The efficacy and safety of once-weekly and once-fortnightly subcutaneous epoetin β in peritoneal dialysis patients with chronic renal anaemia

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Abstract

Background. Reducing the dosage frequency of subcutaneous epoetin in peritoneal dialysis (PD) patients is convenient and should improve patient satisfaction and, possibly, compliance. We investigated if a weekly dosage of epoetin β in PD patients safely maintained haemoglobin (Hb) concentrations equivalent to those obtained with previous twice- or thrice-weekly administration. In addition, we investigated if a fortnightly dosage of epoetin β was safe and as effective as previous weekly administration.

Methods. After a 4 week run-in period, PD patients were switched to either weekly or fortnightly epoetin β administration, depending on their previous treatment schedules, for 25 weeks.

Results. The per-protocol cohort included 128 patients, of whom 54 received epoetin β once weekly and 74 once fortnightly. The mean change in Hb concentration from baseline over weeks 13–25 and the 90% confidence intervals (CIs) remained within the target range (10–12 g/dl) and specified equivalence (±0.75 g/dl) limits in the weekly (−0.34 g/dl; 90% CI: −0.14 to −0.54 g/dl) and fortnightly (−0.39 g/dl; 90% CI: −0.24 to −0.55 g/dl) cohorts. The mean change from baseline in the epoetin β dose was 1.4 IU/kg/week (90% CI: −3.8 to 6.6 IU/kg/week; 2%) in the weekly cohort and 4.41 IU/kg/week (90% CI: 1.7–7.2 IU/kg/week; 13%) in the fortnightly cohort. Both treatment regimens were well tolerated.

Conclusions. In stable PD patients switched from twice- or thrice-weekly to weekly epoetin β treatment, Hb concentrations could be maintained within the specified range over 25 weeks without significant change in their mean epoetin β doses. In patients switched from weekly to fortnightly treatment, Hb concentrations could also be maintained over 25 weeks. There was a small increase in the mean dose during this period, but ≥50% of patients could be maintained without dose increase. Reducing dosage frequency may improve compliance in PD patients who self-administer their epoetin.

Keywords: dosage; epoetin beta; peritoneal dialysis; renal anaemia; subcutaneous

Introduction

Recombinant human erythropoietin (epoetin) is widely used to maintain adequate haemoglobin (Hb) concentrations and avoid transfusion dependency in patients with renal anaemia. Also, studies conducted in patients with renal anaemia have shown that increasing Hb concentration with epoetin treatment is associated with additional benefits, including improved quality of life [1] and reduced morbidity and mortality [2–4].

Subcutaneous (SC) administration of epoetin is more convenient than intravenous (IV) administration in peritoneal dialysis (PD) patients who do not have a fistula [5,6]. The use of the SC route of administration also has a sound economic basis. The dose of epoetin required to maintain Hb levels equivalent to those
Epoetin β in PD patients with chronic renal anaemia

achieved with IV administration is lower (by ~30%) when the SC route is used, resulting in substantially reduced costs [7–10].

Studies have shown that SC epoetin treatment raises and maintains Hb concentrations in PD patients with anaemia [4,10–15]. To date, however, only small-scale studies have compared the efficacy of different epoetin dosage frequencies in PD patients [12–14,16]. These studies suggest that maintenance SC epoetin could be effective when given once weekly or fortnightly (every 2 weeks) to PD patients. However, the results need to be confirmed in larger studies specifically designed to compare different schedules of epoetin administration.

Large-scale, randomized studies have been carried out already in stable haemodialysis patients [17,18]. In a no-difference study, Weiss et al. [17] showed that epoetin β administered once weekly had an efficacy similar to that of twice- or thrice-weekly administration. These results were later confirmed by Locatelli et al. [18], who demonstrated that in stable haemodialysis patients weekly treatment could be considered equivalent to thrice-weekly treatment. In both studies, Hb concentration and haematocrit remained stable over the course of the treatment period without requiring significant changes in epoetin β doses, despite the reduced frequency of its administration.

The ability to administer epoetin β SC weekly or fortnightly to PD patients would improve the convenience and ease of use of the treatment regimen. It is also believed that a reduced frequency may encourage patients to self-administer epoetin [5,6] and it should improve compliance with the treatment.

The aim of the present study was to assess in a large number of PD patients if once-weekly dosage with SC epoetin β was safe and able to maintain an Hb concentration equivalent to that obtained previously with twice- or thrice-weekly administration. Additionally, we examined if fortnightly dosage with epoetin β was safe and able to maintain an Hb level equivalent to that obtained with once-weekly administration.

Subjects and methods

Study design

This was a multicentre, non-randomized, open-label study with two cohorts that was designed to determine whether or not weekly or fortnightly epoetin β regimens could maintain equivalent Hb level to the patients’ previous regimens. Patients entered a 4 week run-in period to assess baseline Hb concentrations under stable conditions. During the run-in, patients received epoetin β (NeoRecombin®; F. Hoffmann-La Roche) through SC injections administered by a pen device (Reco-Pen®; F. Hoffmann-La Roche) according to their pre-study schedule of once-, twice- or thrice-weekly injections.

After the run-in, eligible patients entered the study treatment period. Patients who were receiving two or three epoetin β doses each week (cohort A) were switched to once-weekly treatments and patients receiving epoetin β once weekly (cohort B) were switched to once-fortnightly treatments for 25 weeks. The study design is presented schematically in Figure 1.

Patients

The patients were recruited on the basis of their previous dosing schedules. Written informed consent was obtained from all patients. The study was conducted according to the latest revision of the Declaration of Helsinki and Good Clinical Practice requirements. Local independent ethics committees approved the study.

The compliance of subjects with the inclusion and exclusion criteria was evaluated 1 or 2 weeks before they entered the study and at the end of the run-in phase. The inclusion criteria called for patients to be aged 18 years or older, with chronic renal anaemia and on PD for at least the previous 3 months; clinical stability; stable SC epoetin dosage over the previous 3 months, administered in once-, twice- or thrice-weekly doses; mean weekly epoetin maintenance dose ≤8000 IU in the previous 2 weeks and during the run-in period; delivered dialysis dose (Kt/V) of ≥1.8/week; and adequate iron status [defined as transferrin saturation ≥20% (hypochromic red cells ≤10%) and serum ferritin ≥100 ng/ml] at the screening assessment.

Additional inclusion criteria for the run-in period were a stable treatment regimen and the administration of four identical total weekly doses of SC epoetin β (in once-, twice- or thrice-weekly doses, according to the patient’s previous schedule). The mean Hb concentration during run-in had to be within the 10–12 g/dl range and had to be stable (range of maximum/minimum variation limited to 1.5 g/dl). If transferrin saturation fell below 20% during the study treatment period, IV iron was administered according to the particular centre’s practice (based on current European guidelines) [5].

The exclusion criteria were conditions known to cause anaemia not related to chronic renal disease (haemoglobinopathy, haemolysis, gastrointestinal bleeding in the previous 3 months requiring treatment, acute infection, unstable systemic inflammatory disease, severe hyperparathyroidism, serum aluminium concentration >50 μg/l, albumin <3 g/dl, vitamin B12 or folic acid deficiency); hypertension within the last 6 months requiring interruption of epoetin treatment; current malignancy; newly diagnosed epilepsy; severe diseases (such as stroke, unstable angina pectoris and myocardial infarction) within the last 3 months; thrombocyte count >500 000/μl; life expectancy <12 months; blood transfusions within the last 3 months; pregnancy or lactation; history
of hypersensitivity to epoetin β or constituents of the formulation. Patients medicated intermittently with angiotensin II-receptor antagonists and angiotensin-converting enzyme inhibitors were excluded, although regular antihypertensive treatment with these agents was allowed.

Dosage adjustments

During the run-in phase, the patient’s weekly epoetin β dosage was maintained as in the 2 weeks before enrolment in the study. The starting dose of epoetin β for the study treatment period was the individual weekly dose of epoetin β during the 4 week run-in period, injected SC once weekly for cohort A and double the weekly dose injected SC once-fortnightly for cohort B.

During the study treatment period, the Hb concentration of each patient was maintained within the target range of 10–12 g/dl and within the acceptable distribution range (baseline Hb concentration ±1 g/dl) by adjusting the dose of epoetin β. If Hb increased by >1 g/dl on two sequential measurements compared with baseline, the epoetin β dose was increased by 20% in the weekly treatment cohort and by 30% in the fortnightly cohort. If Hb increased by >1 g/dl above baseline, the individual epoetin β dose was reduced by 20% in both cohorts. Adjustments larger than 20% in the weekly cohort and 30% in the fortnightly cohort or repeated adjustments of epoetin β doses were considered for individual patients, but more than one dose adjustment in any 2 week period was avoided.

Epoetin β administration was interrupted if Hb rose above 14 g/dl and then resumed at 50% of the previous dose once an Hb concentration of 13 g/dl was reached.

Efficacy assessments

The primary efficacy variable was change from baseline in the mean Hb concentration over weeks 13–25 of the study. The first 12 weeks of the study treatment period were excluded from the efficacy evaluation to avoid a carryover effect from the epoetin treatment used before the change in dosage regimen.

Other efficacy variables were changes from baseline in the mean weekly epoetin β dose and haematocrit during weeks 13–25. The number of patients with blood transfusions and the mean number of units of blood transfused were also recorded.

Safety assessments

Adverse events were recorded throughout the study and for a further 15 days after completion.

Blood pressure, heart rate and body weight were determined at 2 week intervals during the run-in period and at 4 week intervals thereafter. In addition, laboratory tests to determine physiological safety (thromocyte counts and blood chemistry) were recorded at the screening visit and every 8 weeks thereafter.

Statistical analysis

We required 80 patients per treatment cohort to detect the equivalent maintenance of Hb level by the new and the pre-study treatment regimens, with a 90% power and a type I error of 5%. Assuming that 20% of patients would be unevaluable for the per-protocol analysis, 100 patients per treatment cohort needed to be enrolled.

The primary objective of the study was to determine if the weekly and fortnightly epoetin β dosages were able to maintain Hb concentrations equivalent to those maintained by the patients’ previous treatment schedules. The regimens were considered to be equivalent if the 90% confidence interval (CI) for the difference between the mean Hb value at baseline and during weeks 13–25 was within the range of −0.75 to +0.75 g/dl.

The primary efficacy variable was analysed using two one-sided paired t-tests, with the paired observations consisting of the baseline Hb concentration (mean of measurements taken at weeks −4, −2 and +1) for each patient and the mean maintenance Hb concentration during weeks 13–25 for each patient.

Secondary efficacy variables were analysed using the mean of the differences between baseline and weeks 13–25 for each patient, and 90% CIs were calculated for the two treatment cohorts. Median (range) values were also determined for Hb level, haematocrit and weekly epoetin β doses during the study treatment period. The study was not designed to determine whether or not equivalent haematocrit and dose requirements of epoetin β could be maintained with the reduced epoetin β administration frequency. However, with respect to the haematocrit, a 90% CI within the range ±2% for the change between baseline and evaluation period was considered not to be clinically relevant.

The main conclusions regarding efficacy are based on the results for the per-protocol population (as recommended in guidelines for studies testing for the equivalence of different treatment regimens [19, http://www.ich.org/ pdflCH/e9.pdf]), although results for the intention-to-treat (ITT) population are also given. The ITT population comprised all patients who had at least one Hb measurement during the study’s treatment period. To avoid bias resulting from the exclusion of patients who could be regarded as non-responders, the last available Hb concentration was used for all patients who withdrew during the first 12 weeks of the study.

Patients were excluded from the per-protocol analysis if the inclusion criteria were not fulfilled and if exclusion criteria related to Hb response were met (haemoglobinopathies, haemolysis, gastrointestinal bleeding or blood transfusions within the last 3 months) or if they discontinued the study during the first 12 weeks of the study treatment period.

Results

A total of 237 patients from 46 European centres were included in the study run-in period. Figure 2 summarizes the flow of patients through the study. As 47 patients discontinued the study during the run-in, 190 patients completed the run-in period and were assigned to the once-weekly (n = 82) or once-fortnightly (n = 108) treatments. One patient from each cohort was excluded from the safety population because they failed to receive the new epoetin β administration schedule. All patients in the safety population were included in the ITT population, apart from one patient who dropped out before a first Hb evaluation. Therefore, 187 patients were included...
in the ITT population (once-weekly cohort, n = 80; once-fortnightly, n = 107).

Nine patients receiving weekly treatment and 10 receiving fortnightly treatment were withdrawn from the study before week 25 for reasons shown in Table 1.

The patients included in the per-protocol population numbered 128 (once-weekly cohort, n = 54; once-fortnightly, n = 74). The reasons for exclusion from the per-protocol analysis included violation of inclusion criteria (18 patients from each cohort), withdrawal from study before week 13 (five patients in each cohort), switching to haemodialysis (one patient receiving weekly treatments and five patients receiving fortnightly treatments), bleeding complications (one patient from the weekly cohort and two patients from the fortnightly cohort) and other protocol violations (two patients from the weekly cohort and three patients from the fortnightly cohort).

Patient demographics and baseline characteristics were similar in the two cohorts (Table 2), apart from their mean weekly epoetin β doses at baseline, which in the fortnightly cohort was approximately half that of the once-weekly cohort. This difference between the two cohorts in dose reflects differences in the clinical conditions of the patients.

Efficacy results

The mean Hb concentration during weeks 13–25 remained within the specified range throughout the study in both the weekly and the fortnightly cohorts (Figure 3). In the per-protocol population, the mean changes in Hb concentration from baseline over weeks 13–25 (−0.34 and −0.39 g/dl in the once-weekly and once-fortnightly cohorts, respectively) and the 90% CI of these changes (−0.14 to −0.54 and −0.24 to −0.55, respectively) were within the specified equivalence range in both cohorts (±0.75 g/dl) (Table 3 and Figure 4). The results for the ITT population were similar to those of the per-protocol population (Figure 4).

The mean changes in haematocrit during weeks 13–25 compared with baseline were small for both cohorts and consistent with the results for Hb concentration in both the per-protocol (Table 3) and ITT populations (data not shown).

The mean weekly epoetin β doses in relation to Hb levels over the course of the study are shown for the two cohorts in Figure 3. In the once-weekly cohort, the mean weekly dose was 65.3 IU/kg at the end point of the study compared with 63.5 IU/kg at baseline, a change of 3%. In the once-fortnightly cohort, the mean weekly dose was 36.2 IU/kg at the end point compared with 33.7 IU/kg at baseline, a change of 7%. In addition, the mean weekly epoetin β doses at baseline and during the analysis period (weeks 13–25) are shown in Table 3. From baseline to weeks 13–25, a mean change of 1.4 IU/kg/week (2%) was observed in the weekly cohort and 4.4 IU/kg/week (13%) in the fortnightly cohort.

In contrast, the median weekly epoetin β dose during the evaluation period remained stable over time, particularly in the fortnightly cohort, and there was no increase in the median weekly dose over the course of the study (Figure 5). Therefore, >50% of the patients in each cohort could be maintained on the new dosing schedules without increases in their doses during the 25 week period.

For the per-protocol population, the median serum ferritin concentration remained >300 μg/l throughout the study treatment period and there were no clinically significant changes from baseline to the end point in either cohort. At the end point, the median serum ferritin concentration of the weekly cohort was 301.7 μg/l [interquartile range (IQR): 185.5–512.4 μg/l] and it was 320.9 μg/l in the fortnightly cohort (IQR: 198.0–442.0 μg/l).
The median transferrin saturation remained at \( \geq 25\% \) throughout the study treatment period for both cohorts. At the end point, the median transferrin saturation was 25\% (IQR: 19.7–34.5\%) amongst those receiving weekly treatment and 31\% (IQR: 21.4–37.0\%) amongst those receiving fortnightly treatment.

Similar percentages of patients in each cohort received iron supplementation during the treatment period. For the safety population, 40 patients (49\%) and 48 patients (45\%) of the weekly and fortnightly cohorts, respectively, took oral iron. Intravenous iron was required by 35\% of patients in both cohorts.

During the study treatment period, four patients in the weekly cohort and five patients in the fortnightly cohort received blood transfusions. The mean numbers of units transfused per patient were 0.12 and 0.35 in the weekly and fortnightly cohorts, respectively. Two patients in the fortnightly cohort received multiple transfusions. In both of these cases, the transfusions were linked to peritonitis and post-operative complications.

**Safety results**

Three patients died during the treatment period for reasons considered unrelated to the studied medication [cardiac failure \( n = 1 \); myocardial infarction \( n = 1 \) and sepsis \( n = 1 \)]. One patient died during the run-in period from an intracranial haemorrhage.

The weekly and fortnightly treatment regimens were well tolerated. Overall, 70\% of the patients in the weekly cohort and 72\% of the patients in the

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**Table 2.** Patient characteristics at baseline, per-protocol population \(( n = 128)\)

<table>
<thead>
<tr>
<th></th>
<th>Once-weekly cohort (( n = 54))</th>
<th>Once-fortnightly cohort (( n = 74))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (male/female)</strong></td>
<td>25/29</td>
<td>35/39</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>53.0 (14.9)</td>
<td>57.6 (13.9)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>166.4 (9.3)</td>
<td>164.2 (9.5)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>72.3 (12.9)</td>
<td>68.5 (13.0)</td>
</tr>
<tr>
<td><strong>Renal anaemia aetiology(^a) ((n))</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>14 (26%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>16 (30%)</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>Hypertensive renal disease</td>
<td>8 (15%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>3 (6%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>4 (7%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>3 (6%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td><strong>Weekly epoetin (\beta) dose (IU/kg)</strong></td>
<td>63.5 (32.1)</td>
<td>33.7 (18.5)</td>
</tr>
<tr>
<td><strong>Hb (g/dl)</strong></td>
<td>11.2 (0.5)</td>
<td>11.1 (0.6)</td>
</tr>
<tr>
<td><strong>Haematocrit (%)</strong></td>
<td>33.7 (2.0)</td>
<td>33.5 (2.5)</td>
</tr>
<tr>
<td><strong>Median transferrin saturation [% (IQR)]</strong></td>
<td>27.9 (22.0–33.5)</td>
<td>28.5 (22.3–34.0)</td>
</tr>
<tr>
<td><strong>Median serum ferritin [\mu g/l (IQR)]</strong></td>
<td>318.2 (179.0–475.8)</td>
<td>315.0 (187.0–450.0)</td>
</tr>
<tr>
<td><strong>Peritoneal dialysis type ((n))</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPD</td>
<td>37 (69%)</td>
<td>59 (80%)</td>
</tr>
<tr>
<td>APD</td>
<td>17 (31%)</td>
<td>15 (20%)</td>
</tr>
</tbody>
</table>

Values are presented as mean (SD).

Baseline values were defined as the mean of three measurements made during the run-in phase for Hb and haematocrit; the mean value over the run-in phase of the weekly epoetin dose; and as measured at week +1 for all other variables.

\(^a\)Most common causes of end-stage renal disease. Data available for 47 patients in the once-weekly cohort and 51 patients in the once-fortnightly cohort.

CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis.

**Fig. 3.** Mean weekly epoetin \(\beta\) dose and Hb concentration over the study treatment period (per-protocol population, \( n = 128 \)). The values at ‘End’ are the means of the last measurements made for each patient either at the completion of the study or at the time of early withdrawal.
fortnightly cohort experienced adverse events, but the investigators considered most of these to be unrelated to treatment. Two patients from each cohort withdrew early because of adverse events. In the once-weekly cohort, one patient withdrew because of aortic valve incompetence and another because of peritonitis. In the once-fortnightly cohort, one patient withdrew because of pericarditis and another as a result of post-operative complications accompanied by moderate headaches.

Peritonitis and hypertension were the most commonly occurring adverse events (Table 4). There were no clinically significant differences in the numbers and types of adverse events observed in the weekly and fortnightly cohorts. The higher incidence of urinary tract infection observed in the fortnightly cohort compared with the weekly cohort (Table 4) was not considered to be related to the studied medication.

During the study, 6 of 81 patients in the weekly cohort and 11 of 107 patients in the fortnightly cohort experienced adverse events that resulted in the modification (decrease or increase) of their epoetin β doses. In only three of these patients was there a possible or probable association between the adverse event (headache and aggravation of hypertension in one patient, headache in one patient and phlebitis in one patient) and epoetin treatment; and their epoetin β doses were decreased. The majority of the remaining adverse events necessitating dose modifications consisted of worsening of anaemia or infections, for which the epoetin β dose was increased.

Mean sitting systolic and diastolic blood pressures remained stable throughout the study for both treatment regimens. There were no clinically relevant changes from baseline in laboratory safety parameters (platelets, albumin, phosphate, potassium and Kt/V) in the two cohorts.

**Discussion**

Two recently reported large-scale, randomized trials of epoetin β treatment in stable haemodialysis patients showed that once-weekly epoetin β was as effective in maintaining stable Hb levels as twice- or thrice-weekly treatments with similar weekly epoetin β dosages [17,18]. To date, however, only small-scale studies have examined the ability of reduced dosing frequencies of epoetin to maintain Hb concentrations in PD patients [12–14,16]. For example, a small, randomized study by Frifelt *et al.* [12] evaluated the effect of 3 months of treatment with once-weekly SC epoetin β 16 continuous ambulatory PD patients who previously had been treated thrice weekly with epoetin. The results were compared with those of 17 patients maintained on their original thrice-weekly regimen throughout the study. There were no significant changes in either cohort in Hb concentration during the study, suggesting that, despite the low numbers of patients, a once-weekly epoetin β regimen may be effective in PD patients. Such studies suggested that further assessment of reduced dosages of epoetin was warranted in PD patients.

Our current study is the first large-scale investigation to confirm the effectiveness of reduced epoetin dosing
frequencies in PD patients. We switched patients with renal anaemia previously maintained on twice- or thrice-weekly epoetin to a once-weekly dose of epoetin β and patients previously stable on once-weekly epoetin to a fortnightly dosing regimen. The treatments were deemed to be equivalent if the 90% CI for the difference between the mean Hb level at baseline and during the evaluation period (weeks 13–25) was within the ±0.75 g/dl range. This value was chosen because it fell within the limits of the target Hb level (10–12 g/dl) used in the study. The target Hb level (10–12 g/dl) was itself based on several guidelines and recommended target levels: British Renal Society, >10 g/dl [20]; Canadian Society of Nephrology, 11–12 g/dl [21]; European Best Practice Guidelines, >11 g/dl [22]; and Health Care and Financing Administration USA, 10.3–12 g/dl [http://cms.hhs.gov/esrd/1d6.pdf 1999].

The mean Hb concentrations remained within 10–12 g/dl in our patients receiving epoetin β once weekly or once fortnightly during the evaluation period (weeks 13–25) and the 90% CI fell within the pre-specified equivalence limit of ±0.75 g/dl. This confirms the equivalence of the less-frequent maintenance treatment of renal anaemia to the patients’ previous dosing regimens. Notably, these results were observed in both the ITT and the per-protocol population (a more-stringent analytical approach for establishing bioequivalence [19,23]) and confirmed the validity of the study.

Subject recruitment was lower than expected, for sample size calculations required us to have 80 patients in each per-protocol cohort. The actual numbers of patients, however, were 54 for the weekly cohort and 74 for the fortnightly cohort. Nevertheless, we do not consider this to have an impact on the interpretation of the data, because the 90% CI for the difference between Hb levels at baseline and during the evaluation period fell within a relatively narrow range (Table 3).

Moreover, in both cohorts Hb remained within the target range throughout the study, although there was a small decrease (≤3.5%) in mean Hb between baseline and the evaluation period. The patients in the weekly cohort did not require any significant increases in their epoetin β doses to maintain their Hb within the target range. During the evaluation period, there was a small increase in the mean dose of epoetin β in the fortnightly cohort, but the magnitude of this increase may be partially explained by the study design.

Differences in the study protocol resulted in greater increases in dose in the fortnightly cohort than the once-weekly cohort. In the event that Hb decreased >1 g/dl, the study protocol stipulated that the epoetin β dose be increased by 30% in the fortnightly cohort, but by 20% in the weekly cohort. Therefore, the patients in the fortnightly cohort were likely to receive larger increases in their epoetin β doses if their Hb levels dropped.

### Table 4. Most frequently reported adverse events (occurring in ≥5% of patients), safety population (n=188)

<table>
<thead>
<tr>
<th></th>
<th>Once-weekly treatment (n=81)</th>
<th>Once-fortnightly treatment (n=107)</th>
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<tbody>
<tr>
<td>Peritonitis</td>
<td>17 (21%)</td>
<td>20 (19%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (12%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (4%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (7%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (1%)</td>
<td>9 (8%)</td>
</tr>
</tbody>
</table>
Importantly, the median weekly doses of epoetin β throughout the study were relatively stable in the fortnightly cohort and they did not increase over time. This finding suggests that the majority of patients had no, or only minor, changes in their doses of epoetin β, while a very small number of patients had higher increases. Because there was no change in the median dose of epoetin β between baseline and the evaluation period in either cohort, it can be inferred that ≥50% of patients in both cohorts could be maintained on the new treatment schedule with their baseline epoetin β doses or lower doses.

With regards to safety, the epoetin β administration regimens used in the study were well tolerated. The majority of adverse events were mild to moderate in intensity and were not considered to be related to the studied medication. There was no difference in safety between the two cohorts.

What are the clinical implications of the results of this study for the management of renal anaemia? A reduction in the frequency of the administration of epoetin β will be more convenient for patients and may improve adherence to treatment. In a recent community-based study that evaluated the compliance of patients self-administering epoetin, non-compliance was found to be relatively common and the most prevalent reason given for missed doses was forgetfulness [23]. The authors suggested that simplifying the dosage regimen by, for example, using once-weekly administration, might improve compliance. Better patient compliance is likely to be associated with enhanced control of Hb and concomitant improvements in the patient’s quality of life and long-term outcome.

Considerable interest is currently focused on the question of extending the dosing intervals of erythropoiesis-stimulating agents (ESAs) beyond the periods predicted solely by their serum half-lives. Whilst the current study extends the evidence for the efficacy of epoetin β in a broad range of applications, here administered fortnightly in a PD population, attempts to modify the dosages and applications of other ESAs have not always been as successful. A preliminary report from a study of 20 PD patients treated with darbepoetin α IV once every 4 weeks suggests that this schedule is safe, but that the need to increase the darbepoetin α dose could arise in certain patients [24]. Indeed, the mean dose required to maintain Hb levels equivalent to the patient’s previous SC epoetin dosing regimen was 33% higher after 6 months of darbepoetin α given once every 4 weeks [24]. Other studies of darbepoetin α, used once monthly SC in the less-challenging pre-dialysis setting, also raise concerns about the applicability of this dosing regimen [25]. Despite patients receiving a stable fortnightly dosing regimen before study entry, substantial dose changes were required to maintain Hb levels with the once-monthly regimen [25]. Therefore, the next generation of ESAs is awaited in order to extend the dosing interval in a broad population of patients.

In conclusion, the present trial is the first large-scale study to demonstrate that stable PD patients with renal anaemia are able to maintain Hb concentrations within a 10–12 g/dl range when switched from treatment with epoetin β twice or thrice weekly to once weekly and from weekly treatment to once-fortnightly. In the once-weekly cohort, target Hb levels could be maintained without significant increases in the mean epoetin β dose. Although there was a small increase in the mean dose during the evaluation period in the fortnightly cohort, ≥50% of those patients could be maintained with their baseline epoetin β doses or lower. The ability to administer epoetin β once weekly or fortnightly provides a greater opportunity to individualize treatment, and may encourage self-administration and adherence to treatment.

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