weeks the subjects reaching an HIV-1 RNA level of < 50 copies/mL in two consecutive occasions continued the previously prescribed therapy for additional 48 weeks. Subjects not reaching 2 consecutive HIV-1RNA levels < 50 copies/mL at week 24 were withdrawn from the study.

A complete screening visit to evaluate the patients prior to the enrollment was performed on Day -14. The Randomization visit was performed on Day 1, and subsequent routine visits were carried out at Weeks 4, 12, 24 and 26 of Phase A. Screened subjects who satisfied the entry criteria of 2 consecutive HIV-1 RNA levels <50 copies/mL entered the Phase B of the study, and further visits were performed at Weeks 8, 16, 24, 32, 40 and 48 (Termination visit) of Phase B. At each visit, laboratory measurements for safety and for the assessment of virologic and immunological parameters, assessment of Quality of Life, patient adherence to therapy and satisfaction and adverse event collection were performed [redacted]

Number of Subjects (Planned and Analyzed):

146 subjects were planned to be enrolled. A total of 167 subjects were screened for the study, of which 152 subjects were randomized and dosed, while 15 subjects were screening failures. 72 subjects received LPV/r + TDF and 80 subjects received LPV/r+ 2NsRTIs as prescribed by the Investigator. All randomized and dosed subjects are included in the analyses.

Diagnosis and Main Criteria for Inclusion:

- HIV positive male or female of at least 18 years of age
- Antiretroviral (ARV) naïve (< 7 days of any ARV treatment)
- Plasma HIV-1 RNA level >400 copies/mL at Screening

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

Lopinavir 400 mg / ritonavir 100 mg BID (Arms A and B): LPV/r 133.3 mg /33.3 mg fixed-dose combination soft gel capsules per os; commercial Lot #s [redacted]

Lopinavir 400 mg / ritonavir 100 mg BID (Arms A and B): LPV/r 200 mg / 50 mg fixed-dose combination tablets per os; commercial Lot # [redacted]

Tenofovir disoproxyl fumarate 300mg QD (Arm A): TDF 300 mg tablets per os, Lot # [redacted]

Duration of Treatment:

72 weeks

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

2 NsRTIs as prescribed by the investigator (Arm B)

Criteria for Evaluation

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

Safety: Adverse events, clinical laboratory data (hematology, clinical chemistry, urinalysis), physical examinations and vital signs. Additional safety criteria to be evaluated included:

- Metabolic toxicity: lipid profile (total cholesterol, HDL/LDL, triglycerides) and glucose measurements.
- Renal toxicity: creatinine, creatinine clearance, serum phosphate.

Statistical Methods

Efficacy:

The primary efficacy variable was the proportion of subjects with plasma HIV-1 RNA below 50 copies/mL at Week 72 (Week 48 of the phase B) of the study.

All laboratory examinations including plasma HIV-1 RNA level measurements and CD4 cell counts were performed in local laboratories. Therefore, a formal comparison of the absolute laboratory values between subjects, between sites or between treatment arms would not be correct. Nevertheless, also mean and/or median values for various laboratory parameters are presented in the statistical tables, but no firm conclusions can be made from the absolute values nor from the mean change values.

Regarding the parameters HIV-1 RNA and CD4 cell count, comparisons of the mean values and the mean changes from Baseline were performed between the treatment arms, since no appropriate classification of these values is available. Regarding HIV-1 RNA values, as defined in the study protocol, all clinical sites used a viral load determination method with lower detection limit 50 copies/mL or less.

All efficacy analyses were based on the Intention-to-Treat population. Moreover, the primary efficacy variable and selected secondary efficacy variables were also analyzed on a Per-Protocol (Completers-Compliers) population.

In the definition of the ITT population to be analyzed, two approaches are used regarding the missing plasma HIV-1 RNA level values:

1. Missing values are considered above 50 copies/mL unless the immediately preceding and immediately following values are below 50 copies/mL (ITT, NC=F “noncompleter = failure” analysis). All values obtained more than one day after study drug discontinuation are considered above 50 copies/mL.
2. The second ITT approach involves observed results only, and excludes any missing values from the analysis.

The PP population included those subjects who had completed the study and had not had significant protocol violations/deviations (PP-CC “Completers-Compliers” analysis). Two approaches have been used to define protocol completers, due to the qualification criterion of 2 consecutive negative viral loads verified only at the end of the Run-In phase (Phase A) of the study. Therefore, the subjects considered non-completers for the PP population are:

1. in Phase A : those subjects who discontinue in Phase A because of any reason different from Virologic Failure (i.e. not reaching 2 consecutive negative viral load values).
2. Phase B : those subjects who discontinue in Phase B because of any reason.

For the PP population, the non-compliers were defined as subjects who have any protocol deviation judged significant with regard to the subject's protocol adherence according to Abbitt Italy Clinical Research Physician. These subjects were excluded from the PP-CC population.

The assignment of subjects to the pre-defined study populations was blinded. All the decisions are made without knowing the subject allocation to the treatment group.

Quantitative variables are described by the number of available and missing observations, mean, median, standard deviation, 95% CI for the mean, the range (minimum and maximum) and the first and third quartiles. All these variables are derived using the SAS MEANS procedure.

Qualitative variables are described by absolute frequency and percentage, derived using the SAS FREQ procedure. Missing values are tabulated with their frequency but are not included in the calculation of percentages.

The significance level for all the statistical analyses is set at 0.05 for two tails test.

Statistical Methods – Efficacy: (Continued)

For the primary efficacy endpoint, the estimate of the proportion of subjects with HIV-1 RNA levels below 50 copies/mL was provided for each treatment arm, along with the corresponding two-sided 95% confidence interval for the difference in proportions (two-drug arm minus three-drug arm), based on the normal approximation to the binomial distribution. If the lower limit of the confidence interval was above -10%, the two-drug arm would be considered non-inferior to the three-drug arm.

Differences between randomized treatment arms were assessed using Chi-Square or Fisher's exact test.

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Statistical Methods

Safety:
Safety was assessed using reports of adverse events and changes from Baseline in laboratory determinations and vital signs. Adverse events were coded using the MedDRA dictionary (version 9.0), to classify adverse events into a system organ class and preferred term. Treatment emergent adverse events (i.e., adverse events with onset date after the first dose of study treatment and within 30 days after the last dose of study medication) are summarized. Non Treatment Adverse Events are summarized as well.

Adverse events for which the investigator classifies the relationship to drug as "possible", "probable", "certain", or whose classification is missing have been considered drug-related.

The treatment proportions were compared by means of a Pearson Chi square test or Fisher's exact test (SAS FREQ procedure). These p-values were used as a flagging system. In the same way, for the more frequent adverse events (e.g. those AEs having an incidence of at least 10% in the total of subjects), the application of statistical methods for comparison of incidences have been considered.

To perform a comparison between the treatment arms, the values of haematology, biochemistry and urinalyses parameters were divided into classes: within or outside of Normal Range of the local laboratory, clinically significant or not regarding values outside Normal Range, as reported by the Investigator.

The proportions of subjects with total cholesterol, triglycerides, blood glucose values of toxicology Grade I-II-III-IV were compared between groups considering the worst grade achieved throughout the study.

Summary/Conclusions

Baseline Characteristics:

The two treatment groups were comparable for all demographic and Baseline disease characteristics except CD4 cell count. At Baseline, the mean CD4 cell count was 244.77 cells/mm^3 (CI95% [215.5, 274.05]) in the 2-drug-arm and 200.74 cells/mm^3 (CI95% [174.7, 226.77]) in the 3-drug-arm, with an ANOVA test p=0.026; slightly lower in the three-drug regimen. However, the number and proportion of subjects with Baseline CD4 cell count ≤ 200 cells/mm^3 remained comparable in the two treatment arms: 29 subjects (40.3%, CI95% [28.97, 51.63]) in the 2-drug-arm and 41 subjects (51.3%, CI95% [40.35, 62.25]) in the 3-drug-arm, with a Chi-Square test p= 0.175.

At Baseline, the Investigator-selected NsRTIs in the 3-drug-arm were distributed as follows: LPV/r+3TC/AZT 46 subjects (57.5%, CI95% [46.67, 68.33]), LPV/r+3TC/ABC 20 subjects (25%, CI95% [15.51, 34.49]), and LPV/r+other NsRTIs 14 subjects (17.5%, CI95% [9.17, 25.83]).

Qualification for the Treatment Phase:

At the end of the Run-in Phase, the number and proportion of subjects not reaching 2 consecutive HIV-1 RNA values below 50 copies/mL was 11 (15.3%, CI95% [6.98, 23.62]) in the 2-drug-arm and 7 (8.8%, CI95% [2.56, 14.94]) in the 3-drug-arm, with a Chi-Square test p=0.213.

Efficacy Results:

Antiviral Efficacy:

Using the ITT (NC=F) analysis, the proportion of subjects with plasma HIV-1 RNA below 50 copies/mL at Week 72 (Week 48 of the phase B) of the study was 51.4% (CI95% [39.86, 62.94]) in the 2-drug-arm and 52.5% (CI95% [41.56, 63.44]) in the 3-drug-arm. The difference between arms was not statistically significant, with a Chi-Square test p=0.891. The difference of proportions was –1.11 with a CI95% of [-18.34, 16.11] and as the lower limit of the confidence interval of the difference of proportions between treatment arms was under the study-defined treshold of -10%, the primary hypothesis of non-inferiority of the two-drug arm could not be confirmed. In the observed data (On-Treatment; PP, CC) analysis, 87% of subjects in the 2-drug-arm and 93% of subjects in the 3-drug-arm achieved plasma HIV-1 RNA <50 copies/mL at Week 72. The difference between arms was not statistically significant, with a Fisher's exact test p=0.468. The difference of proportions was –5.84 with a CI95% of [-21.25; 9.56]
The number (and proportion) of subjects reaching a HIV-1 RNA level below 50 copies/mL along the study was 56 (77.8%) in the 2-drug-arm and 61 (76.3%) in the 3-drug-arm. Mean time to achieve HIV-1 RNA levels below 50 copies/mL was 18.21 weeks (CI95% [15.86, 20.56]) in the 2-drug-arm and 16.92 (CI95% [15.11, 18.73]) in the 3-drug arm, with an ANOVA test p=0.381. Mean time until HIV-1 RNA nadir was 22.35 weeks (CI95% [18.02,26.68]) in the 2-drug-arm and 19.26 (CI95% [16.07, 22.46]) in the 3-drug arm, with a Wilcoxon test p=0.248.

The mean change in log plasma HIV-1 RNA values from baseline to the different time points of the study was comparable in the two treatment arms, except for the mean change in log plasma HIV-1 RNA from Baseline to week 12 which was –2.7 in the 2-drug-arm and –2.92 in the three-drug arm, with an ANOVA p=0.036; slightly in favour of the three-drug regimen.

The proportion of subjects with plasma HIV-1 RNA below 50 copies/mL at all the available study time points was comparable in the two treatment arms.

The proportion of subjects with plasma HIV-1 RNA below 400 copies/mL at all the available study time points was comparable in the two treatment arms.

Efficacy Results – *Antiviral Efficacy*: (Continued)

The number and proportion of subjects with viral blips (HIV-1 RNA above 50 copies/mL after having reached a value below 50 copies) after Week 24 of the study was 9 (12.5%) in the 2-drug-arm and 4 (5.0%) in the 3-drug-arm, with a Chi-Square p=0.099.

Immunological Efficacy

The analysis of CD4 cell count evolution and mean changes from Baseline to the different time points of the study were performed in subgroups of subjects with baseline CD4 cell counts above or below/equal to 200 CD4 cells/mm^3.

In subjects with CD4 cell counts at Baseline > 200 cells/mm^3, the CD4 cell counts and the mean changes from Baseline were comparable in the two treatment arms.

In subjects with Baseline CD4 cell counts ≤ 200 cells/mm^3 the mean CD4 cell counts were comparable from Baseline through Week 24. Instead, at Week 32 the mean CD4 cell counts were 328 and 231.48 in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.020; at Week 48 370.06 and 261.19, in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.016; at Week 56 406.75 and 289.7 in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.019; at Week 64 430.93 and 296.04, in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.011; and at Week 72 441.73 and 318.38, in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.041, with an overall difference in favour of the 2-drug-arm.

In subjects with Baseline CD4 cell counts ≤ 200 cells/mm^3 the mean changes in the CD4 cell counts from Baseline were comparable from Baseline through Week 40. At Week 48 the mean changes in the CD4 cell counts from Baseline were 243 and 154.62, in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.024; at Week 56 288.93 and 181.26, in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.025; at Week 64 311.43 and 187.7, in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.012; and at Week 72 331.86 and 216.33, in the 2-drug-arm and the 3-drug-arm, respectively, with an ANOVA test p=0.052, with an overall difference in favour of the 2-drug-arm.

To investigate this difference in subjects with Baseline CD4 cell counts ≤ 200 cells/mm^3, a further subgroup analysis according to the 2NsRTIs prescribed by the Investigator was performed on the 3-drug-arm. Statistically significant differences between the subgroups LPV/r+(3TC/AZT), LPV/r+(3TC/ABC) and LPV/r+other NsRTIs were detected only at some time points and in subjects with CD4 cell counts at Baseline > 200 cells/mm^3, namely in the mean CD4 cell counts and in the mean changes from Baseline at Weeks 56 (p=0.027 and p=0.048, respectively) and 64 (p=0.030 and p=0.050, respectively). No significant differences were detected in the mean CD4 cell counts nor in the mean changes from Baseline in the CD4 cell counts in the different 2NsRTI subgroups of the 3-drug-arm subjects with Baseline CD4 cell counts ≤ 200 cells/mm^3.

HIV-1 RNA slopes and CD4 cell count slopes along the study period were not different between treatment arms.

Efficacy Results – *Immunological Efficacy*: (Continued)
Regarding the Quality of Life questionnaire, although the differences were not statistically significant, the majority of the dimensions of the MOS-HIV Health Survey increased more from baseline in the 2-drug arm at Week 24 and at Week 48 (Week 24 of phase B). This trend changed at Week 72 (Week 48 of phase B) where the majority of dimensions increased more in the three-drug regimen, still not reaching statistical significance. However, at Week 72 (Final or Discontinuation Visit) the questionnaire was completed only by 59% of subjects (66% in the 2-drug-arm and 54% in the 3-drug-arm).

Finally, the 2-drug regimen showed a significantly lower rate of missing doses in the last week preceding the end-of-study visit, compared to the 3-drug regimen. However, at Week 72 (Week 48 of phase B; Final or Discontinuation Visit) also the Adherence questionnaire was completed only by 57% of subjects (61% in the 2-drug-arm and 54% in the 3-drug-arm).

Safety Results:

The global number and proportion of subjects who interrupted the study for any reason was 30 (41.67%) in the 2-drug-arm and 35 (43.75%) in the 3-drug-arm. 11/30 drop-outs in the 2-drug-arm and 7/35 in the 3-drug-arm were mandated due to HIV1-RNA >50 copies/mL at Week 24.

Adverse events:
The number and proportion of subjects with at least one adverse event (AE) of any severity and of any relationship to study drug(s) during the study was 61 (84.7%, CI95% [76.38, 93.02]) in the 2-drug-arm and 67 (83.8%, CI95% [75.73, 91.87]) in the 3-drug-arm, with a Chi-Square test p=0.870.

There were no substantial differences between the two treatment arms in terms of distribution of adverse events by SOC (System Organ Class) or event severity as judged by the Investigator. The number and proportion of subjects with at least one AE considered by the Investigator to be related to the study drug(s) was 39 (54.2%, CI95% [42.69, 65.71]) in the 2-drug-arm and 52 (65.0%, CI95% [54.55, 75.45]) in the 3-drug-arm, with a Chi-Square test p=0.174. The number and proportion of subjects with at least one serious AE during the study was 10 (13.9%, CI95% [5.91, 21.89]) in the 2-drug-arm and 7 (8.8%, CI95% [2.59, 15.01]) in the 3-drug-arm, with a Chi-Square test p=0.315. The number and proportion of subjects with at least one AE which caused discontinuation from the study was 9 (12.5%, CI95% [4.86, 20.14]) in the 2-drug-arm and 6 (7.5%, CI95% [1.73, 13.27]) in the 3-drug-arm, with a Chi-Square test p=0.302.

The most frequently reported adverse events considered by the Investigator to be related to Lopinavir/Ritonavir were Diarrhoea, 34.7% (CI95% [23.70, 45.70]) in the 2-drug-arm and 23.8% (CI95% [14.47, 33.13]) in the 3-drug-arm, with a Chi-square test p=0.136; Hypertriglyceridaemia, 12.5% (CI95% [4.86, 20.14]) in the 2-drug-arm and 15.0% (CI95% [7.18, 22.82]) in the 3-drug-arm, with a Chi-square test p=0.656; and Vomiting, 9.7% (CI95% [2.86, 16.54]) in the 2-drug-arm and 3.8% (CI95% [0, 7.99]) in the 3-drug-arm, with a Fisher test p=0.193.

The most frequently reported adverse events considered by the Investigator to be related to Tenofovir (two-drug arm) were: Diarrhoea (5.6%), and Nausea (5.6%).

The most frequently reported adverse events considered by the Investigator to be related to NsRTIs (three-drug arm) were: Diarrhoea (6.3%), Vomiting (6.3%), and Asthenia (6.3%).

Two deaths were reported during the treatment period, both in the two-drug arm. Either of the events leading to death (Pneumonia and Burkitt's Lymphoma) was considered by the Investigator to be not related to the study drug(s).

Safety Results: (Continuing)

Metabolic toxicity:

The frequency of subjects with total cholesterol, triglycerides, and blood glucose values of toxicology Grade I-II-III-IV were compared between groups considering the worst grade achieved throughout the study. The number and proportion of subjects with Grade III-IV total cholesterol alterations during the study were 3 (4.17%) in the 2-drug-arm and 7 (8.75%) in the 3-drug arm. The number and proportion of subjects with Grade III-IV triglyceride alterations during the study were 5 (6.94%) in the 2-drug-arm and 9 (11.25%) in the 3-drug arm. There were no Grade III-IV glucose alterations in none of the treatment arms. The number and proportion of subjects with Grade I-II hyperglycemia during the study were 5 (6.94%) in the 2-drug-arm and 16 (20.0%) in the 3-drug arm.

The number and proportion of subjects with total cholesterol values outside normal range and not considered clinically significant by the Investigator at Baseline was 17 (28.3%) in the 2-drug-arm and 15 (23.4%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 19 (30.6%) in the 2-drug-arm and 33 (52.4%) in the 3-drug-arm, with no substantial changes in the proportions of clinically significant out-of-range values.

The number and proportion of subjects, with the relative CI95%, with HDL cholesterol values at Baseline within normal range was 28 (51.9%) in the 2-drug-arm and 28 (46.7%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 34 (66.7%) in the 2-drug-arm and 36 (69.2%) in the 3-drug-arm.

The number and proportion of subjects with LDL cholesterol values at Baseline outside normal range and not considered clinically significant by the Investigator was 2 (3.8%) in the 2-drug-arm and 5 (8.9%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 8 (18.2%) in the 2-drug-arm and 12 (27.9%) in the 3-drug-arm, with no clinically significant out-of-range values.

The number and proportion of subjects with triglyceride values at Baseline outside normal range and not considered clinically significant by the Investigator was 10 (16.7%) in the 2-drug-arm and 13 (20.0%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 23 (37.1%) in the 2-drug-arm and 22 (34.9%) in the 3-drug-arm. The number and proportion of subjects with triglyceride values at Baseline outside normal range and considered clinically significant by the Investigator was 0 (0%) in the 2-drug-arm and 2 (3.1%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 7 (11.3%) in the 2-drug-arm and 6 (9.5%) in the 3-drug-arm.

The number and proportion of subjects with glucose values at Baseline outside normal range and not considered clinically significant by the Investigator was 3 (5.0%) in the 2-drug-arm and 5 (7.7%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 3 (4.8%) in the 2-drug-arm and 4 (6.3%) in the 3-drug-arm. The number and proportion of subjects with glucose values at Baseline outside normal range and considered clinically significant by the Investigator was 1 (1.7%) in the 2-drug-arm and 1 (1.5%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 1 (1.6%) in the 2-drug-arm and 2 (3.1%) in the 3-drug-arm.

Renal toxicity:

The number and proportion of subjects with serum creatinine values at Baseline outside normal range and not considered clinically significant by the Investigator was 2 (3.3%) in the 2-drug-arm and 3 (4.6%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 0 (0%) in the 2-drug-arm and 2 (3.2%) in the 3-drug-arm, with no clinically significant out-of-range values.

Safety Results: (Continuing)

The value of creatinine clearance was calculated by the Investigators by using the Cockroft-Gault formula, and the normal ranges of the formula were applied. The number and proportion of subjects with creatinine clearance values at Baseline outside normal range and not considered clinically significant by the Investigator was 20 (33.9%) in the 2-drug-arm and 26 (40.0%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 28 (46.7%) in the 2-drug-arm and 23 (39.0%) in the 3-drug-arm. The number and proportion of subjects with creatinine clearance values at Baseline outside normal range and considered clinically significant by the Investigator was 1 (1.7%) in the 2-drug-arm and 0 (0%) in the 3-drug-arm. At Week 72 (Week 48 of phase B) of the study no clinically significant out-of-range values were reported in none of the treatment arms.

The number and proportion of subjects with serum phosphate values at Baseline outside normal range and not considered clinically significant by the Investigator was 4 (7.7%) in the 2-drug-arm and 8 (14.3%) in the 3-drug-arm, and at Week 72 (Week 48 of phase B) of the study 8 (14.3%) in the 2-drug-arm and 10 (19.6%) in the 3-drug-arm, with no clinically significant out-of-range values.

Conclusions:

The antiviral activity of a two-drug regimen of LPV/r + Tenofovir appears comparable to that of a standard-of-care three-drug regimen of LPV/r + 2 NsRTIs as prescribed by the Investigator. There were no statistically significant differences between the two treatment groups in any of the antiviral efficacy endpoints at any time points during the study.

There were no statistically significant differences between treatment groups in any of the immunological efficacy endpoints at any time points during the study, with the exception of a more pronounced mean CD4 cell count increase in the two-drug arm in subjects with a Baseline CD4 cell count ≤ 200 cells/mm^3.

The treatment groups were comparable with regard to the overall incidence of adverse events, to the drug-related adverse event incidence, and to Grade I-IV laboratory abnormality incidence. Adverse event profiles were similar in character between the two treatment arms.

This data demonstrates that a two-drug regimen of LPV/r + Tenofovir and a standard-of-care three-drug regimen of LPV/r + 2 NsRTIs chosen by the Investigator are comparable in safety, antiviral efficacy and immunological efficacy in ARV-naïve HIV-1 positive patients. However, the primary hypothesis of non-inferiority of the two-drug arm could not be confirmed.