



2.0 Synopsis

Abbott France	Individual Study Table Referring to Item of the Submission:	(For National Authority Use Only)
Name of Study Drug: Kaletra®	Volume:	
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Title of Study: A Pilot, Open-Label, Randomized, Comparative Study of the Antiviral Efficacy of Lopinavir /Ritonavir Single-Drug Regimen versus Lopinavir /Ritonavir in Combination with Lamivudine/Zidovudine in Antiretroviral Naïve Patients.		
Investigators: Multi-center study. Coordinating Investigator: Prof. JF Delfraissy, [REDACTED]		
Study Sites: [REDACTED] redacted information 08Aug2014 21 centres in France, 5 in Italy, 4 in Germany, 4 in Spain, 2 in Poland. In total, there were 31 active centres.		
Publications: as of May 27, 2008 1) One-year Fat Tissue Distribution Changes in Antiretroviral Naïve Human Immunodeficiency Virus (HIV)-infected Patients Treated with Lopinavir/ritonavir (LPV/r) monotherapy versus LPV/r with zidovudine/lamivudine (AZT/3TC) in the MONARK Trial. JF. Delfraissy, P. Flandre, P. Ngo Van, I. Cohen-Codar, MA. Valantin, C. Lascoux, P. Morlat, F. Boué, JP. Chauvin, F. Emery Salbert, I. Gaultier, R. Rode, M. Norton, C. Roux, S. Kolta. 4th International Conference on HIV Pathogenesis, Treatment and Prevention Sydney, Australia 22-25 July 2007. Poster WEPEB118LB. 2) The Monark trial: where now for boosted protease inhibitor monotherapy ? Andrew Hilla, Bernard Hirschelb and Christine Katlamac. AIDS, 2008, 22:777–779. 3) XVI International AIDS Conference - Toronto Canada - 13-18 August 2006 - Oral Presentation #LB202. 48-week analysis of LPV/r monotherapy compared to LPV/r + AZT/3TC in antiretroviral-naïve patients: MONARK trial. JF Delfraissy, P Flandre, C Delaunay, A Horban, PM Girard, C Rouzioux, M Norton, I Cohen Codar, P NgoVan, JP Chauvin. 4) AIDS 2008, 22:385–393. Efficacy and safety of lopinavir/ritonavir monotherapy compared to standard-of-care lopinavir/ritonavir plus zidovudine and lamivudine in antiretroviral-naïve HIV-infected patients: Week 48 results from the randomized Monark trial. Jean-François Delfraissy, Philippe Flandre, Constance Delaunay, Jade Ghosn, Andre Horban, Pierre-Marie Girard, Michael Norton, Christine Rouzioux, Anne-Marie Taburet, Isabelle Cohen-Codar, Philippe Ngo Van and Jean-Pierre Chauvin. 5) 11th EACS 2007 - Oct 24-27, 2007, Madrid – Oral presentation. Prognostic Factors of Virological Success in Antiretroviral-naïve Patients Receiving LPV/r Monotherapy in the MONARK Trial. Flandre		



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<p>P, Delaugerre C, Ghosn J, Chaix ML, Horban A, Girard PM, Gladysz A, Cohen-Codar I, NgoVan P, Taburet AM, Rouzioux C, Delfraissy JF.</p> <p>6) XVII International AIDS Conference - Mexico City, 3-8 August 2008 – Poster. Week-96 end of trial analysis of antiretroviral (ARV)-naïve patients randomized to the lopinavir/ritonavir (LPV/r) single drug arm in the Monark trial. Jade GHOSN, Philippe FLANDRE, Constance DELAUGERRE, Marie-Laure CHAIX, Pierre DELLAMONICA, Richard A. RODE, Yue WANG, Michael NORTON, Isabelle COHEN-CODAR, Philippe NGOVAN, Christine ROUZIOUX, and Jean-François DELFRAISSY.</p> <p>7) XV International HIV Drug Resistance Workshop - 13 - 17June , 2 006 • Sitges, Spain – Oral presentation + poster. Drug Resistance Outcomes in a Trial Comparing Lopinavir/ritonavir (LPV/r) Monotherapy to LPV/r + Zidovudine/Lamivudine (MONARK Trial). M Norton, C Delaugerre, G Batot, JF Delfraissy, C Rouzioux.</p> <p>8) 16th International HIV Drug Resistance Workshop – June 2007: Oral presentation + Poster. Protease Gene Mutations In a Trial Comparing First Line Lopinavir/ritonavir Monotherapy to Lopinavir/ritonavir + Zidovudine/Lamivudine (MONARK Trial). C Delaugerre, P Flandre, ML Chaix, P. Dellamonica, F. Raffi,H Jäger, D Schürmann, P. NgoVan, M. Norton, I. Cohen Codar, JF Delfraissy, C Rouzioux.</p> <p>9) 15th Conference on Retroviruses and Opportunistic Infections (CROI) • 2 - 7 February 2008 • Boston (USA): poster presentation #781. Impact of a 48-week Lopinavir/r Monotherapy on HIV1-DNA in Blood Cells in the MONARK Trial. Avettand-Fenoel V, Flandre Ph, Chaix ML, Ghosn J, Delaugerre C, Raffi F, NgoVan Ph, Cohen-Codar I, Delfraissy JF, Rouzioux C.</p> <p>10) 8th International Congress on Drug Therapy in HIV Infection,12-16 November 2006 PL 13.3 Oral presentation. Impact of a LPV/r monotherapy on self-reported side effects and global health perception among antiretroviral-naïve patients: 48-week analysis of the MONARK trial. B Spire, F Marcellin, I Cohen Codar, B Knysz, C Lascoux, MA Valantin, M Norton, P Ngo Van, JF Delfraissy.</p> <p>11) Manuscript in Antiviral Therapy. June 2008, vol. 13, Issue 4. Impact of a LPV/r monotherapy on self-reported side effects and general health perception among antiretroviral-naïve patients: 48-week analysis of the MONARK trial. Bruno Spire, Fabienne Marcellin, Isabelle Cohen-Codar, Philippe Flandre, Francois Boue, Pierre Dellamonica, François Raffi, Michael Norton, Philippe Ngo Van, Jean-François Delfraissy.</p> <p>12) 9th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV – Sydney - July 19-21, 07 : Submitted as Late-Breaker: Poster. One-year Fat Tissue Distribution Changes in Antiretroviral Naïve HIV-infected Patients Treated with Lopinavir/ritonavir (LPV/r) monotherapy versus LPV/r with zidovudine/lamivudine (AZT/3TC) in the MONARK Trial. JF. Delfraissy, P. Flandre, P. Ngo Van, I. Cohen-Codar, MA. Valantin, C. Lascoux, P. Morlat, F. Boué, JP. Chauvin, M. Norton, C. Roux, S. Kolta.</p> <p>13) XV International HIV Drug Resistance Workshop • 13 - 17June , 2 0 0 6 • Sitges , Spain – Oral</p>		



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<p>presentation + poster. Absence of HIV-1 shedding in the male genital tract after one-year of lopinavir/ritonavir alone or in combination with Combivir®: a substudy of Monark trial. J.Ghosn, G. Peytavin, J. Galimand, PM. Girard, F. Raffi, JF Delfraissy, I. Cohen-Codar, C. Rouzioux, and ML Chaix.</p> <p>14) Journal of Antimicrobial Chemotherapy (JAC) 2008. Absence of HIV-1 shedding in male genital tract after one year of first-line lopinavir/ritonavir alone or in combination with Combivir®. Jade Ghosn, Marie-Laure Chaix, Gilles Peytavin, Jean-Louis Bresson, Julie Galimand, Pierre-Marie Girard, François Raffi, Isabelle Cohen-Codar, Jean-François Delfraissy and Christine Rouzioux.</p> <p>15) XVII International HIV Drug Resistance Workshop – Sitges, Spain, June 2008: Poster. Exploration of a novel resistance pathway through Gag protein cleavage site: Week-96 final analysis of patients failing on a first-line lopinavir/ritonavir single drug regimen in the Monark trial. Jade Ghosn, Constance Delaugerre, Marie-Laure Chaix, Philippe Flandre, Julie Galimand, Isabelle Cohen-Codar, Michael Norton, Jean-François Delfraissy, And Christine Rouzioux.</p>		
Studied Period (Years): 2003-2007 Initiation Date: 25 August 2003 Completion Date: 15 February 2007		Phase of Development: III
Objectives: <p>The primary objective of this study was:</p> <ul style="list-style-type: none">To compare over at least 48 weeks in antiretroviral-naïve patients the antiviral activity of a lopinavir/ritonavir (LPV/r)-single drug regimen versus a Highly Active Antiretroviral Therapy (HAART) standard triple regimen of LPV/r in combination with zidovudine (AZT) and lamivudine (3TC). <p>The secondary objectives of this study were:</p> <ol style="list-style-type: none">To compare between the two arms over at least 48 weeks:<ul style="list-style-type: none">CD4 evolution.In failing patients: occurrence of mutation in the HIV protease and reverse transcriptase.Occurrence of Acquired Immunodeficiency Syndrome (AIDS) clinical events.Safety of Nucleoside Reverse Transcriptase Inhibitor (NRTI)-sparing versus a Protease Inhibitor (PI) with 2 NRTIs regimen: clinical and biological tolerance, i.e. mitochondrial		



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<p>toxicity, fat redistribution with Dual-Energy X-ray Absorptiometry (DEXA)-scan, metabolic toxicity (lipid profile, glucose, insulin).</p> <ul style="list-style-type: none">• Patient's adherence and Quality Of Life (QoL). <p>2. To assess in the LPV/r single-drug regimen arm over 96 weeks:</p> <ul style="list-style-type: none">• Virological control.• CD4 evolution.• Safety.		
Methodology: Phase III, open-label, randomized, comparative, multicenter study.		
Number of Subjects (Planned and Analyzed): Planned: 120 subjects (i.e. 70 and 50 subjects in the LPV/r monotherapy group and LPV/r tritherapy group, respectively).		
Analyzed	Kaletra® (LPV/r)	Reference (ZDV/3TC/LPV/r)
Randomized:	83 (61.0%)	53 (39.0%)
Completed:	45 (54.2 %)	15 (28.3%)
Prematurely terminated:	38 (45.8%)	38 (71.7%)
Diagnosis and Main Criteria for Inclusion: Subjects had to meet the following inclusion criteria: <ol style="list-style-type: none">1. Subject had voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), after the nature of the study had been explained and the subject had had the opportunity to ask questions. The informed consent had to be signed before any study-specific procedures were performed.2. Subject was at least 18 years of age.3. If female, subject was not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or was childbearing potential and practicing one barrier method of birth control.4. If female, the results of a urine pregnancy test performed at screening (urine specimen obtained no earlier than 28 days prior to study drug administration) was negative.5. Subject was not breast-feeding.		



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<div><div><div>6. Subject was naïve to antiretroviral treatment with reverse transcriptase inhibitor or PI.</div><div>7. Subject had a plasma HIV Ribonucleic Acid (RNA) level ≤ 100 000 copies/mL at screening.</div><div>8. Subject had a CD4 cell count ≥100 cells/mm³ at screening.</div><div>9. Vital signs, physical examination and laboratory results did not exhibit evidence of acute illness.</div><div>10. Subject had a Karnofsky Score greater than or equal to 70.</div><div>11. Subject had no significant history of cardiac, renal, neurologic, psychiatric, oncologic, endocrinologic, metabolic or hepatic disease that could adversely affect his/her participating in this study.</div><div>12. Subject did not require and agreed not to take any of the following medications for the duration of the study: midazolam, triazolam, terfenadine, astemizole, cisapride, pimozide, propafenone, flecainide, certain ergot derivatives (ergotamine, dihydroergotamine, ergonovine, and methylelrgonovine), rifampin, lovastatin, simvastatin, and St. John’s wort.</div><div>13. Subject agreed not to take any medication during the study, including over-the-counter medicine, herbal medications, alcohol or recreational drugs without the knowledge and permission of the principal investigator.</div><div>14. Subject had not been treated for an active AIDS-defining opportunistic infection within 30 days of screening. Subjects who were on stable maintenance therapy for an opportunistic infection might be enrolled after consultation with Abbott.</div></div></div> <div>Subjects had to have none of the following exclusion criteria:</div> <div><div>1. Subject with an HIV primo-infection status.</div><div>2. Presence of the following mutations:<div><div>- In the protease: one among 32, 47, 48, 50, 82, 84, 90, OR more than 3 mutations from the other points of the Lopinavir (LPV) mutation score : 10, 20, 24, 46, 53, 54, 63, 71.</div><div>- In the reverse transcriptase: 215 or 184.</div></div></div><div>3. Subject had a recent (within the past 6 months) history of drug and/or alcohol abuse.</div><div>4. Subject had a history of psychiatric illness.</div><div>5. Screening laboratory analyses showed any of the following abnormal laboratory results:<div><div>- Hemoglobin ≤ 8.0 g/dL,</div><div>- Absolute neutrophil count ≤ 750 cells/μL,</div><div>- Platelet count ≤ 50,000 per mL,</div><div>- Alanine AminoTransferase (ALT) or ASpartate aminoTransferase (AST) ≥ 3.0 x Upper Limit of Normal (ULN),</div><div>- Creatinine ≥ 1.5 x ULN,</div></div></div><div>6. Subject had received any investigational drug within 30 days prior to study drug administration.</div><div>7. For any reason, subject was considered by the investigator to be an unsuitable candidate for the study.</div></div>			



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Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Co-formulated LPV/r soft gel capsules containing 133.3 mg lopinavir and 33.3 mg ritonavir per capsule, and administered orally. Batch number: [REDACTED] redacted information 08Aug2014		
Duration of Treatment: 48 weeks in the triple drug regimen arm and 96 weeks in the single drug regimen arm.		
Reference Therapy, Dose and Mode of Administration, Lot Number: Co-formulated AZT/3TC tablets containing 300 mg zidovudine and 150 mg lamivudine per tablet, and administered orally. Batch number [REDACTED]		
Criteria for Evaluation: redacted information 08Aug2014		
Efficacy:		
<u>Primary efficacy variable:</u> The primary efficacy variable was the proportion of subjects with plasma HIV RNA level below 400 copies /mL at Week 24 AND below 50 copies /mL at Week 48.		
<u>Secondary efficacy variables:</u>		
<u>Virologic response</u>		
<ul style="list-style-type: none">Proportion of patients with HIV RNA level below 400 copies/mL at the following visits:<ul style="list-style-type: none">- Week 24- Week 48Proportion of patients with HIV RNA level below 50 copies/mL at the following visits:<ul style="list-style-type: none">- Week 24- Week 48HIV plasma viral load evolution from baseline to weeks 24 and 48,Slopes of HIV RNA decrease,Time until HIV RNA nadir,Time until first HIV RNA level < 400 copies/mL and < 50 copies/mL, respectively,		



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<ul style="list-style-type: none">• Evolution from baseline to 48 weeks of proviral Deoxyribonucleic Acid (DNA), including intracellular genotype,• Correlation of early virologic response (HIV RNA decrease during the first 4 weeks) and plasma LPV/r C trough (Lopinavir/ritonavir trough plasma concentrations),• In failing patients: occurrence of mutation on the HIV protease and Reverse Transcriptase (RT), and if deemed necessary phenotype,• Time to:<ul style="list-style-type: none">- Virologic failure- Premature discontinuation			
<u>Immunologic response:</u> <ul style="list-style-type: none">• CD4 variation.			
Safety: <p>Adverse event monitoring, clinical laboratory data (hematology, clinical chemistry), physical examinations and vital signs were assessed throughout the study. The following additional safety criteria were to be evaluated:</p> <ul style="list-style-type: none">• Mitochondrial (mt) toxicity: mtDNA/nuclear DNA (nDNA) ratio,• Morphologic toxicity: DEXA-scan and anthropomorphic measurements,• Metabolic toxicity: lipid profile (cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL), triglycerides, glucose and insulin measurements).			
Statistical Methods: <ul style="list-style-type: none">• Primary analysis <p>Fisher’s exact test was used to compare the proportion of subjects with virologic response (HIV-1 RNA < 400 copies/mL at Week 24 and < 50 copies/mL at Week 48) in the two LPV/r-containing arms.</p> <ul style="list-style-type: none">• Secondary analysis<ul style="list-style-type: none">• Fisher’s exact test was used to compare the proportion of subjects with HIV-1 RNA < 400 copies/mL at week 24 and the proportion of patients < 50 copies/mL at Week 48 in the two LPV/r-containing arms.• Non-parametric tests (Wilcoxon and Kruskal-Wallis) were used to compare:<ul style="list-style-type: none">- Change in viral load from entry to Weeks 4 and 8,			



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<ul style="list-style-type: none">- Change in viral load from entry to Week 48,- Change in CD4 cells count from entry to Weeks 24, 48 and 96,- Concentrations of LPV trough concentration at Weeks 4, 24 and 48, <p>in the two LPV/r-containing arms.</p> <ul style="list-style-type: none">• The Kaplan-Meier method and the log-rank test were used to compare:<ul style="list-style-type: none">- Time to reach a first HIV RNA < 400 copies/mL and a first HIV-1 RNA < 50 copies/mL,- Time to premature discontinuation,in the two LPV/r-containing arms.• Non-parametric tests were used to compare HIV-1 RNA decrease at Week 4 and Week 8 between responders (patients reaching the primary endpoint) and non-responders.• Non-parametric tests were used to compare concentrations of LPV trough concentration at week 4, 24, 48, between responders (patients reaching the primary endpoint) and non-responders.• Changes from study entry to Weeks 24 and 48 in levels of mitochondrial toxicity, metabolic toxicity (lipid profile, glucose and insulin measurements) and fat redistribution (DEXA-scan and anthropomorphic measurements) were estimated and compared using Wilcoxon non parametric test.• Number of minor adverse events was summarized at each study visit.• Severe adverse events and adverse events requiring drug discontinuation were summarized by treatment arm.• The level and change from baseline of the following parameters: lymphocytes markers CD4, lymphocytes markers CD8, haemoglobin, creatinine, total bilirubin, total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, glucose, ASAT ALAT, were given at weeks 0, 4, 12, 24, 32, 40, 48, 60, 72, 84 and 96.• The 6 scores of World Health Organisation Quality Of Life (WHOQOL) HIV BREF questionnaire representing the social, psychological, environmental, independence and spirituality domain were compared in the two groups using a t-test or a Mann-Whitney U test according to the skewness of the distribution of each examined dimension.• Augmented Symptom Distress Module (ASDM): Self-reported symptoms and self-reported disturbing symptoms were summarized by treatment arm. Rates of occurrence of each symptom were compared using Fisher’s exact test. The number of self reported symptoms was computed (simple or weighted with respect to the associated distress) and compared between treatment arms using non-parametric test.		



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Summary/Conclusions:		
<p>Efficacy Results:</p> <p>A total of 83 and 53 subjects were randomly assigned to the LPV/r monotherapy and LPV/r tritherapy groups, respectively.</p> <p>In the Intent-To-Treat (ITT) analysis, 53 subjects (63.9%) in the LPV/r monotherapy group and 40 subjects (75.5%) in the LPV/r tritherapy group were responders according to the primary efficacy criterion, i.e. had HIV-1 RNA < 400 copies/mL at week 24 and < 50 copies/mL at week 48. This difference was not statistically significant (p = 0.19).</p> <p>However, results in the on-treatment analysis showed a statistically significant difference between the two groups: the proportion of responders was significantly lower in subjects receiving LPV/r monotherapy (80.3%) than in subjects treated with LPV/r tritherapy (97.6%) (p = 0.02).</p> <p>Few significant differences were obtained between the two groups in the secondary efficacy criteria. No statistically significant difference was demonstrated between the two groups in terms of the proportions of subjects with HIV-1 RNA < 400 copies/mL at week 24 or < 50 copies/mL at week 48 (ITT analysis). However, in the on-treatment analysis, fewer subjects on LPV/r monotherapy had an HIV-1 RNA level of less than 50 copies/mL at week 48 compared with those on LPV/r tritherapy (83.6% versus 97.6%, respectively, p = 0.03).</p> <p>A statistically significant difference was not observed between groups with respect to the time until first HIV-1 RNA level < 400 copies/mL was reached (p = 0.42). The majority of subjects in both treatment arms had reached an HIV-1 RNA level of less than 400 copies/mL by week 4. Almost all subjects in both treatment arms had a viral load of less than 400 copies/mL by week 16. A statistically significant difference between treatment arms was also not observed for the time until first HIV-1 RNA level < 50 copies/mL was reached.</p> <p>Overall, similar decreases in viral load from baseline, indicated by the decrease in HIV-1 RNA, were observed in the two groups at weeks 4 and 8. Broadly similar decreases in viral load from baseline were also observed in responders and non-responders in the LPV/r monotherapy and LPV/r tritherapy groups. No statistically significant differences were observed between responders and non-responders in each treatment arm with regard to the change in viral load from baseline to weeks 4 and 8.</p> <p>Moreover, the reduction in viral load from baseline to week 48, expressed in either per millions of leucocytes or per millions of CD4, was also similar in the two groups.</p> <p>At week 4, a statistically significantly higher mean plasma LPV trough concentration was found in the LPV/r monotherapy group compared with that obtained in the LPV/r tritherapy group (6532.7 ± 3737.6 ng/mL versus 5201.4 ± 3715.8 ng/mL, p = 0.03). The same trend was also observed at week 48 (5042.6 ± 2992.9 ng/mL versus 3967.2 ± 2622.6 ng/mL, respectively), although the difference between treatment arms was not statistically significant (p = 0.06). The trough concentration of LPV was higher in the LPV/r tritherapy group relative to the LPV/r monotherapy group at week 24. In addition, mean</p>		



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plasma LPV trough concentrations were in the same range in subjects who were responders and those who were non-responders in both of the LPV/r monotherapy and LPV/r tritherapy treatment arms at weeks 4, 24 and 48.

Finally, similar CD4 cell count increases were found in the two groups, except at week 24, where a statistically significant difference in the immunological response was found (140.1 ± 92.2 cell/mm³ in the LPV/r monotherapy group versus 103.7 ± 94.4 cell/mm³ in the LPV/r tritherapy group [p = 0.02]).

Of the 39 subjects with available genotypic results, approximately half of subjects in each treatment group experienced any changes to the protease gene. Three major PI-associated resistance mutations (M46I, L76V, V82A/V) emerged in 5 subjects on LPV/r monotherapy, only. The most frequently reported mutation was L76V. From the genotypic resistance data, it was concluded that the barrier for the development of PI resistance was lower with LPV/r monotherapy in comparison with LPV/r tritherapy.

No significant changes were observed in the 6 QoL scores. The proportion of subjects who changed from a negative to a positive perception in the general health status from baseline to week 24 and week 48 increased significantly in the monotherapy arm (p <0.0001).

Subjects treated with the standard triple-drug therapy reported significantly more symptoms over 48 weeks of treatment than patients treated with LPV/r monotherapy (Incidence Rate Ratio (IRR) [95% CI] of 1.3 [1.1; 1.6], p = 0.001, and 1.4 [1.2; 1.7], p = 0.0004 for the total number of symptoms and the number of symptoms causing discomfort, respectively).

Safety Results:

A total of 77 subjects (92.8%) experienced 417 Treatment-Emergent Adverse Events (TEAEs) in the LPV/r monotherapy group while 46 subjects (86.8%) experienced 228 TEAEs in the LPV/r tritherapy group with no statistically significant difference in the proportion of subjects who reported at least one TEAE (Chi2 test=0.248). In both groups, gastrointestinal disorders (92 subjects, 67.6%) were the most frequently involved System Organ Class (SOC). Diarrhea (56 subjects, 41.2%) was the most common reported TEAE by Preferred Term (PT).

The majority of TEAEs reported during the study were mild (106 subjects, 77.9%) or moderate (91 subjects, 66.9%) in intensity. Few severe TEAEs were reported: 26 TEAEs were rated as severe in 14 subjects (16.9%) in the LPV/r monotherapy group, while 7 TEAEs were severe in intensity in 4 subjects (7.5%) in the LPV/r tritherapy group. The most frequently reported severe TEAE by PT was increased ALT (3 subjects, 2.2%).

There was a similar proportion of subjects who experienced at least one Serious Adverse Event (SAE) in both groups (Chi2 test=0.165): in the LPV/r monotherapy group, 22 SAEs were reported in 15 subjects (18.1%), while 10 SAEs were reported in 5 subjects (9.4%) in the LPV/r tritherapy group. No deaths were reported during the study. The number of SAEs which were considered by the Investigator to be probably or possibly related to the study medication was limited in both groups: 4 SAEs (three cases of



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elevation in ALT levels and one case of diabetes mellitus) in the LPV/r monotherapy group, and 2 SAEs (dyspepsia and asthenia) in the LPV/r tritherapy group.

Both treatment groups were well balanced with regard to the incidence of TEAEs considered to be drug-related (72.3% in the LPV/r monotherapy group versus 73.6% in the LPV/r tritherapy group, Chi2 test=0.868) and the incidence of TEAEs which led to discontinuation from the study (12.0% in the LPV/r monotherapy group versus 13.2% in the LPV/r tritherapy group, Chi2 test=0.842).

There were no clear trends towards change in hematology and clinical chemistry laboratory parameters from baseline to endpoint in both treatment groups. Overall, the proportions of subjects in the two treatment groups who experienced a normal to low or high shift in laboratory values were relatively similar, apart from the incidence of subjects under LPV/r tritherapy experiencing a decrease in Red Blood Cells (RBC), hemoglobin, or hematocrit or an increase in AST, or bicarbonates. In both groups, increase in total cholesterol, LDL, bicarbonates and triglycerides were the most frequently reported individual changes.

No major differences between the two groups were found with respect to vital signs, physical examinations and anthropomorphic measurements. Regarding DEXA scans results, a significantly lower incidence of lipoatrophy was observed in the LPV/r monotherapy arm compared to the LPV/r tritherapy group (27.3% versus 4.9% respectively, p=0.018). However, trunk fat accumulation did not differ between the 2 treatment arms.

Conclusions:
<ul style="list-style-type: none">• In the ITT analysis, approximately two thirds of subjects were responders according to the primary efficacy criterion, i.e. had HIV-1 RNA < 400 copies/mL at week 24 and < 50 copies/mL at week 48 in each arm with no statistically significant difference between the LPV/r monotherapy and LPV/r tritherapy groups.• Few significant differences were observed between the two groups in the secondary efficacy criteria.• The barrier for the development of PI resistance was lower with LPV/r monotherapy in comparison with LPV/r tritherapy. In three of the five subjects who developed a major PI mutation while on LPV/r monotherapy, intensification of AZT/3TC therapy led to viral suppression.• A trend towards the improvement of health scores was observed for subjects receiving LPV/r monotherapy from baseline to week 48.• A comparable safety profile was observed in both groups.