A randomized trial to evaluate lopinavir/ritonavir versus saquinavir/ritonavir in HIV-1-infected patients: the MaxCmin2 trial

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Objective: To assess the rate of protocol-defined treatment failure and safety of lopinavir/ritonavir (LPV/r) and saquinavir/ritonavir (SAQ/r).

Design: Open-label, prospective, randomized (1:1), international multi-centre trial.

Methods: Adult HIV-1-infected patients were assigned LPV/r 400/100 mg twice daily or SAQ/r 1000/100 mg twice daily with two or more nucleoside reverse transcriptase inhibitors (NRTIs)/non-NRTIs. All patients, whether on or off the assigned treatment, were followed for 48 weeks.

Results: Of 339 randomized patients, 324 initiated assigned treatment (intention-to-treat/exposed [ITT/e] population). At 48 weeks, treatment failure occurred in 29/163 (18%) and 53/161 (33%) of patients in the LPV/r and SAQ/r arms, respectively (ITT/e, *P*=0.002, log rank test). In an analysis that also considered those patients who discontinued treatment as having failed treatment (ITT/e/discontinuation=failure), 40/161 (25%) LPV/r-treated individuals versus 63/161 (39%) SAQ/R-treated individuals failed treatment (*P*=0.005, log rank test). Discontinuation of the assigned treatment occurred in 23/163 (14%) patients in the LPV/r-treated group, compared with 48/161 (30%) in the SAQ/r-treated group (ITT/e; *P*=0.001). The primary reasons for premature discontinuation were non-fatal adverse events (LPV/r: 12/163; SAQ/r: 21/161) and patients' choice (LPV/r: 7/163; SAQ/r: 8/161). In the on-treatment analysis of time to treatment failure, no difference was observed between the two arms (*P*=0.27, log rank test).

Conclusion: LPV/r had better antiretroviral effects compared with SAQ/r at the doses and in the formulations studied. This may have been a result of patients' preferences and ability to adhere to assigned therapy, rather than a result of differences in the intrinsic potency of the study protease inhibitors.

Introduction

Ritonavir-boosted protease inhibitor (PI) treatment results in increased PI plasma concentrations [1], which have been associated with improved treatment outcomes [2,3]. One study of lopinavir/ritonavir (LPV/r) 400/100 mg twice daily had a better virological and immunological outcome compared with an un-boosted PI [4]. Treatment with LPV/r has been associated with significant increases in lipid markers [5], and increased lipid levels in patients treated with combination antiretroviral treatment are associated with an increased risk of development of myocardial infarction [6]. The first comparative study of ritonavir-

boosted PI regimens for the treatment of adult HIV-1 infection, the MaxCmin1 trial, found indinavir/ritonavir (IDV/r) 800/100 mg twice daily and saquinavir soft gel/ritonavir (SAQ/r) 1000/100 mg twice daily to have equivalent virological and immunological efficacy, with a higher rate of discontinuation in the IDV/r arm [7]. Furthermore, low-dose ritonavir boosting resulted in a more favourable lipid profile for saquinavir compared with indinavir [7].

The MaxCmin2 trial was designed to assess the efficacy and safety of LPV/r 400/100 mg twice daily compared with SAQ/r 1000/100 mg twice daily, the primary outcome being protocol-defined treatment failure.

Methods

MaxCmin2 was a randomized (1:1), Phase IV, open-label, multi-centre trial involving 36 sites in 12 countries on 3 continents. The trial was conducted in accordance with the Helsinki II Declaration and the Good Clinical Practice guidelines [ICH-GCP Guideline (CPMP/ICH/135/95)]. Independent ethics committees or institutional review boards approved the protocol. Patients were assessed for eligibility at a screening visit and provided written informed consent before the conduct of any trial-specific procedure. Eligible patients were 18 years or older, had documented HIV-1 infection (confirmed by ELISA), were not pregnant or breastfeeding, and did not have a serious medical condition at time of screening. Furthermore, all laboratory values had to be judged clinically non-significant by the treating physician. Patients for whom a regimen including a ritonavir-boosted PI was indicated were enrolled, including those who were antiretroviral-treatment naive, PI naive or PI experienced with virological failure or intolerance to PIs. PI-experienced patients with previous use of either of the study drugs were not precluded from participation. However, only patients with a clinical estimate of an equal chance of benefit/risk for the two study PIs at time of screening, and with no evidence of past or current virological failure on the study PIs, could be randomized. Before randomization, the treating physician decided on the concomitant use of at least two nucleoside reverse transcriptase inhibitors (NRTIs) and/or non-NRTIs (NNRTIs). Computerized block randomization was performed at the Copenhagen HIV Programme (CHIP). Randomization was stratified according to geographical region of site and PI experience.

All randomized patients were followed, irrespective of whether they started on or discontinued the assigned treatment, at baseline (first day of intake of assigned treatment) and at weeks 4, 12, 24, 36 and 48. During follow-up visits the following procedures were performed: clinical evaluation, safety analyses on blood, plasma HIV-1 RNA viral load (pVL) and $CD4^+$ cell count. At baseline, week 4 and week 48, fasting total cholesterol, low-density lipoprotein (LDL) cholesterol and total triglyceride levels were measured. Following completion of the trial, genotypic resistance testing was performed centrally (AB Laboratories, Luxembourg) in batches using stored plasma from patients with a plasma viral load of over 500 copies per ml at baseline and during follow-up. Resistance was as defined by the International AIDS Society-USA guidelines (October 2003 version).

When data became available showing comparable pharmacokinetics between the two formulations of saquinavir when boosted with ritonavir [8], patients who were randomized to receive SAQ/r (n=23) were allowed to change from saquinavir soft gel formulation (Fortovase®) to hard gel formulation (Invirase®) without this being considered discontinuation of the assigned treatment. During the trial, modification of the assigned treatment was allowed in cases of protocol-defined observed virological failure (see below) or treatment-limiting toxicities. Of note, patients experiencing observed virological failure according to the protocol's definition were allowed to continue on the assigned treatment at the discretion of the treating physician.

The protocol-defined primary endpoint in the study was treatment failure, defined as a composite of observed virological failure, withdrawal of consent to participate, loss of a patient to follow-up, and death.

Definition of observed virological failure

For patients entering the study with a pVL of less than 200 copies per ml, observed virological failure was defined as a pVL of 200 copies per ml or more at any time point.

For patients entering the study with a pVL of 200 copies per ml or more, the following were classified as observed virological failure: any rise in pVL of 0.5 $\log_{10}$ or more at a study-specific visit; a 0.5 $\log_{10}$ or less reduction in pVL from baseline if the pVL was 200 copies per ml or more at week 4; a 1.0 $\log_{10}$ or less reduction in pVL from baseline if the pVL was 200 copies per ml or more at week 12; and a pVL of 200 copies per ml or more at week 24.

All cases of suspected observed virological failure were confirmed by a second pVL determination performed after 2 or more weeks. Once reconfirmed, the time of observed virological failure was defined as the time of the first measurement that met the failure criteria.

Definition of clinical failure

The development of a new AIDS-defining disease or relapse of a previously successfully treated AIDS-defining disease.

Table 1. Baseline characteristics

Patient characteristic	LPV/r (*n*=163)	SAQ/r (*n*=161)	Total (*n*=324)
Median age (IQR)	40 (35–47)	40 (35–50)	40 (35–48)
Males, *n* (%)	124 (76)	131 (81)	255 (79)
Median duration of HIV, years (IQR)	2.4 (0.3–7.1)	3.4 (0.3–8.1)	2.8 (0.3–7.5)
Antiretroviral naive, *n* (%)	56 (34)	50 (31)	106 (33)
PI naive, *n* (%)	78 (48)	77 (48)	155 (48)
PI experienced, *n* (%)	85 (52)	84 (52)	169 (52)
HIV exposure group, *n* (%)			
Homosexual/bisexual	72 (44)	75 (47)	147 (45)
Intrvenous drug users	13 (8)	13 (8)	26 (8)
Haemophiliac	1 (1)	3 (2)	4 (1)
Transfusion	3 (2)	0 (0)	3 (1)
Heterosexual	65 (40)	58 (36)	123 (38)
Other/unknown	9 (6)	12 (7)	21 (6)
Race, *n* (%)			
White	121 (74)	120 (75)	241 (74)
Black	31 (19)	31 (19)	62 (19)
Asian	4 (2)	1 (1)	5 (2)
Other/unknown	7 (4)	9 (5)	16 (5)
Clinical category C, *n* (%)	50 (31)	52 (32)	102 (31)
Median HIV-1 RNA, copies/ml log10 (IQR)	4.6 (3.5–5.3)	4.4 (3.1–5.1)	4.6 (3.4–5.2)
HIV-1 RNA <400 copies/ml, *n* (%)	34 (21)	35 (22)	69 (21)
Median $CD4^+$ cell count, 106/l (IQR)	239 (95–420)	241 (86–400)	240 (94–419)
Median nadir $CD4^+$ cell count, 106/l (IQR)	100 (32–209)	101 (32–219)	101 (32–210)
Exposed to NRTIs, *n* (%) [median]	106 (65) [2]	111 (69) [2]	217 (67) [2]
Exposed to NNRTIs, *n* (%) [median]	47 (29) [0]	57 (35) [0]	104 (32) [0]
Exposed to PI, *n* (%) [median]	85 (52) [1]	83 (52) [1]	168 (52) [1]

IQR, interquartile range; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-NRTI; SAQ/r, saquinavir/ritonavir; PI; protease inhibitor.

Power calculation and statistics

The trial was powered to show equivalence between the study arms with an 80% chance that the 95% confidence interval for the difference in protocol-defined treatment failure rates would exclude a difference greater than 15% in either direction. This was based on a sample size of 150 per arm and an estimated underlying failure rate of 20% in both arms.

Per protocol, the primary population for analysis was the intention-to-treat/exposed (ITT/e) population, including all randomized patients who had taken at least one dose of the assigned treatment, irrespective of whether they remained on this treatment during the 48 weeks of follow-up. This analysis is also termed 'ITT/e, discontinuation included' [9]. Furthermore, the protocol stipulated ITT/e analyses where discontinuation of the assigned treatment constituted protocol-defined treatment failure [ITT/e/discontinuation=failure (ITT/e/d)]. Exploratory on treatment efficacy and safety analyses were performed in accordance with Committee for Proprietary Medicinal Products guidelines regarding analysis of equivalence trials.

All statistical analyses were performed using STATA software (StataCorp. 2001. Stata Statistical Software: Version 8.0, College Station, Texas, USA). The Chi-square test and Fisher's exact test were used for the comparison of categorical variables between treatment arms. Continuous variables were analysed using Student's t-tests or the Kruskall–Wallis test, depending on the distribution. Cox analysis was performed and Kaplan–Meier plots were produced for the 'time to event' analyses containing sufficient numbers ($n>25$). The Farrington–Manning method was used for the formal test of proportions of individuals failing treatment at week 48 (ITT/e). Multivariable models were developed to identify possible independent predictors of protocol-defined treatment failure and development of adverse events (AEs). For the week 24 interim analysis presented to the Data Safety and Monitoring Board, the Peto method of repeated significance testing was used to test for treatment difference, with a *P*-value of 0.001 as the significance level, giving a significance level of 0.05 (two-sided) for the final week 48 analysis.

Role of sponsor

The CHIP developed the protocol and served as the sponsor of the trial. Roche Pharmaceuticals provided financial support for the conduct of the trial. The conditions for this support were outlined in a contract between the two parties. This contract stipulates that the database will remain at CHIP at all times, that only analyses approved by the trial steering committee are to be conducted, and that such analyses will be performed by CHIP. Furthermore, the contract stipulates that Roche cannot veto the public presentation of any results from the trial.

Results

Baseline characteristics and follow-up

From June to December 2001, 339 patients were randomized, of whom 324 initiated the assigned treatment. Of the randomized patients, four in the LPV/r arm and 11 in the SAQ/r arm did not initiate the assigned treatment.

No differences were observed at baseline in medical history, demographics, or clinical and laboratory measurements, or in exposure to antiretroviral treatment before baseline (Table 1). No individuals entering the trial had previously been exposed to LPV/r. There were 16 (10%) and 25 (16%) individuals who had previously been exposed to SAQ (hard or soft gel) in the LPV/r and SAQ/r arms, respectively. None of these patients had experienced virological failure while receiving SAQ before entry in this trial. The median length of duration for previous use of saquinavir was 65 [interquartile range (IQR) 18–131] and 78 (IQR 33–163) weeks for the LPV/r arm and the SAQ/r arm, respectively. The proportion of individuals on different combinations of NRTIs at baseline (that is, start of assigned treatment) was well balanced between the study arms (data not shown). A small number of individuals received an NNRTI at baseline (six in the LPV/r arm and seven in the SAQ/r arm).

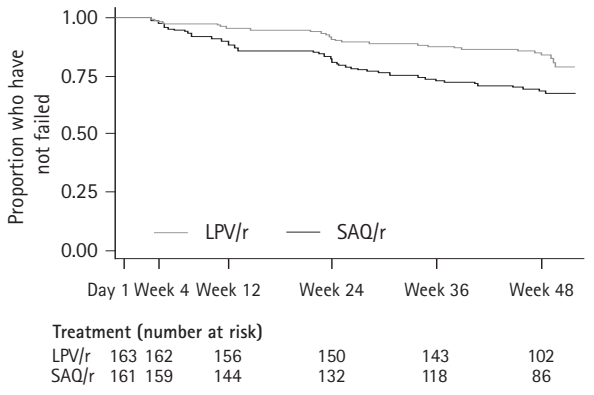
The disposition of patients at week 48 is shown in Table 2. Outcome data at week 48 were available for 304 of the 324 (94%) patients who initiated the assigned treatment. There were differences between the two arms in the proportion of patients who were lost to follow-up (3% and 9% in the LPV/r and the SAQ/r arms, respectively, P=0.02). The 71 patients who prematurely discontinued the assigned treatment did so primarily due to clinical non-fatal treatment-limiting AEs [n=33 (46%); 12 individuals in the LPV/r-treated group versus 21 individuals in the SAQ/r-treated group, P=0.09 (chi-squared test)] and patient's choice [n=15 (21%)]. Of note, among the treatment-limiting AEs, most patients discontinued because of low-grade AEs: grade 1 (n=5), grade 2 (n=18) and grade 3 (n=10). Only three individuals discontinued the assigned treatment due to observed virological failure.

At week 48, 253 of 324 (78%) of the individuals who initiated the assigned treatment (ITT/e) remained on drug [140 of 163 (86%) in the LPV/r arm and 113 of 161 (70%) in the SAQ/r arm (P=0.001)]. There was no significant difference between study arms in the time to discontinuation of the assigned treatment (ITT/e, P=0.81, log rank test). The mean duration of exposure to the study drugs was 45 (IQR 43–47) weeks in the LPV/r arm and 41 (IQR 38–43) weeks in the SAQ/r arm. During follow-up, only two individuals in each study arm reduced the dose of LPV/r or SAQ.

Table 2. Patient disposition at week 48

Status	LPV/r, *n* (%)	SAQ/r, *n* (%)	Total, *n* (%)
Randomized	167	172	339
Initiated assigned treatment	163 (98)	161 (94)	324 (96)
Never initiated assigned treatment	4 (2)	11 (6)	15 (4)
Initiated but permanently discontinued assigned treatment	23 (14)	48 (30)	71 (22)
Reason for discontinuation			
Observed virological failure	0 (0)	3 (6)	3 (4)
Death	0 (0)	3 (6)	3 (4)
Clinical non-fatal adverse event	12 (52)	21 (44)	33 (46)
Laboratory adverse event	1 (4)	1 (2)	2 (3)
Patient choice	7 (30)	8 (17)	15 (21)
Lost to follow-up	2 (9)	4 (8)	6 (8)
Other	1 (4)	8 (17)	9 (13)
Completed 48 weeks of assigned treatment	140 (86)	113 (70)	253 (78)
Patients with an outcome at week 48	158 (97)	146 (91)	304 (94)

Figure 1. Proportion of individuals experiencing protocol defined treatment failure through week 48 (ITT/e)



Virological, immunological and clinical outcome

In the primary ITT/e study population, a higher proportion of protocol-defined treatment failures were observed in the SAQ/r arm. We did not find any evidence at the 5% significance level to reject the hypothesis of non-equivalence; that is, a difference in success rates between the two treatments of more than 15% (P=0.61). The difference in the proportion of patients responding in each arm was 15.1% with a 95% confidence interval of (5.8, 24.5%).

At the completion of the trial, 82 individuals in the ITT/e population had experienced the composite protocol-defined treatment failure endpoint [observed virological failure (n=69), withdrawn consent (n=3), lost to follow-up (n=6) or death (n=4)]. Twenty-nine were in the LPV/r arm (90% due to observed virological failure) and 53 were in the SAQ/r arm (81% due to observed virological failure). The time to protocol-defined treatment failure was shorter in the SAQ/r arm compared with the LPV/r arm (Figure 1; P=0.002, log rank test). The median pVL at time of protocol-defined treatment failure was lower (marginally statistically significant, P=0.08) in the LPV/r arm (1775; IQR 613–11963) compared with the SAQ/r arm (17717; IQR 561–69322). Only 18% of the study individuals had a pVL of less than 400 copies per ml at the time at which they met the protocol's treatment failure criteria. This was comparable in the two treatment arms. Of the individuals who met the criteria for protocol-defined treatment failure, 78% remained on the assigned treatment, with more individuals remaining on treatment with LPV/r than with SAQ/r (90% versus 72%, respectively; P=0.06, Chi-squared test). A further finding, although not statistically significant, was that more individuals were on any antiretroviral treatment at the time of protocol-defined treatment failure in the LPV/r arm compared with the SAQ/r arm (90% versus 72%, respectively; P=0.09).

In the ITT/e/d analysis, the time to protocol-defined treatment failure was longer in the LPV/r arm compared with the SAQ/r arm (P=0.005, log rank test). In this analysis, a total of 103 individuals fulfilled the protocol's treatment failure criteria (40 individuals in the LPV/r arm and 63 individuals in the SAQ/r arm); 36 (35%) of these events were due to discontinuation of the randomized treatment (12 versus 24, respectively) and 53 (51%) due to observed virological failure (24 versus 29). Of note, the difference in numbers of observed virological failure between the two arms in the ITT/e/d analysis (5) compared with the ITT/e analysis (17) imply that 14 (33%) individuals with ITT/e observed virological failure experienced their failure after they had discontinued SAQ/r.

In the on-treatment analysis, 53 individuals experienced protocol-defined treatment failure with no difference observed in rate of failure between the two study arms (P=0.27, log rank test).

There was no difference in the proportion of individuals with a pVL of less than 50 copies per ml (Figure 2, ITT/e). The proportion of individuals with a pVL less than 50 and 400 copies per ml was lower in the SAQ/r arm from week 24 onwards compared with the LPV/r arm, although this was only significant for the less than 400 copies per ml cut-off. Conversely, in the on-treatment analysis the proportion of individuals being suppressed was not statistically different between the two study arms.

The mean and median increases in CD4$^+$ cell count from baseline were modest, and there were no statistical differences between the two arms of the trial (data

Figure 2. Proportion of patients with pVL <50 c/ml (ITT/e, ITT/e/d, and on-treatment [OT] analyses)

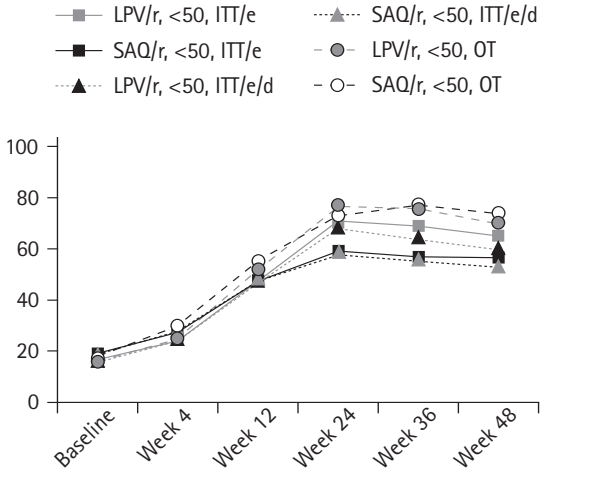


Table 3. Lipid levels at baseline, week 4 and week 48

	LPV/r			SAQ/r		
Lipid levels	Individuals with value, *n*	Median value (IQR)	Individuals above normal, *n* (%)	Individuals with value, *n*	Median value (IQR)	Individuals above normal, *n* (%)
Total cholesterol (normal range 3.4–6.2 mmol/l)						
Baseline	153	4.6 (3.8–5.4)	17 (11)	156	4.5 (3.7–5.4)	21 (13)
Week 4	147	4.9 (4.2–5.8)	25 (17)	149	5.3 (4.4–6.1)	35 (23)
Week 48	153	5.1 (4.4–6.0)	31 (20)	139	5.2 (4.5–6.1)	28 (20)
LDL cholesterol (normal range 1.7–3.2 mmol/l)						
Baseline	125	2.7 (2.0–3.3)	39 (31)	133	2.5 (1.8–3.2)	37 (28)
Week 4	117	2.7 (2.1–3.3)	41 (35)	115	3.1 (2.3–3.8)	55 (48)
Week 48	118	2.8 (2.3–3.4)	37 (31)	118	3.1 (2.3–3.7)	58 (49)
Total triglycerides (normal range 0.5–2.3 mmol/l)						
Baseline	157	1.8 (1.1–2.5)	40 (25)	160	1.7 (1.0–3.0)	56 (35)
Week 4	149	2.3 (1.6–3.5)	72 (48)	152	1.8 (1.2–2.7)	49 (32)
Week 48	153	2.2 (1.5–3.3)	71 (46)	140	1.7 (1.1–2.7)	49 (35)

IQR interquartile range; LPV/r, lopinavir/ritonavir; SAQ/r, saquinavir/ritonavir.

not shown). The median (IQR) time from baseline to an increase of over 100 $CD4^+$ cells per μl was 12 weeks for both arms of the trial.

Twenty-one individuals experienced clinical failure (CDC category C) and/or death, five in the LPV/r arm and 16 in the SAQ/r arm. The 21 individuals experienced a total of 25 events, of which 18 were CDC category C events (4 versus 14) and 7 were deaths (all in the SAQ/r arm). Most of the 18 CDC category C events occurred relatively shortly after baseline [11 (3–120) days from baseline in the LPV/r arm and 86 (44–165) days in the SAQ/r arm] and predominantly in individuals with existing severe immunodeficiency. The rate of clinical failure was higher in the SAQ/r arm than in the LPV/r arm (ITT/e, P=0.02, log rank test). No significant difference was seen between study arms in the latest $CD4^+$ cell count before development of clinical failure.

Resistance testing

Baseline genotypic resistance test results were available for 207 of 324 (64%) study individuals, 104 and 103 in the LPV/r arm and SAQ/r arm, respectively. No difference was seen between study arms in the number of NRTI-, NNRTI- or PI-related resistance mutations. Similarly, no difference was seen in the proportion of individuals with thymidine-associated mutations, or multidrug resistance mutations to NRTIs and NNRTIs. In the LPV/r arm, 1 of 104 individuals had a primary resistance mutation to lopinavir; in the SAQ/r arm, 8 of 103 individuals had one (n=6) or two (n=2) primary resistance mutations to saquinavir.

Adverse events

A total of 142 AEs of grade 3 or 4 were reported in the study. Of these, gastrointestinal events were the most frequent (n=24). Of the patients exposed to the study medication, 74 of 324 (23%) experienced at least one AE of grade 3 or 4. There was no significant difference between the study arms in the number of individuals experiencing a grade 3 or 4 AE. A total of 31 laboratory AEs of grade 3 or 4 were recorded, 18 in LPV/r arm and 13 in the SAQ/r arm. Laboratory AEs were primarily hepato-biliary (LPV/r: 8; SAQ/r: 6). Of note, laboratory events were only reported if deemed of clinical significance by the treating physician.

Lipids

The median fasting baseline lipid values for the LPV/r group were 4.6 mmol/l for total cholesterol, 2.3 mmol/l for LDL cholesterol and 1.8 mmol/l for total triglyceride. For the SAQ/r group, the baseline lipid values were 4.5 mmol/l (total cholesterol), 2.3 mmol/l (LDL cholesterol) and 1.7 mmol/l (total triglyceride). Normal ranges for these lipids are 3.4–6.2 mmol/l (total cholesterol), 1.7–3.2 mmol/l (LDL cholesterol) and 0.5–2.3 mmol/l (total triglyceride). The proportion of patients with increased total cholesterol values at baseline was low and without difference between the study arms, 11% versus 13% in the LPV/r arm and the SAQ/r arm, respectively. The proportion of patients with increased total cholesterol values increased at week 4 in both arms and remained stable (20% in both study arms at week 48; Table 3). The proportions of patients with increased LDL cholesterol and total triglyceride values at baseline were high – 31% and 25% in the LPV/r arm

and 28% and 35% in the SAQ/r arm, respectively. LDL cholesterol cannot be reliably assessed in many patients if the total triglyceride level is over 4.5 mmol/l. The proportion of patients with missing LDL values because of increased (over 4.5 mmol/l) triglyceride levels at baseline, week 4 and week 48 was 7/11, 9/16 and 18/26 in the LPV/r arm and 4/13, 9/15 and 7/12 in the SAQ/r arm, respectively. Use of a lipid-lowering agent could influence the above factors; however, only five patients in each study arm used these agents at some point during follow-up.

Discussion

Fewer patients in the LPV/r arm compared with the SAQ/r arm experienced the primary efficacy outcome of the study – protocol-defined treatment failure through week 48 (ITT/e). Therefore, the trial null hypothesis of non-equivalence could not be rejected. Similarly, fewer individuals in the LPV/r arm experienced protocol-defined treatment failure in the ITT/e/d analysis. Significantly more patients in the SAQ/r arm discontinued the assigned treatment for reasons other than lack of virological efficacy. Based on results of the trial, LPV/r should be preferred over SAQ/r in the doses and formulations studied. It should be noted that the term 'observed virological failure' used in this trial (see the section on methods) might be different from what is considered failure in a clinical setting. This is reflected by the fact that most individuals experiencing observed virological failure did not change treatment, which would otherwise be recommended [11]. Conversely, the analytic approach used in this report is consistent with how virological outcome studies have been evaluated in the past several years [10].

In the intention-to-treat analyses, the proportion of individuals with pVL values below 50 copies per ml at the completion of the trial was not significantly different between the trial arms, although a trend consistent with the primary findings was observed, and this trend was statistically significant if the cut off for pVL was set to be 400 copies per ml instead.

By contrast, in the on-treatment analyses, no statistical differences in virological outcome between the two study arms were seen. Of note, the on-treatment analysis of protocol-defined treatment failure and of pVL suppression did not show consistent trends – the treatment failure analysis favoured the LPV/r arm, whereas the suppression analysis favoured the SAQ/r arm. On balance, the on-treatment analysis does suggest that the intrinsic efficacies of the two ritonavir-boosted PI regimens are fairly comparable.

This trial included both treatment-experienced and treatment-naive individuals, which could potentially affect the outcome. However, no difference was found in previous exposure to and use of antiretroviral drugs and combinations thereof at baseline except for exposure to the study PI: none of the individuals in the LPV/r arm had been exposed to lopinavir before randomization, whereas 16% of individuals in the SAQ/r arm had been exposed to saquinavir. Resistance testing was not mandatory at enrollment, but efforts were made to exclude people that may have had acquired resistance mutations to the study PIs before enrollment. Retrospective genotypic resistance testing was performed on stored baseline samples. Only one individual in the LPV/r arm and eight individuals in the SAQ/r arm had resistance mutations to the study drug they had been assigned to, so it is unlikely that the primary efficacy outcome of the study is affected by this. To further elucidate whether baseline characteristics may have influenced the efficacy outcomes, two substudies are currently investigating the role of genotypic-resistance mutations at baseline and the single-nucleotide polymorphisms in the multidrug resistance 1 locus of host DNA on the time to observed virological failure.

The trial was not powered to compare risk in clinical failure, but we observed an increased risk of clinical failure for individuals randomized to the SAQ/r arm. However, most of the clinical events occurred early in the trial and were probably predominantly linked to pre-existing severe immunodeficiency as opposed to being a consequence of lack of effect of the antiretroviral regimen administered. The immunological response was comparable between the two arms. Additionally, only two individuals in the LPV/r arm and three individuals in the SAQ/r arm progressed from CDC category A or B to category C or death. Therefore, the observed difference may be the result of a type I error.

One consistently observed difference was that individuals in the LPV/r arm (compared with the SAQ/r arm) had significant increases from baseline in triglycerides at week 4 and week 48. Similar findings have been observed in healthy volunteers and HIV-infected individuals [5,12]. Other drugs that could potentially influence triglyceride levels (for example, stavudine) were well balanced between the two groups at baseline and during follow-up (data not shown). It is likely that the lopinavir component and/or the combined effect of lopinavir and ritonavir cause the triglycerides lipids to increase, as the same ritonavir dosing was used in both arms of the trial. However, another possibility is that this effect is caused by ritonavir and the difference between the arms is explained by the ritonavir metabolism being affected differently by lopinavir compared with saquinavir. In the MaxCmin1 trial, in which ritonavir was also dosed as 100 mg twice daily in both arms, higher ritonavir trough levels were observed in the

indinavir/ritonavir arm compared with the saquinavir/ritonavir arm [7]. Therefore, treatment with LPV/r more adversely affects triglyceride levels than SAQ/r treatment.

Whereas the triglyceride levels were affected differently by the two regimens, the cholesterol levels increased slightly but comparably in both arms. The number of individuals with available LDL cholesterol measurements was lower than for the two other lipid factors, and this was especially so in the LPV/r arm. This is because LDL cholesterol cannot be reliable estimated if the triglyceride levels are high. As the triglyceride levels were higher in the LPV/r arm than in the SAQ/r arm during follow-up, this intrinsically impairs the ability to assess whether the two study arms affect LDL cholesterol differently. Hence, the effect of the two ritonavir-boosted PI regimens on the levels of total cholesterol is comparable.

In conclusion, in this open-label study of a heterogeneous population – reflecting the real clinic situation – the primary outcome of the trial (that is, time to protocol-defined treatment failure) occurred more quickly in the SAQ/r arm compared with the LPV/r arm. This difference is probably caused by differences between a small fraction of the participants in their acceptance and/or tolerability of the regimens. Regardless, more individuals in the LPV/r arm remained virologically suppressed on study drug at week 48.

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Appendix

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