Efficacy and safety of twice-daily versus three-times daily saquinavir soft gelatin capsules as part of triple combination therapy for HIV-1 infection

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Objective: The objective of this study was to determine whether a triple therapy regimen incorporating twice-daily saquinavir is as effective as a three-times daily regimen.

Methods: This was an open-label, Phase III, multicentre, 48-week study involving 837 HIV-1-infected patients randomised to one of the following: saquinavir soft gel capsule (SGC) 1200 mg three-times daily, plus two nucleoside reverse transcriptase inhibitors (NRTIs) (arm A); saquinavir SGC 1600 mg twice-daily, plus two NRTIs (arm B); saquinavir SGC 1200 mg twice-daily and nelfinavir 1250 mg twice-daily, plus a single NRTI (arm C). The primary outcome measure was the virological response in arm A versus B and in arm A versus C with respect to the percentage of patients whose plasma HIV-1 RNA levels fell below the level of quantification for the Amplicor assay (<400 copies/ml) at weeks 24 and 48.

Results: At 48 weeks, the percentage of patients with plasma HIV-1 RNA levels <400 copies/ml was 47.1% (arm A), 45.3% (arm B) and 42.7% (arm C) in the intention-to-treat analysis. The treatment difference between arm B–arm A was –1.8% (95% confidence intervals –10.1, 6.5) and for arm C–arm A was –4.5% (95% confidence intervals –12.7, 3.7) in the intention-to-treat analysis. These differences fell within the maximum allowable difference (±12%) for arm B compared with arm A. At week 24, the percentage of patients with HIV-1 RNA levels <400 copies/ml was 59.6% (arm A), 57.6% (arm B) and 51.3% (arm C).

Conclusions: A twice-daily triple therapy regimen incorporating saquinavir SGC plus two NRTIs was of equivalent efficacy to the three-times daily regimen studied. All regimens were generally well tolerated.

Introduction

The introduction of triple combination therapy, usually including an HIV protease inhibitor (PI), has reduced mortality and opportunistic infections in large population-based cohorts of people with HIV infections [1,2]. A number of recent studies have shown that long-term treatment success is critically dependent on high levels of adherence to combination therapy [3,4], and optimising adherence must, therefore, be a priority [5].

With adherence during chronic therapy correlated with the number of daily doses [6–8], the development of antiretroviral regimens that can be administered once- or twice-daily is likely to enhance adherence compared with regimens requiring more frequent dosing [9]. Since most nucleoside reverse transcriptase inhibitors (NRTIs) that are used in combination are taken twice-daily, the administration of a PI with the same schedule should increase the simplicity and desirability of the combination.

As part of combination therapy, saquinavir has been shown to delay disease progression and death [10]. In the soft gelatin capsule (SGC) formulation (Fortovase®), saquinavir administered three-times daily has a durable effect up to 72 weeks and is well tolerated [11,12]. Based on the results of two randomised clinical trials, saquinavir SGC has comparable efficacy to indinavir [13] and nelfinavir [14].

The recommended dosing schedule for saquinavir SGC is 1200 mg three-times daily. The 1200 mg dose provides improved antiviral activity compared with the hard gelatin capsule (HGC) formulation (Invirase®) administered at a dose of 600 mg three-times daily [15]. Use of the SGC formulation (1200 mg three-times

daily) increases the exposure (AUC_8) to saquinavir at least eightfold compared with the HGC formulation (600 mg three-times daily) [16], providing, in antiretroviral-naive patients, C_{min} concentrations of saquinavir six-times the EC_{50} (the concentration of saquinavir required to produce 50% of the maximum antiviral response) of 50.44 ng/ml [17]. This improved pharmacokinetic profile may allow twice-daily dosing while still providing effective suppression of viral replication.

Exposure to saquinavir can be further enhanced by combining its administration with another PI [18], for example, nelfinavir [19,20]. The dual PI combination of saquinavir 1200 mg/nelfinavir 750 mg (three-times daily) has been tested in previous clinical trials [14,21]. Nelfinavir is approved for use at a dose of 1250 mg twice-daily in the USA, and the improvements in the pharmacokinetic profile of saquinavir that nelfinavir co-administration provides may enable twice-daily dosing of saquinavir without the need to increase the 1200 mg registered dose.

The present study was designed to test the hypothesis that reducing the dose frequency of saquinavir SGC from three-times daily to twice-daily might be possible without compromising efficacy, by comparing the efficacy and safety of saquinavir SGC administered either twice-daily (1600 mg) or three-times daily (1200 mg), in combination with two NRTIs. The second objective of the study was to investigate the efficacy and safety of saquinavir SGC 1200 mg twice-daily plus nelfinavir 1250 mg twice-daily (approved US dosage) plus a single NRTI, compared with saquinavir SGC three-times daily 1200 mg in combination with two NRTIs. The respective dose combinations were selected to provide similar saquinavir plasma exposure to the licensed regimen of saquinavir SGC 1200 mg three-times daily, based on pharmacokinetic modelling and taking into account the nonlinear pharmacokinetic profile of saquinavir [22].

Materials and methods

This was a Phase III, multicentre, randomised, open-label study conducted at 83 centres in the USA (n=79) and Europe (n=4), which compared the efficacy and safety of twice-daily and three-times daily saquinavir SGC when used as part of triple combination therapy for HIV-1 infection. The study was designed as an equivalence trial for efficacy, with a primary analysis at 24 weeks and a treatment extension to 48 weeks.

Male or female (non-pregnant) adults (≥16 years) with HIV-1 RNA at least 5000 copies/ml were enrolled in the study, regardless of their CD4 cell count. Participants were either antiretroviral-naive (had received no more than 2 weeks of previous antiretroviral therapy) or NRTI-experienced (had received greater than 3 months of therapy with NRTIs in total but no more than 2 weeks of previous treatment with PIs or non-NRTIs). Patients who fell in between greater than 2 weeks but less than 3 months of therapy with NRTIs were not excluded from the study. For the purpose of classifying such patients as antiretroviral-naive or NRTI-experienced, they were evaluated on a case-by-case basis depending on the exact length of treatment and reason(s) for discontinuation of that short-term therapy.

Inclusion criteria were alanine and aspartate aminotransferase ≤3× the upper limit of the normal range (ULN), bilirubin ≤2.5× ULN, creatinine ≤2.5 mg/dl, white blood cells ≥1000 $\times 10^3$ cells/l, haemoglobin ≥9.0 g/dl and platelets ≥50 000 cells/mm^3. Exclusion criteria included patients with malabsorption syndrome, active opportunistic infection, and any grade 3 or above laboratory or clinical abnormality. Active use of non-prescription drugs or alcohol, which in the opinion of the investigator would not affect study adherence, was permitted.

The study was performed in accordance with Good Clinical Practice as set out in the Declaration of Helsinki and its amendments, and ethical approval was obtained from the institutional review boards/ethical committees of participating centres. All participants provided written informed consent and were free to withdraw from the study at any time.

Treatment programme

After screening, qualifying patients were randomly assigned (according to a list generated by the study monitor) to receive at least 48 weeks of treatment with one of the following three regimens: saquinavir SGC 1200 mg (Fortovase®; 200 mg capsules; supplied by Roche) three-times daily plus two NRTIs (arm A); saquinavir SGC 1600 mg twice-daily plus two NRTIs (arm B); and saquinavir SGC 1200 mg twice-daily plus nelfinavir 1250 mg (Viracept®; 250 mg tablets) twice-daily plus a single NRTI (arm C). Randomisation was stratified by the last screening plasma HIV-1 RNA value (>5000–≤30 000 vs >30 000 copies/ml) and previous antiretroviral treatment experience (antiretroviral-naive versus NRTI-experienced).

Treatment was continued until the last enrolled patient reached 48 weeks of therapy. Patients were instructed to take saquinavir SGC within 2 h of a meal, nelfinavir with food and concomitant NRTIs according to the manufacturers' recommendations. For antiretroviral-naive participants in arms A and B, concomitant NRTIs were preferably stavudine (40 mg twice-daily) plus lamivudine (150 mg twice-daily), and for patients in arm C, stavudine alone, as appropriate. In NRTI-experienced participants, concomitant NRTIs were selected to minimise the use of those given in the past

and it was required that at least one NRTI in the new regimen should not have been taken previously. The site's Principal Investigator selected specific NRTIs in each case.

Therapy intensification was allowed at week 20 in treatment-adherent patients with <1 log HIV-1 RNA decrease from baseline or with HIV-1 RNA >2000 copies/ml at 16 weeks on treatment (confirmed by a second HIV-1 RNA test at least 10 days apart); and/or at week 24 in patients who were considered to be delayed responders (patients with continuously declining HIV-1 RNA levels) at week 20, but who did not attain a full response (plasma HIV-1 RNA levels <400 copies/ml) by week 24. According to the protocol, patients were required to withdraw from the study in the event of a virological relapse (two HIV-1 RNA values >400 copies/ml ≥10 days apart) following a virological response (two consecutive values <400 copies/ml ≥10 days apart) despite compliance with the treatment regimen, or protocol violation, and these and all other reasons for withdrawal were recorded.

Evaluations

Plasma HIV-1 RNA values (Roche Amplicor HIV Monitor® and UltraSensitive® assays), CD4 cell counts, AIDS-defining events, adverse events and laboratory parameters were assessed at screening (2 weeks prebaseline), baseline, weeks 2 and 4, every 4 weeks from week 4 until week 24, every 8 weeks from week 24 until week 48, and at study discontinuation. Baseline values for HIV-1 RNA and CD4 cell counts were defined as the average of the last screening and last baseline values. Adherence with treatment was estimated at each visit by a returned pill count and the investigator's assessment of compliance (yes or no). Adverse events were graded by intensity and their relationship to the study medications was assessed. Serious adverse events, including death, were reported according to Food and Drug Administration (FDA) regulations. AIDS-defining adverse events (which complied with the 1993 Centers for Disease Control definitions of AIDS-defining adverse events) were recorded in the same way as all other adverse events. Laboratory abnormalities were graded.

Statistical analyses

The primary outcome measure was the proportion of patients with HIV-1 RNA suppression <400 copies/ml using the Amplicor assay. Secondary efficacy analyses included the proportion of patients with HIV-1 RNA suppression <50 copies/ml using the UltraSensitive assay, time to virological response, change from baseline in plasma HIV-1 RNA values and CD4 cell counts, levels of adherence to treatment, incidence of AIDS-related events, other adverse events, and laboratory abnormalities.

The trial was designed to compare arm A with arms B and C at week 24 and week 48, using the proportion of patients with HIV-1 RNA values <400 copies/ml. The comparison between arm A versus arm B and arm A versus arm C was expressed in terms of the difference in the proportion of patients with HIV-1 RNA values <400 copies/ml (arm B–arm A or arm C–arm A). The prespecified criterion for equivalence (based on the FDA equivalence criterion) in the proportion of patients with HIV-1 RNA values <400 copies/ml would be met if the 95% confidence intervals (CI) for the difference in percentage of patients whose HIV-1 RNA was <400 copies/ml, adjusted for multiple comparisons, was within ±12%. The planned sample size was 280 patients per arm, which was estimated to provide 80% power in obtaining a CI on the difference between arms within the range ±12%, allowing for a 15% withdrawal rate.

Additional predefined statistical analyses were performed for some of the secondary parameters. The same statistical methodology for the primary efficacy parameter was used for the proportion of patients with HIV-1 RNA values <50 copies/ml. The time to virological response (time for the viral load to fall below both 400 and 50 copies/ml) for arms B or C compared with arm A was analysed using Kaplan–Meier analyses. Cox regression was used to explore the effect of treatment, prior NRTI experience, and prebaseline HIV RNA. The change from baseline in HIV-1 RNA and CD4 count was analysed using analysis of variance (ANOVA).

Non-compliance (defined as taking less than 80% of any of the three study medications dispensed at the previous visit) was defined as two or more visits where the returned pill count and the investigator's assessment both indicated non-compliance. Compliance was only determined up to week 24.

All efficacy analyses were performed on the intention-to-treat (ITT) population, which included all patients who were randomised and took at least one dose of study medication; patients discontinued for any reason were considered as treatment failures. In addition, analyses were performed on the on-treatment (OT) population, which included only those patients with an available evaluation at that time point. Patients who received intensified therapy were treated as withdrawals from the time of intensification and were included in the OT population up until the time of intensification.

The safety population included all randomised patients who had at least one post-baseline safety assessment. Patients who received intensified therapy were included in the safety analysis under their original treatment assignment.

Results

Patient characteristics

The trial started in October 1997 and finished in November 1999. Of approximately 1274 patients screened, 895 patients were randomised to treatment and their progress through the trial is shown in Figure 1. Fifty-five patients withdrew from the study in the 3–4 days between randomisation and receiving study medication, resulting in 840 patients that received the study drugs (arm A, *n*=281; arm B, *n*=279; arm C, *n*=280). Three of these 840 randomised patients who were dispensed study drugs did not take any study medication and were excluded from the ITT analysis, leaving 837 patients in the ITT population (arm A, *n*=280; arm B, *n*=278; arm C, *n*=279). The safety population consisted of 815 randomised patients who had at least one post-baseline safety assessment (arm A, *n*=274; arm B, *n*=270; arm C, *n*=271).

The baseline characteristics of the participants in the three arms of the study were similar, as shown in Table 1. There was a higher proportion of women in arm B (23%) compared with the other two arms (13–16%). Similar proportions of patients in each arm had a high viral load (HIV RNA values >30 000 copies/ml) and had received previous treatment with NRTIs. There was little difference between arms in the prior antiretroviral agents received.

Follow-up and discontinuation of treatment

A total of 388 patients (46%) withdrew from the study prior to 48 weeks (arm A, *n*=124; arm B, *n*=127; arm C, *n*=137), with the reasons for withdrawal being similar between groups. Although 5% (46/837) of patients withdrew due to lack of therapeutic efficacy, most withdrawals were for reasons not directly related to the efficacy of the study medications. Failure to return (111/837; 13%), refusal of treatment (87/837; 10%) and adverse events (94/837; 11%) were the most common reasons for withdrawal in all groups. After meeting the intensification criteria, 2% of patients intensified therapy (five patients in arm A, seven in arm B and five in arm C).

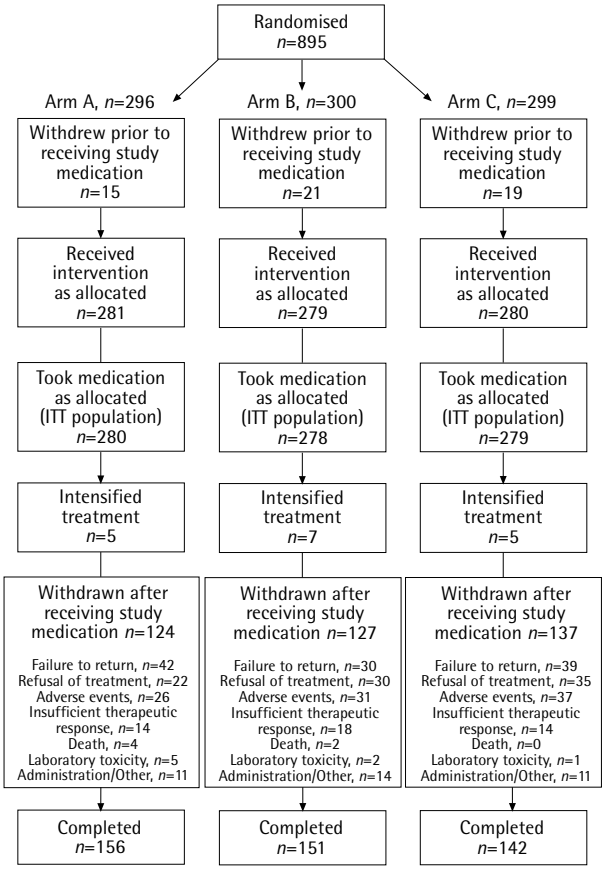
Additionally, at least 13 patients (1.6%) were withdrawn from the study due to incarceration, and at least 18 patients (2%) were lost to follow-up having moved so that they were no longer under the care of the original centre and were not near an alternative study site.

Patients using non-prescription drugs or alcohol were not excluded from the trial, and many of these patients did not complete the study.

Suppression of plasma HIV-1 RNA to undetectable levels

Similar suppression of HIV-1 replication was observed in all three treatment arms. The proportion of patients with HIV-1 RNA values <400 copies/ml (by the Amplicor assay) is shown in Figure 2, which illustrates the results for both the ITT (dashed lines) and OT population (solid lines).

Figure 1. Progress of patients throughout the trial



ITT, intention-to-treat.

The treatment differences in the proportion of patients with HIV-1 RNA values <400 copies/ml for arm B versus arm A at weeks 24 and 48 for both the ITT and the OT population fell within the maximum allowable difference (±12%) using a 95% CI (Table 2). This illustrates that the twice-daily dosing regimen for saquinavir SGC was equivalent to the three-times daily regimen according to the primary outcome criterion. For arm C versus arm A, this was also true of the OT analysis, with the lower 95% CI falling within ±12% at both 24 and 48 weeks. However, according to the ITT analyses of arm C versus arm A at 24 and 48 weeks, the 95% CI fell outside the defined ±12% CI region. This indicates that the saquinavir/nelfinavir twice-daily regimen was not equivalent to the three-times daily saquinavir regimen, according to the primary outcome criterion at 24 and 48 weeks.

The proportion of patients with HIV-1 RNA values falling below the level of detection for the more sensitive

Table 1. Summary of patient characteristics at baseline: intention-to-treat population

Characteristic	Arm A: saquinavir soft gel capsule 1200 mg three-times daily (*n*=280)	Arm B: saquinavir soft gel capsule 1600 mg twice-daily (*n*=278)	Arm C: saquinavir soft gel capsule 1200 mg twice-daily+nelfinavir 1250 mg twice-daily (*n*=279)
Male [*n* (%)]	244 (87)	214 (77)	235 (84)
Female [*n* (%)]	36 (13)	64 (23)	44 (16)
Race [*n* (%)]			
Caucasian	142 (51)	141 (51)	150 (54)
African American	90 (32)	98 (35)	92 (33)
Hispanic/other	48 (17)	38 (14)	35 (13)
Asian	–	1 (0)	2 (1)
Age (years)			
Mean ±SD	37.7 ±8.7	37.0 ±8.8	36.1 ±9.0
Weight (kg)			
Mean ±SD	76.2 ±14.9	75.6 ±15.1	78.1 ±16.7
Plasma HIV-1 RNA (log_{10} copies/ml)			
Mean ±SD	4.8 ±0.7	4.7 ±0.6	4.8 ±0.6
CD4 cell count (cells/mm^3)			
Mean ±SD	307 ±223	323 ±230	311 ±223
Prior NRTI experience [*n* (%)]	74 (27)	65 (23)	78 (28)
Number of prior antiretroviral agents [mean (range)]	2.3 (1–6)	2.3 (1–6)	2.5 (1–6)
Prior antiretroviral therapy (%)			
Zidovudine	85	89	94
Lamivudine	65	55	65
Stavudine	27	25	28
Didanosine	20	22	24
Zalcitabine	10	17	14
Other	18	17	17
Starting new NRTIs (%)			
2	62	63	NA
1	30	34	91
0	7	3	8
Stratification (HIV-1 RNA)			
Antiretroviral-naive patients [*n* (%)]			
≥5000–30000 copies/ml	64 (23)	71 (26)	67 (24)
>30000 copies/ml	142 (51)	142 (51)	134 (48)
NRTI-experienced patients [*n* (%)]			
≥5000–30000 copies/ml	38 (14)	35 (13)	35 (13)
>30000 copies/ml	36 (13)	30 (11)	43 (15)

UltraSensitive assay (<50 copies/ml) are shown in Figure 3, again illustrating the results for both the ITT (dashed lines) and OT population (solid lines).

The treatment differences in the proportion of patients with HIV-1 RNA values <50 copies/ml for arm B or C versus arm A at weeks 24 and 48 are shown together with the 95% CI (Table 2). For ITT analyses, these comparisons fell within the maximum allowable difference (±12%) using a 95% CI, indicating that both twice-daily regimens were equivalent to the three-times daily regimen in terms of viral suppression <50 copies/ml. The OT analysis also provided further support for the equivalence conclusion from the ITT analysis.

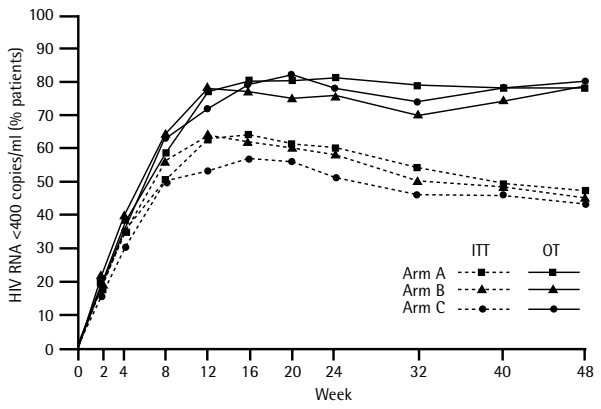
Changes from baseline in plasma HIV-1 RNA

The mean change in plasma HIV-1 RNA values from baseline was similar between treatment arms.

Comparing arm A with arms B or C, there were no significant differences in the time to virological response at week 48 (Cox regression analysis) or in the magnitude of the change from baseline to week 48 in log_{10} HIV-1 RNA values (as determined by ANOVA) (ITT population; $P>0.2$ for all comparisons).

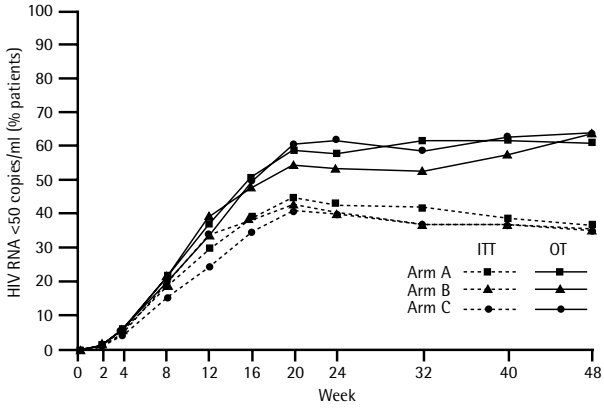
When data from naive patients only were assessed, the changes from baseline in plasma HIV-1 RNA were similar to those seen in the overall group (data not shown).

Figure 2. Proportion of patients with HIV-1 RNA <400 copies/ml (Amplicor assay)



ITT, intent-to-treat; OT, on-treatment.

Figure 3. Proportion of patients with HIV-1 RNA <50 copies/ml (UltraSensitive assay)



ITT, intent-to-treat; OT, on-treatment.

Changes from baseline in CD4 cell counts

Significant increases from baseline in CD4 cell counts were seen in all three treatment arms at all time points. The CD4 cell count increased progressively during treatment, reaching +144, +139 and +166 cells/mm^3 by 24 weeks, and +213, +184 and +223 cells/mm^3 by 48 weeks, for arms A, B, and C, respectively (OT analysis) (Figure 4). Using ANOVA, there was no significant difference between arms B or C compared with arm A in the change in CD4 cell counts from baseline to week 48 (arm B versus arm A, P=0.0746; arm C versus arm A, P=0.7373).

When data from naive patients only were assessed, the changes in mean CD4 cell counts from baseline to both week 24 and week 48 were higher than those seen in the overall group of patients (changes from baseline in arm A: +231 versus +213 cells/mm^3; arm B: +212 versus +184 cells/mm^3; arm C: +237 versus +223 cells/mm^3 at 48 weeks in naive patients and the overall group, respectively).

Compliance with therapy

For patients who remained in the study, compliance with all the treatment regimens, as estimated by the returned pill count and the investigator's assessment (yes/no), was reasonably high over the first 24 weeks of the study; 82–84% of OT patients showed at least 80% adherence at all study visits.

Adverse events

All three regimens were generally well tolerated over the 48 weeks of therapy. Most adverse events were

Table 2. Treatment differences in percentage of patients with HIV-1 RNA <400 copies/ml (Amplicor assay) and <50 copies/ml (UltraSensitive assay) at weeks 24 and 48

HIV RNA <400 copies/ml (Amplicor assay)

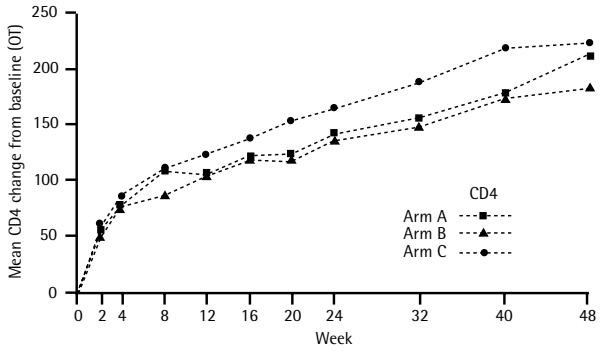
	HIV-1 RNA (% patients)			Treatment difference (%, [95% CI])	
	Arm A	Arm B	Arm C	Arm B–Arm A	Arm C–Arm A
24 week ITT	59.6	57.6	51.3	–2.1 (–10.3, 6.1)	–8.4 (–16.6, –0.2)
24 week OT	80.5	76.4	78.0	–4.1 (–12.1, 3.8)	–2.5 (–10.6, 5.6)
48 week ITT	47.1	45.3	42.7	–1.8 (–10.1, 6.5)	–4.5 (–12.7, 3.7)
48 week OT	78.0	78.8	79.5	0.9 (–8.1, 9.8)	1.5 (–7.6, 10.5)

HIV RNA <50 copies/ml (UltraSensitive assay)

	HIV-1 RNA (% patients)			Treatment difference (%, [95% CI])	
	Arm A	Arm B	Arm C	Arm B–Arm A	Arm C–Arm A
24 week ITT	42.9	41.0	40.1	–1.8 (–10.0, 6.3)	–2.7 (–10.9, 5.5)
24 week OT	58.0	54.2	61.5	–3.9 (–13.5, 5.8)	–3.5 (–6.3, 13.3)
48 week ITT	37.1	36.3	34.8	–0.8 (–8.8, 7.2)	–2.4 (–10.3, 5.6)
48 week OT	61.3	63.5	64.4	2.2 (–8.4, 12.7)	3.1 (–7.6, 13.8)

ITT, intention-to-treat; OT, on-treatment.

Figure 4. CD4 count: mean changes from baseline



OT, on-treatment.

mild (gastrointestinal symptoms were the most frequently reported), however, 11% of patients discontinued treatment due to adverse events. There was little difference between treatment arms in the overall incidence of adverse events, with 47–52% of patients in each arm reporting at least one adverse event of moderate or severe intensity, and possibly or probably related to the study medication.

Over 48 weeks, the most common adverse events considered at least possibly related to study medications and of moderate or severe intensity, occurred in ≥3% of patients and are shown in Table 3. There were few clear differences between treatment arms in the pattern or incidence of adverse events (Table 3): the level of diarrhoea was significantly higher in arm C compared with arm A ($P<0.002$) or arm B ($P<0.001$), and the level of nausea was significantly lower in arm C compared with arm A ($P=0.001$). Other than the occurrence of headache being significantly higher in arm A compared with arms B or C ($P=0.02$), there were no other statistically significant differences between treatment arms in terms of the adverse events in Table 3.

Seventeen patients (six in arm A, five in arm B and six in arm C) experienced a total of 23 serious adverse events, which were considered to be possibly or probably related to the study medication. These events were most frequently associated with the gastrointestinal

Table 3. Percentage of patients with clinical adverse events considered at least possibly related to treatment, and of moderate or severe intensity or life threatening, occurring in ≥3% of patients, or with marked laboratory shifts (grade 0 to grades 3 or 4, and grade 1 to grade 4) occurring in >1% of patients, regardless of relationship to treatment

Adverse event (ordered by body system)	Arm A: saquinavir soft gel capsule 1200 mg three-times daily (*n*=274)	Arm B: saquinavir soft gel capsule 1600 mg twice-daily (*n*=270)	Arm C: saquinavir soft gel capsule 1200 mg twice-daily+nelfinavir 1250 mg twice-daily (*n*=271)
Gastrointestinal system, *n* (%)			
Diarrhoea	50 (18)	40 (15)	80 (30)
Nausea	47 (17)	31 (11)	22 (8)
Vomiting	15 (5)	17 (6)	9 (3)
Abdominal pain	16 (6)	16 (6)	9 (3)
Neurological disorder, *n* (%)			
Headache	20 (7)	8 (3)	8 (3)
Peripheral neuropathy	10 (4)	13 (5)	6 (2)
General disorder, *n* (%)			
Fatigue	11 (4)	13 (5)	6 (2)
Laboratory shifts, *n* (%)			
↓ Neutrophils*	31 (11)	33 (12)	35 (13)
↑ Creatinine phosphokinase†	20 (7)	12 (4)	15 (6)
↑ Aspartate aminotransferase‡	10 (4)	9 (3)	8 (3)
↑ Alanine aminotransferase§	4 (2)	10 (4)	9 (3)
↑ γ-Glutamyl-transferase∫	2 (<1)	6 (2)	15 (6)
↑ Triglycerides¶	5 (2)	5 (2)	6 (2)
↓ Haemoglobin**	-	4 (2)	1 (<1)
↑ Alkaline phosphatase††	-	2 (<1)	3 (1)

*Defined as fall from 1000–1500/mm^3 to <5000/mm^3 or from >1500/mm^3 to ≤749/mm^3.
†Defined as rise from 1.1–1.5 to 6.0×the upper limit of the normal range (ULN) or from <1.0 to ≥3.1×ULN.
‡Defined as rise from 1.25–2.5×ULN to >10×ULN or from <1.25×ULN to ≥5×ULN.
§Defined as rise from 1.25–2.5 to >10×ULN or from <1.25 to ≥5×ULN.
∫Defined as rise from 1.25–2.5 to >10×ULN or from <1.25 to ≥5×ULN.
¶Defined as rise of ≥750 mg/dl.
**Defined as fall from 8.0–9.4 to <6.5 g/dl or from >9.4 to ≤6.9 g/dl.
††Defined as rise from 1.25–2.5 to >10×ULN or from <1.25 to ≥5×ULN.

body system (six patients). The six deaths up until week 48 (four in arm A and two in arm B) were all considered to be unrelated to the study drugs. There were no significant differences between arms with respect to clinically notable laboratory abnormalities (Table 3). Marked neutropenia occurred in 11–13% of patients, which was unexpected. This occurred early on in the study and was determined as being due to a delay in specimen transfer to the central laboratories, after the correction of which neutrophil counts returned to values around those anticipated.

AIDS-defining events

AIDS-defining events occurred in 47 patients (6%) during the 48-week study period (16, 17 and 14 patients in arms A, B and C, respectively). The most common AIDS-related events were oral or oesophageal candidiasis (11 events), *Pneumocystis carinii* pneumonia (5), herpes zoster (6), retinitis (defined independently from cytomegalovirus) (4), cachexia (4), and Kaposi's sarcoma (4), with no clear differences seen between treatment arms.

Effects of treatment on lipid levels

In a retrospective search of the safety database, increases in lipid concentrations, as measured by changes in either triglyceride levels (change from baseline grade 0 or 1 [not defined in protocol] to a subsequent grade 2 [400–750 mg/dl], 3 [751–1200 mg/dl] or 4 [>1200 mg/dl]) or cholesterol levels (change from <200 mg/dl at baseline to >200 mg/dl post-baseline), occurred in 0.7, 1.5 and 2.6% patients from arms A, B and C, respectively, with an overall incidence of 1.6% (13/815 patients). Laboratory grade shifts in non-fasting triglyceride levels (as defined above) from baseline occurred in 0.35, 0.75 and 2.2% of patients from arms A, B and C, respectively (1.1% of patients overall). Cholesterol level shifts (as defined above) occurred in 0.35, 1.11 and 2.2% of patients from arms A, B and C, respectively (1.2% of patients overall).

At week 48, the mean changes from baseline in fasting cholesterol were 55, 31 and 27 mg/dl, in fasting triglycerides were 157, –17 and 95 mg/dl, and in fasting glucose were –9, –5 and 3 mg/dl, in arms A, B and C, respectively.

Discussion

When used as part of a triple therapy regimen and considering the primary outcome (% patients with HIV-1 RNA <400 copies/ml, Amplicor assay, ITT analysis), saquinavir SGC at a dosage of 1600 mg twice-daily was found to be equivalent to 1200 mg three-times daily at 24 and 48 weeks. The use of an ITT analysis whereby missing values are considered failures is a conservative assessment, tending to underestimate the response rate and reflect the withdrawal rate. The OT analysis supported the equivalence conclusion from the primary analysis. The saquinavir SGC 1200 mg plus nelfinavir 1250 mg plus one NRTI arm also demonstrated similar efficacy to the saquinavir SGC three-times daily triple therapy arm as determined by secondary efficacy parameters (percentage of patients with HIV-1 RNA values <400 copies/ml, Amplicor assay, OT analysis at 24 and 48 weeks). However, according to the primary efficacy analysis, saquinavir SGC 1200 mg plus nelfinavir 1250 mg plus one NRTI was not equivalent to saquinavir SGC 1200 mg three-times daily plus two NRTIs at 24 and 48 weeks. In addition to the above, both the twice-daily regimens were as effective as the three-times daily regimen using the more stringent criterion for virological response of ≤50 copies/ml (UltraSensitive assay, ITT analysis).

This is the first clinical study to show formal equivalence between twice- and three-times daily administration of saquinavir SGC in the absence of co-administered ritonavir (used for pharmacokinetic enhancement purposes). The efficacy results seen in this large study were similar to those reported in other studies with the SGC 1200 mg three-times daily plus two NRTIs regimen [14,23]. Out of the other PIs, nelfinavir 1250 mg twice-daily provides equivalent efficacy to the standard regimen of 750 mg three-times daily [24], whereas a previous study comparing the use of twice- and three-times daily indinavir was terminated prematurely as patients in the twice-daily arm experienced significantly inferior levels of viral suppression compared with the three-times daily regimen [25]. However, the suppression of HIV RNA associated with saquinavir-containing regimens in the current study (43–47 and 78–80% of patients with HIV RNA <400 copies/ml, ITT and OT analysis, respectively) are similar to those reported historically with combination therapy including indinavir three-times daily (48% and 86% of patients with HIV RNA <400 copies/ml, ITT and OT analysis, respectively) [26].

Although the withdrawal rate seen in this study was relatively high (46% overall), this was broadly comparable with other recent trials of a similar size involving protease inhibitors (for example, withdrawal rate in an indinavir treatment arm of 43% [26] has been reported). In addition, because similar proportions of patients withdrew in each arm and most withdrawals were for reasons unrelated to treatment, this withdrawal rate would not be expected to affect any comparisons between regimens.

All treatments were generally well tolerated, and the adverse event profile for saquinavir SGC administered

either twice-daily or three-times daily was consistent with previous studies of saquinavir SGC three-times daily, with diarrhoea and nausea being reported most frequently [12,15,27]. We observed that the level of diarrhoea was significantly higher and the level of nausea significantly lower in the dual PI arm compared with the three-times daily arm; the difference in nausea between arms B and C was not significant. The administration of saquinavir SGC at the higher dose of 1600 mg twice-daily did not lead to unexpected adverse events, nor to any increase in the incidence of overall or particular adverse events compared with saquinavir SGC three-times daily.

Antiretroviral therapy has been associated with lipodystrophy, a syndrome of peripheral fat wasting, central adiposity, hyperlipidaemia and insulin resistance [28]. While the exact cause of this is unclear, PIs have been suggested as possible contributors. In this study, lipid level elevations were rarely reported at 48 weeks, which might suggest that these combinations had a relatively low risk of fat redistribution. However, fat redistribution was not prospectively monitored from the beginning of the study and possible cases were not confirmed by standardised objective tests.

While the results show that saquinavir twice-daily regimens are equivalent to three-times daily regimens, a saquinavir 1600 mg dose consists of eight capsules. Twice-daily dosing of saquinavir can also be achieved in clinical practice by the addition of a second PI (generally ritonavir) to the triple-therapy regimen for the purpose of pharmacokinetic enhancement. By increasing the exposure to saquinavir [18], addition of a second PI not only allows a reduced dosing frequency, but, when using ritonavir, the administration of a lower saquinavir dose (400–1000 mg saquinavir twice-daily doses have been reported) and a potentially reduced pill burden are also allowed. Dual PI combinations as part of quadruple therapy have been shown to be at least as effective as triple therapy regimens [14,29]. Of note is the fact that the combined saquinavir SGC/nelfinavir arm in this study only included one NRTI, whereas this combination is generally used as part of quadruple therapy.

In conclusion, when combined with two NRTIs, saquinavir SGC twice- and three-times daily triple combination regimens are comparable in terms of HIV-1 RNA suppression, increases in CD4 cell counts, and tolerability. The twice-daily regimen can be considered to be a safe and effective treatment in the management of HIV infection.

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Appendix

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