Long-term efficacy and safety of twice-daily saquinavir soft gelatin capsules (SGC), with or without nelfinavir, and three times daily saquinavir-SGC, in triple combination therapy for HIV infection: 100-week follow-up

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As part of triple combination antiretroviral therapy (ART), the recommended dose of the protease inhibitor (PI) saquinavir (SQV) in the soft gelatin capsule (SGC) formulation (Fortovase®) is 1200 mg three times daily [1]. This dose provides effective viral suppression and is well tolerated in patients with HIV infection [2,3]. In an effort to simplify dosing schedules, studies have investigated the feasibility of twice-daily dosing with SQV, because plasma exposure to SQV can be further enhanced by the co-administration of another PI, such as nelfinavir (NFV) [4] or ritonavir (RTV) [5-7]. Indeed, exposure to SQV-SGC (1200 mg) has been shown to be increased when it is administered with NFV (750 mg twice daily) [4]. At 48 weeks, a study showed that SQV-SGC twice daily, plus either two nucleoside reverse transcriptase inhibitors (NRTIs) or one NRTI and NFV, provided comparable efficacy and tolerability to SQV-SGC three times daily combined with two NRTIs [8]. In order to provide data on the long-term potency and safety of these regimens we present here the long-term follow-up of this study, reporting efficacy and safety for up to 100 weeks.
Materials and methods

A long-term follow-up to the original 48-week, Phase III, randomized, multicentre, open-label study was conducted in both antiretroviral-naive and NRTI-experienced HIV-infected patients. Full details of this 48-week trial – performed at 83 centres in the USA and Europe – have been published previously [8]. Patients were randomized to receive one of three treatment regimens: SQV-SGC 1200 mg three times daily plus two NRTIs (arm A); SQV-SGC 1600 mg twice daily plus two NRTIs (arm B); or SQV-SGC 1200 mg twice daily plus NFV 1250 mg twice daily plus one NRTI (arm C). Full inclusion and exclusion criteria have also previously been described [8].

The study was designed and monitored in accordance with Good Clinical Practice (GCP). Ethics approval was obtained from institutional review boards/local ethics committees of participating centres. Written informed consent was obtained from all study participants.

The primary objective of the long-term analysis reported here was to assess the efficacy and safety of three regimens of SQV-SGC after 48 weeks, and up to 100 weeks, of therapy. Once patients reached 48 weeks, they had the option of continuing in the study until a common study closure date (CSCD), or of withdrawing at that time. The CSCD was the date on which the last randomized patient reached 48 weeks of treatment.

The efficacy variables evaluated in this long-term follow-up study were antiretroviral activity – as assessed by changes in HIV-1 RNA values – and CD4 cell counts. Plasma HIV-1 RNA levels (<400 copies/ml [Roche Amplicor® assay] and <50 copies/ml [Roche Ultrasensitive® assay]), changes from baseline in HIV RNA values, CD4 cell counts, adverse events and clinical laboratory parameters were assessed at weeks 48, 60, 80 and 100.

Data are presented for a modified intention-to-treat (ITT) population and an on-treatment (OT) population; all patients are included in the safety analyses. The modified ITT populations included patients who continued in the study past week 48 and who were then placed in 60, 80 or 100 week groups depending on their duration of follow-up. Patients had the potential to reach 60, 80 or 100 weeks of treatment prior to the CSCD (week 48 for the last randomized patient), depending on their time of randomization. For example, in order for a patient to be included in the week 100 modified ITT population at the CSCD, the patient had to be enrolled at least 52 weeks earlier than the last randomized patient. Fisher’s Exact Test was used to compare statistically the proportion of modified ITT patients with HIV RNA values <50 and <400 copies/ml at 100 weeks in treatment arms A, B and C, respectively. A χ² test was used to compare statistically the reasons for withdrawal (failure to return for re-assessment, refusal of treatment, insufficient therapy and adverse events) among all three treatment groups and a P-value of <0.05 was considered statistically significant.

Results

Study population

The baseline demographics of the study participants were similar in all three treatment arms and have been published elsewhere [8].

At 48 weeks, the initial ITT population (all patients who were randomized and took at least one dose of study medication) consisted of 837 patients (n=280 arm A, n=278 arm B, n=279 arm C). Of these, 388 patients withdrew prior to week 48 (n=124 arm A, n=127 arm B, n=137 arm C). The main reasons for withdrawal were similar between treatment groups and included failure to return for re-assessment (111/837; 13%), refusal of treatment (107/837; 13%) and adverse events (94/837; 11%). Therefore, a total of 449 patients continued beyond 48 weeks of treatment. Seven patients had no follow-up data after 48 weeks, resulting in 442 patients with evaluable data for this long-term analysis (n=152 arm A, n=150 arm B, n=140 arm C). All 442 patients were included in the final long-term safety analysis.

Between 48 and 100 weeks, 94 patients withdrew from the study: 31 patients from arm A; 26 patients from arm B; and 37 patients from arm C. The main reasons for discontinuation of treatment were: failure to return for re-assessment in 27 patients (n=8 arm A, n=8 arm B, n=11 arm C); refusal of treatment in 25 patients (n=6 arm A, n=6 arm B, n=11 arm C); insufficient therapy in 20 patients (n=1 arm A, n=4 arm B, n=5 arm C); and adverse events in 14 patients (n=3 arm A, n=4 arm B, n=7 arm C). Of these adverse events, most were of a gastrointestinal nature and considered possibly or probably related to study treatment.

The complete study duration up to the CSCD was 115 weeks and enrollment took place over the first 67-week period. After the initial 48 weeks of treatment with study drug, the mean duration of follow-up in days (SD) was 226 (112), 221 (111) and 216 (104), for treatment arms A, B and C, respectively. As the CSCD was based on the last enrolled patient’s first dose date, not all patients had the potential to complete the 115-week study duration. Consequently, the modified ITT population for 100 weeks consisted of 190 patients (n=65 arm A, n=67 arm B, n=58 arm C).

At 48 weeks, the OT population (only patients with an available evaluation at that time point) consisted of 470 patients. By week 100, the OT population included 102 patients (n=36 arm A, n=40 arm B, n=26 arm C) in total.
Continued suppression of HIV-1 replication was observed in all treatment arms from week 48 through to week 100. The proportion of patients in the OT population with HIV-1 RNA values <400 and <50 copies/ml up to 100 weeks is shown in Figure 1. For arms A, B and C, the proportion of patients with HIV-1 RNA values <400 and <50 copies/ml was similar to those reported at 48 weeks. No statistically significant difference in the proportion of patients with HIV RNA values <400 and <50 copies/ml was observed among the three treatment arms.

The proportion of patients with HIV-1 RNA values <400 and <50 copies/ml at weeks 48 and 100 in the modified ITT population is presented in Table 1. When arm A was compared with arm B at 100 weeks, there was no significant difference in the proportion of patients with HIV RNA values <400 or <50 copies/ml. Similarly, no significant difference in the proportion of patients with HIV RNA values <50 copies/ml was reported among arms A, B or C. However, a statistically significant difference was observed between arm C and arms A or B in the proportion of patients with HIV RNA values <400 copies/ml at 100 weeks (arm A vs arm C, \( P = 0.0166 \); arm B vs arm C, \( P = 0.0269 \)).

The mean plasma HIV-1 viral load across all treatment arms was 4.7 log10 copies/ml at baseline. From week 48 to 100, the mean change in plasma HIV-1 RNA values was similar among treatment arms in the OT population (Figure 2).

In the OT population, increases in CD4 cell counts from baseline were seen in all treatment arms throughout the entire study period. Mean baseline CD4 cell counts were 307, 323 and 311 cells/mm³ for arms A, B and C, respectively. At the end of the 48-week study, initial CD4 cell counts had increased by +213, +184 and +223 cells/mm³, respectively. The CD4 cell count continued to increase progressively during the long-term follow-up, and at 100 weeks had reached +361, +273 and +309 cells/mm³, respectively (Figure 2).

Safety and tolerability
From week 48 onwards, there was no difference between treatment arms in the overall incidence of adverse events, with 8–9% of patients (13/152 arm A, 12/150 arm B, 11/140 arm C) reporting at least one adverse event of moderate or severe intensity that was considered possibly or probably related to study medication. Most of these adverse events were gastrointestinal disorders (3–5% of patients [5/152 arm A, 7/150 arm B, 5/140 arm C]). Diarrhoea was the most frequent gastrointestinal disorder and was reported by 3% (4/152 and 2% (4/140) of patients in treatment arms A and C, respectively. Only one patient (arm B) experienced a serious adverse event, diagnosed as pancreatitis, which was considered to be possibly related to the study medication.

Adverse events were a more common reason for treatment withdrawal in arm C (dual PI arm), than in either arm A (SQV-SGC three times daily) or arm B (SQV-SGC twice daily): 5 vs 2 and 3%, respectively. Similarly, other common reasons for withdrawal also occurred more frequently in arm C, including refusal of treatment (4% arm A, 5% arm B, 8% arm C) and lost to follow-up (5% arm A, 5% arm B, 7% arm C). Overall, there was no statistically significant difference

Figure 1. Mean proportion of patients with HIV-1 RNA levels <400 and <50 copies/ml (on-treatment population)
Table 1. Proportion of patients with HIV RNA values <400 and <50 copies/ml at weeks 48 and 100 (modified intention-to-treat population)

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
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<tbody>
<tr>
<td>Proportion &lt;400</td>
<td>47 (132/280)</td>
<td>45 (126/287)</td>
<td>43 (119/279)</td>
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<tr>
<td>copies/ml, %</td>
<td>37 (104/280)</td>
<td>36 (101/278)</td>
<td>35 (97/279)</td>
</tr>
<tr>
<td>Proportion &lt;50</td>
<td>28 (16/58)</td>
<td>28 (16/58)</td>
<td>22 (13/58)</td>
</tr>
<tr>
<td>copies/ml, %</td>
<td>47 (132/280)</td>
<td>45 (126/287)</td>
<td>43 (119/279)</td>
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Arm A: saquinavir 1200 mg three times daily plus two nucleoside reverse transcriptase inhibitors (NRTIs).
Arm B: saquinavir 1600 mg twice daily plus two NRTIs.
Arm C: saquinavir 1200 mg twice daily plus nelfinavir 1250 mg twice daily plus one NRTI.

between treatment arms with regard to reasons for withdrawing from the study.

During the long-term follow-up period, laboratory grade shifts occurring in ≥3% of patients were only observed with creatine kinase: arm A, six (3.9%) patients; arm B, five (3.3%) patients; arm C, five (3.6%) patients. Laboratory grade shifts in creatine kinase were defined as changes from grade 0 (baseline/screening) to grade 3 (3.1–6.0 x the upper limit of the normal range [ULN]) or 4 (>6.0 x ULN) or changes from grade 1 (baseline/screening) to grade 4.

Although no laboratory grade shifts in cholesterol were reported, 2.7% (22/814) of patients received lipid-lowering agents during the entire 100-week study treatment period (n=5 arm A, n=7 arm B, n=10 arm C). Of these agents, atorvastatin was the drug most frequently taken (n=2 arm A, n=4 arm B, n=5 arm C).

Discussion

This follow-up extension of the original 48-week study demonstrates that all three ART regimens (SQV-SGC 1200 mg three times daily plus two NRTIs [arm A]; SQV-SGC 1600 mg twice daily plus two NRTIs [arm B]; and SQV-SGC 1200 mg twice daily plus N FV 1250 mg twice daily plus one NRTI [arm C]) maintain long-term viral suppression, with continued increases in CD4 cell counts in HIV-1-infected patients, for at least 2 years. In addition, there were no additional, or increase in the incidence of, adverse events among all three treatment regimens.

These long-term efficacy results extend those of the earlier 48-week study [8]. At 48 weeks, the proportion of patients with viral load suppression (<400 copies/ml) was 47% (arm A), 45% (arm B) and 43% (arm C) in the ITT population [8]. At 100 weeks this degree of viral suppression was maintained at 49 and 48% for arms A and B, respectively. However, there was a significantly smaller proportion of patients (28%) in arm C who maintained a HIV RNA level <400 copies/ml, compared with both arm A, SQV-SGC 1200 mg three times daily (P=0.0166) and arm B, SQV-SGC 1600 mg twice daily (P=0.0269). This difference might have been due to a slightly higher withdrawal rate seen in arm C (26%), compared with arm A (20%) and arm B (17%) (P=0.07). Increases in CD4 cell counts from baseline continued to be observed from 48 to 100 weeks in all three treatment arms.

The level of suppression of HIV-1 replication still observed at 100 weeks in this study is similar to that seen at 24 and 48 weeks in previous evaluations of SQV-SGC 1200 mg three times daily in triple combination therapy [9,10]. In one study, 42% of patients had HIV RNA values <400 copies/ml at 48 weeks [10]. In addition, the long-term efficacy demonstrated with SQV-SGC in this study is comparable to that observed in PI-naive patients receiving other PI-based ART, such as indinavir 800 mg three times daily, at 100 weeks [11].

The sustained efficacy of the three regimens is consonant with the SQV plasma concentrations measured in a subset of patients enrolled in the initial 48-week study [12]. Full pharmacokinetic profiles of SQV were performed in 36 PI-naive subjects randomized to all three treatment arms, up to and including week 60 [12]. The results of this pharmacokinetic analysis showed that there was relatively little change in SQV plasma concentrations over the entire 60-week time period [12].

During this follow-up study, there was no increase in the proportion of patients reporting adverse events and, more importantly, no additional adverse events were reported between week 48 and 100. As with the 48-week study, gastrointestinal events were the most frequently reported.

Between week 48 and 100, no laboratory grade shifts in cholesterol levels were seen, although 2.7% of patients received lipid-lowering agents, mainly atorvastatin. In a study conducted in 100 HIV-infected patients receiving a lopinavir/ritonavir (400/100 mg twice-daily) treatment regimen, cholesterol (>300 mg/dl) baseline levels were elevated in 15% of patients following 108 weeks of treatment [13]. The higher percentage of subjects with elevated cholesterol on lopinavir/ritonavir as compared with that seen in this study on other PIs suggests there may be differences between PIs and their effects on cholesterol metabolism.

The clinical course of HIV disease has changed dramatically since the introduction of highly active antiretroviral therapy (HAART) regimens [14]. Strict adherence to this therapy is necessary to maintain the clinical benefits. However, HAART regimens can be complex as they have high pill counts, frequent dosing...
intervals and food restrictions. Simplifying HAART regimens by using antiretroviral regimens that can be administered once daily or twice daily may improve adherence and ultimately enhance patient outcome [15–17]. The findings reported here suggest that the long-term efficacy and safety of SQV-SGC regimens are not compromised by reducing the dose frequency from three times daily to twice daily.

In conclusion, twice-daily triple therapy regimens with SQV-SGC as the sole PI can be considered equally effective and well tolerated in the long-term treatment of HIV-1 infection as triple therapy regimens that include SQV-SGC three times daily. Although the dual PI arm of SQV-SGC plus NFV twice daily is also effective, in the long term this treatment regimen may be less acceptable to patients, as reflected in the slightly higher withdrawal rate.

**Acknowledgements**

This study was supported by Roche Laboratories Inc., Nutley, NJ, USA.

**References**


