

## Once-weekly epoetin beta is highly effective in treating anaemic patients with lymphoproliferative malignancy and defective endogenous erythropoietin production

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**Summary.** Epoetin beta, three-times weekly (t.i.w.), is effective in reversing anaemia in lymphoproliferative disorders. The current study investigated whether an epoetin beta dose of 30 000 IU given subcutaneously once weekly (q.w.) was at least as effective as 10 000 t.i.w. administration in anaemic patients with lymphoproliferative malignancy and defective endogenous erythropoietin (Epo) production. Overall, 241 anaemic patients with multiple myeloma, low-grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, all with serum Epo values  $\leq 100$  mU/ml, were randomized to receive the q.w. ( $n = 119$ ) or t.i.w. ( $n = 122$ ) regimen for 16 weeks. The primary efficacy criterion, i.e. the time-adjusted area under the haemoglobin–time curve from weeks 5–16, was comparable between the q.w. and t.i.w. groups [differ-

ence =  $-0.20$  g/dl (90% confidence interval  $-0.52$ – $0.11$ )]. Moreover, response rates were high and similar in both arms (72% vs 75%, q.w. and t.i.w. groups respectively). Baseline serum Epo was predictive of response: the lower serum Epo, the higher the likelihood of response ( $P = 0.002$ ). Thus, epoetin beta administered q.w. is an effective and convenient treatment for anaemia in patients with lymphoproliferative disorders. Tailoring this treatment modality to subjects with defective endogenous Epo production represents a rational use of epoetin from both a medical and a community perspective.

**Keywords:** anaemia, erythropoietin, chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, multiple myeloma.

Recombinant human Epo (rHuEpo, or epoetin) is remarkably effective and well tolerated in the treatment of anaemic patients with defective production of the endogenous hormone. This is particularly true for uraemia, which represents the prototype of Epo deficiency, so that the treatment of this condition is currently considered the gold standard of epoetin use (Tong & Nissenson, 2001). Erythropoietin production, however, is reduced in several other conditions, which include anaemia secondary to malignant disorders or as a result of their treatment (Cazzola *et al*, 1997). Based on a systematic review of the literature, the recent guidelines of the American Society of Clinical Oncology and the American Society of Hematology

(Rizzo *et al*, 2002) recommend use of epoetin as a treatment option for patients with chemotherapy-associated anaemia with a haemoglobin concentration below 10 g/dl, and advise subcutaneous administration thrice weekly at a starting dose of 150 U/kg.

Three European trials in the last few years have studied the efficacy of epoetin beta in anaemic patients with multiple myeloma, non-Hodgkin's lymphoma and chronic lymphocytic leukaemia, most of whom were receiving concurrent or recent chemotherapy for their disease (Cazzola *et al*, 1995; Osterborg *et al*, 1996, 2002). Despite considerable differences in their designs, all three studies showed that defective endogenous Epo production was a major predictor of response to treatment. In particular, Osterborg *et al* (2002) demonstrated that epoetin beta treatment was effective in relieving anaemia and improving quality of life in severely anaemic, transfusion-dependent patients with a low serum Epo concentration. These

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observations have reinforced the concept that epoetin treatment is primarily effective in the treatment of endogenous Epo deficiency.

Although effective, the conventional regimen of thrice-weekly (t.i.w.) subcutaneous administration of epoetin is costly and cumbersome, and there is a need for improvement (Bunn, 2002). In stable haemodialysis patients, subcutaneous administration of epoetin beta once weekly (q.w.) has been shown to be as safe and effective in maintaining haemoglobin levels as a t.i.w. schedule (Weiss *et al.*, 2000; Locatelli *et al.*, 2002). As regards cancer patients, an uncontrolled, non-randomized, community-based study employing epoetin alpha at a dose of 40 000 IU q.w. has reported improvements in haemoglobin and quality of life similar to the conventional t.i.w. dosing ( $3 \times 10\,000$  IU) (Gabrilove *et al.*, 2001).

In order to properly assess the effectiveness of a once-weekly dosing regimen in the epoetin treatment of anaemic patients with lymphoproliferative malignancy, we conducted a prospective randomized trial comparing the efficacy and safety of subcutaneous epoetin beta 30 000 IU q.w. vs 10 000 IU t.i.w. in individuals with evidence of defective endogenous Epo production, as indicated by low serum Epo levels.

#### PATIENTS AND METHODS

The present study was an open-label, randomized, parallel-group, multicentre, phase III trial conducted between September 2000 and December 2001 at 51 centres in 12 countries, promoted and supported by F. Hoffmann–La Roche Ltd, Basel, Switzerland. The design and conduct of the study complied with the ethical principles of good clinical practice, in accordance with the Declaration of Helsinki and local legal requirements. The study was approved by an independent ethics committee at each centre; all patients provided written informed consent before enrolment.

**Patients.** Adult patients ( $\geq 18$  years) eligible for study inclusion had a histologically confirmed diagnosis of low-grade non-Hodgkin's lymphoma (NHL), multiple myeloma (MM) or chronic lymphocytic leukaemia (CLL), a Hb level of 9–11 g/dl and a serum Epo level  $\leq 100$  mU/ml. If systemic anticancer therapy was to be given, it was to continue for at least 4 months from the time of the first study treatment. Patients also had to have a World Health Organization (WHO) performance status grade of 0–2 and a life expectancy  $> 6$  months.

Exclusion criteria were: transfusion of red blood cells during the 2 months prior to the study, therapy-resistant hypertension, acute or chronic bleeding requiring treatment in the 3 months prior to study commencement, antitumour therapy in the week before the screening visit (with the exception of corticosteroids and/or low-dose chlorambucil), scheduled bone marrow transplantation during the study period, functional iron deficiency (transferrin saturation  $< 20\%$ ) which could not be treated with intravenous (i.v.) iron supplementation prior to the start of study treatment, thrombocytopenia or thrombocytosis (platelet count  $< 50$  or

$> 450 \times 10^9/l$  respectively), vitamin B<sub>12</sub> or folic acid deficiencies, haemolysis (haptoglobin  $< 0.30$  mg/l), epilepsy, pregnancy, or lactation.

**Study procedures.** Patients eligible for study inclusion were randomized 1:1 [stratified according to malignancy type, platelet count at screening ( $< 100 \times 10^9/l$ ,  $\geq 100 \times 10^9/l$ ) and study centre] to receive epoetin beta t.i.w. (10 000 IU per dose) or q.w. (30 000 IU per dose) for 16 weeks, using the RecoPen® (F. Hoffmann–La Roche, Basel, Switzerland) subcutaneous self-injection delivery system. For patients who failed to respond after 4 weeks of therapy (as indicated by receipt of a blood transfusion in the previous week or an increase in Hb of  $< 0.5$  g/dl vs baseline), the dose of epoetin beta was doubled. Thus, the dose per injection for the t.i.w. group increased to 20 000 IU and the dose for the q.w. group increased to 60 000 IU (administered as 30 000 IU twice weekly). Conversely, if Hb increased by more than 2 g/dl within the same period, the dose of study medication was reduced by 50%. If Hb exceeded 14 g/dl, the study medication was suspended until Hb declined to  $\leq 13$  g/dl when therapy was reinstated at 50% of the previous dose. Blood transfusions were to be avoided at Hb levels  $> 8.5$  g/dl unless medically indicated, e.g. when marked symptoms related to anaemia such as angina pectoris was present. Haemoglobin was measured at screening, during the first week of therapy and every 2 weeks thereafter.

Enrolled patients with a screening transferrin saturation of  $< 20\%$  were to receive i.v. iron supplementation to ensure that adequate iron was rapidly available for erythropoiesis. Following randomization, iron supplementation was also to be performed if the transferrin saturation fell below 20%. The preferred route of administration of supplemental iron was i.v.; however, if this was not possible, then oral iron supplementation was given. Adverse events, haematological parameters, concomitant medications, blood transfusions and antitumour therapy were documented throughout the course of the study.

**Efficacy assessments.** The primary efficacy variable was the time-adjusted Hb area under the curve between weeks 5 and 16 (Hb AUC<sub>5–16</sub>). The Hb AUC was determined by the trapezoid rule, and was then divided by the time interval from the first Hb measurement to the last Hb measurement between weeks 5 and 16. All available Hb values were taken into account, whether they were measured at a protocol-specified visit or determined immediately preceding a blood transfusion at non-protocol-specified visits. The Hb values measured in the 3 weeks following a blood transfusion were replaced by the Hb value measured immediately before the blood transfusion to correct for the increased Hb caused by the blood transfusion.

Secondary efficacy parameters included response rate (defined as an increase in Hb of  $\geq 2$  g/dl vs baseline without blood transfusion in the previous 6 weeks), change in Hb from baseline, Hb nadir at 4-week intervals, the percentage of patients with corrected anaemia (Hb nadir  $\geq 11$  or 12 g/dl) at 4-week intervals, transfusion-free or severe anaemia-free (Hb  $< 8.5$  g/dl) survival, and transfusion requirements (number of patients and units transfused). Various clinical

parameters were measured with the aim of identifying those predictive of response to epoetin beta. These parameters could be divided into those measured at baseline (serum Epo) and those measured early in the course of treatment [changes in Hb levels and in soluble transferrin receptor (sTfR) levels].

**Laboratory measurements.** Blood counts were obtained with the use of automated counters. Circulating Epo levels were measured by a photometric enzyme immunoassay for the quantitative in-vitro determination of human erythropoietin in antibody-precoated microtitre plates (Roche Diagnostics, Mannheim, Germany). The amount of sTfR was estimated by an immunoturbidimetric assay using an automated clinical chemistry analyser (Roche Diagnostics). In order to detect Epo-specific antibodies in serum, the above photometric enzyme immunoassay for the quantitative in-vitro determination of human Epo was employed, adopting a two-step procedure with a displacement step.

**Statistical analysis.** We planned to enrol 230 patients with low-grade NHL, MM or CLL that, with an assumed loss-to-follow-up rate of ~20%, would provide 93 patients per treatment arm. This would be sufficient to demonstrate with 80% power ( $\alpha = 0.05$ ) that epoetin beta administered q.w. is non-inferior to the t.i.w. regimen with respect to the primary efficacy variable.

The primary efficacy variable was analysed for the intent-to-treat (ITT) population and the per protocol (PP) population (Table I) was analysed using an analysis of covariance (ANCOVA) model; 'treatment group' was the main factor, with 'underlying malignant disease' and 'baseline Hb values' as covariates. Based on the least squares means and the corresponding standard errors of the ANCOVA model, 90% and 95% confidence intervals were calculated for the difference in Hb-AUCs between the two treatment groups at a significance level of 5%.

The time to first response was analysed using the log-rank test, adjusted for underlying malignant disease. The response curves were estimated using Kaplan-Meier techniques. Transfusion-free or severe anaemia-free survival was analysed using a Cox proportional hazard model,

adjusted for the type of underlying malignant disease at a significance level of 5% (Wald  $\chi^2$  test). The rate of failure was defined as the first date with Hb < 8.5 g/dl, a blood transfusion or death. Kaplan-Meier methods were used to estimate the transfusion-free or severe anaemia-free survival curves. Transfusion requirements were compared between treatment groups with the Cochrane-Maentel-Haenzel test, unadjusted and adjusted for underlying malignant disease.

The change from baseline to final Hb value and the Hb nadir in any 4-week interval was analysed separately using ANCOVA models with the main factor 'treatment group', and 'underlying malignant disease' and 'baseline Hb value' as covariates. The influence of various clinical parameters on response was analysed using Cox's proportional hazard models.

## RESULTS

Of a total of 322 patients screened for serum Epo, 241 were found to have levels  $\leq 100$  mU/ml (Table I): these subjects were enrolled into the study and randomized to the two treatment groups (q.w.,  $n = 119$ ; t.i.w.,  $n = 122$ ). There were no major differences in the demographic and baseline clinical characteristics of the two treatment groups (Table II). Multiple myeloma was the predominant tumour type in both groups (~70%). The vast majority of patients were receiving concurrent chemotherapy or had received recent chemotherapy for their disease: only 6/237 (2.5%) subjects did not receive chemotherapy before or during the study. In total, 22 patients (9%) were withdrawn from the study (q.w.,  $n = 14$ ; t.i.w.,  $n = 8$ ). The main reasons for withdrawal were death ( $n = 12$ ), adverse events ( $n = 4$ ) and refusal of treatment ( $n = 4$ ).

### Increase in haemoglobin over time

Mean baseline Hb values at the start of study treatment were similar for both groups (Table II). The change in Hb level over time is depicted in Fig 1. Following 8 weeks of treatment, median changes in Hb were > 2 g/dl in both

**Table I.** Patient distribution into the study populations.

Study population	Serum	Serum	
	Epo > 100 mU/ml, <i>n</i>	Epo $\leq$ 100 mU/ml, <i>n</i>	
Screened for serum Epo ( <i>n</i> = 322)	81	241	
		Once-weekly (q.w.), <i>n</i>	Thrice-weekly (t.i.w.), <i>n</i>
Randomized ( <i>n</i> = 241)	–	119	122
Safety ( <i>n</i> = 237)*	–	118	119
Intent to treat ( <i>n</i> = 229)†	–	115	114
Per protocol ( <i>n</i> = 205)‡	–	101	104

\*Four patients were excluded from the safety population (q.w.,  $n = 1$ ; t.i.w.,  $n = 3$ ) as they did not receive epoetin beta.

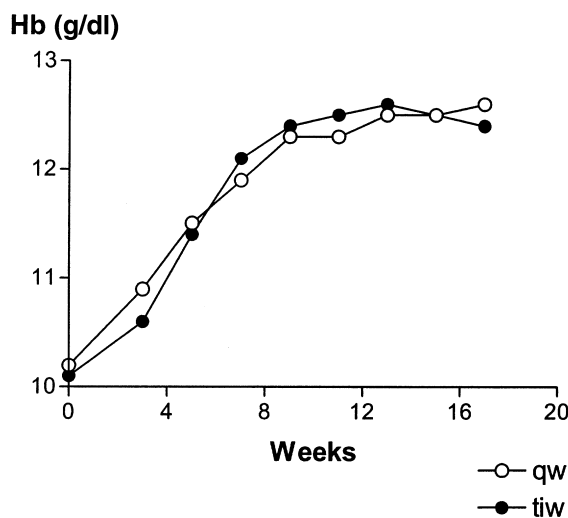
†Eight patients were excluded from the intent-to-treat population (q.w.,  $n = 3$ ; t.i.w.,  $n = 5$ ) as they had only one Hb level measured between weeks 5 and 16.

‡Twenty-four patients were excluded from the per protocol population for violations of the study criteria (q.w.,  $n = 14$ ; t.i.w.,  $n = 10$ ).

**Table II.** Patient demographics and baseline characteristics (safety population).

	Once weekly (n = 118)	Three-times weekly (n = 119)
Sex, n (%)		
Male	55 (47)	47 (39)
Female	63 (53)	72 (61)
Age, years; median (range)	67 (38–82)	65 (33–90)
Body weight, kg, mean $\pm$ SD	68.6 $\pm$ 12.3	66.9 $\pm$ 13.8
Tumour classification		
MM	78 (66)	80 (67)
NHL	16 (14)	16 (14)
CLL	24 (20)	23 (19)
Haemoglobin (g/dl), mean $\pm$ SD	10.2 $\pm$ 1.0	10.1 $\pm$ 1.0
Serum Epo (mU/ml); median (range)	41 (5–97)	41 (6–97)
Serum ferritin ( $\mu$ g/l); median (range)	245 (12–1342)	223 (1–1820)
No chemotherapy prior to epoetin beta therapy	39/118 (33)	38/119 (32)
No chemotherapy concurrent with epoetin beta therapy	13/118 (11)	19/119 (16)
No chemotherapy at all	2/118 (2)	4/119 (3)

CLL, chronic lymphocytic leukaemia; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.



**Fig 1.** Time course of mean haemoglobin (Hb) level in anaemic patients with lymphoproliferative malignancies treated with epoetin beta 30 000 IU q.w. (n = 101) or 10 000 IU t.i.w. (n = 104) (PP population).

treatment groups; the difference between the groups was  $\sim$ 0.2 g/dl at any time point.

The time-adjusted Hb AUC<sub>5–16</sub> was calculated for each patient in both treatment groups from the PP population. The median Hb-AUC<sub>5–16</sub> was similar in both groups (differences  $\sim$ 0.2–0.3 g/dl). ANCOVA confirmed that the median estimates of Hb-AUC<sub>5–16</sub> were similar between the q.w. and t.i.w. groups (12.05 vs 12.27 g/dl) with the overall difference being 0.22 [–0.53, 0.10, 90% confidence interval (CI)]. Differences between the t.i.w. and q.w. groups did not exceed 0.6 g/dl at any time. These data were confirmed when the analysis was performed on the

ITT population. The differences in the Hb-AUC<sub>5–16</sub> between the two treatment groups were similar across the three types of lymphoproliferative malignancies investigated (Table III).

#### Response rate and time to response

The proportion of patients who responded to treatment was similar in both groups (72 vs 75% for q.w. vs t.i.w. dosing, ITT population). Median time to response was 71 d for the q.w. group and 57 d for the t.i.w. group ( $P = 0.57$ ).

#### Haemoglobin nadirs and correction of anaemia

Mean Hb nadir values were determined over 4-week intervals and are presented in Fig 2 (ITT population). Values were similar for both groups throughout the study period. Confidence intervals (90%) were largely within the range of –0.5 to +0.5, ruling out the possibility of a significant difference between treatment groups.

Correction of anaemia (defined as a Hb nadir  $\geq$  11 or  $\geq$  12 g/dl in a 4-week interval) was achieved in 79% and 81% of patients (Hb  $\geq$  11 g/dl) and 60% and 64% of patients (Hb  $\geq$  12 g/dl) in the q.w. and t.i.w. groups respectively (ITT population).

#### Blood transfusions

Mean Hb values before blood transfusion were the same for both groups (7.4 g/dl), and the overall incidence of transfusion in the study was low (11% of patients). The percentage of patients receiving at least one transfusion was marginally lower in the q.w. group (9%) compared with the t.i.w. group (14%) but this difference was not significant (Cochrane–Maentel–Haenzel test,  $P = 0.14$  adjusted for underlying disease).

Analysis of transfusion-free or severe anaemia-free survival confirmed that the number of patients requiring transfusions was low and that the rates were similar

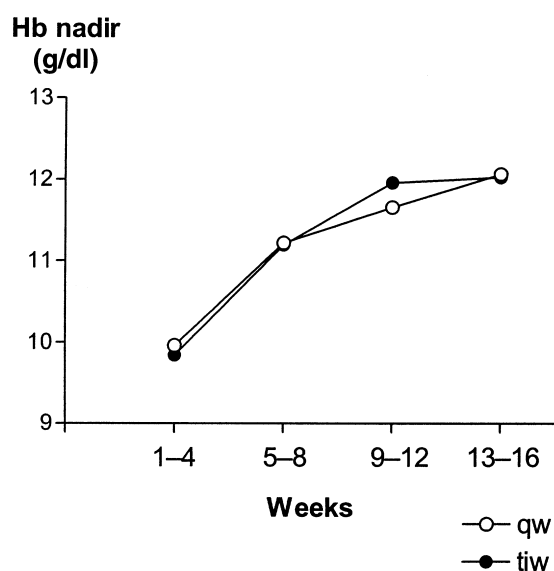
**Table III.** Change in the area under the haemoglobin–time curve between weeks 5 and 16 (Hb-AUC<sub>5–16</sub>) in anaemic patients with lymphoproliferative malignancies treated with epoetin beta 30 000 IU q.w. or 10 000 IU t.i.w. (per protocol population).

	Mean Hb-AUC (g/dl)		
	30 000 IU q.w.	10 000 IU t.i.w.	Difference (90% CI)
Total population*	12.05	12.27	-0.22 (-0.53, 0.10)
Multiple myeloma†	12.11	12.25	-0.14 (-0.49, 0.21)
Non-Hodgkin's lymphoma†	11.51	12.13	-0.62 (-1.81, 0.56)
Chronic lymphocytic leukaemia†	12.32	12.54	-0.21 (-1.03, 0.61)

\*Per protocol (PP) population.

†Intent-to-treat (ITT) population.

CI, confidence interval.



**Fig 2.** Mean haemoglobin (Hb) nadir at 4-weekly intervals in anaemic patients with lymphoproliferative malignancies treated with epoetin beta 30 000 IU q.w. ( $n = 115$ ) or 10 000 IU t.i.w. ( $n = 114$ ) (ITT population).

between the two groups (Cox regression analysis adjusted for underlying malignant disease,  $P = 0.50$ ).

#### *Epoetin beta doses, iron supplementation and safety*

The mean weekly epoetin beta dose between weeks 5 and 16 was 323 IU/kg in the once-weekly group and 267 IU/kg in the thrice-weekly group (ITT). Therefore, the once-weekly to thrice-weekly dose ratio during this period was 1.21 (95% CI 0.90; 1.61). The observed difference could be attributed to the small CLL subgroup (24 vs 24 patients, ratio 2.29), while no difference was observed in the majority of patients with multiple myeloma or NHL (95 vs 98 patients, ratio 1.02). The difference observed in the small CLL subgroup was determined by the fact that a few patients receiving epoetin beta thrice weekly achieved a response quickly, which was maintained with low doses of the drug.

Overall, there was a decrease in the median and mean weekly dose per kg in both treatment groups by week 8 to the end of the study in both the PP and the ITT population.

Similar proportions of patients needed i.v. (44% vs 39%) and oral (75% vs 67%) iron supplementation in the q.w. and the t.i.w. group respectively.

Treatment with epoetin beta was well tolerated. Eighty-four patients (71%) in each treatment group reported at least one adverse event. Only 12 patients (10%) in the q.w. and 22 patients (18%) in the t.i.w. group were considered to have treatment-related adverse events. The most common adverse events for the q.w. and t.i.w. groups were infections (37% vs 38%), gastrointestinal disorders (31% vs 31%), general disorders (16% vs 18%) and vascular disorders (15% vs 18%).

Evaluation of anti-Epo antibodies was planned at baseline and during week 17 of study. All of the 118 patients in the once-weekly group and 119 in the thrice-weekly group that were analysed were negative for anti-epoetin beta antibodies.

#### *Predictors and early indicators of response to epoetin beta*

Both baseline clinical parameters and changes in clinical parameters early in the study period were assessed for predictive power of response to epoetin beta. At baseline, serum Epo level ( $P = 0.002$ ) was found to be predictive of response (Table IV). Changes in Hb between weeks 1 and 3 ( $P < 0.00001$ ), and changes from baseline in sTfR levels in weeks 2 and 3 ( $P < 0.01$ ) were found to be early indicators of response.

## DISCUSSION

This study is the first to investigate the relative efficacy and safety of q.w. and t.i.w. epoetin regimens in a powered comparison. Its results demonstrate that epoetin beta given once weekly is as effective and well tolerated as a three-times-weekly schedule in treating anaemic patients with lymphoproliferative disorders and reduced endogenous Epo production.

The current study was designed to test the hypothesis that epoetin beta given once weekly was not inferior to the

**Table IV.** Baseline predictors and early treatment indicators of response to epoetin beta.

	Hazard ratio (95% CI)	P-value
Baseline		
Haemoglobin, g/dl	0.884 (0.756–1.035)	0.125
Serum creatinine, mmol/l	1.000 (0.996–1.003)	0.881
Serum Epo (mU/ml)	0.989 (0.982–0.996)	0.002
Early treatment		
Hb increase from week 1–3 (0.1 g/dl)	1.053 (1.038–1.069)	<0.00001
sTfR level increase from baseline		
> 15% vs ≤ 15%	1.604 (1.137–2.265)	0.007
> 20% vs ≤ 20%	1.635 (1.178–2.270)	0.003
> 25% vs ≤ 25%	1.695 (1.238–2.322)	0.001

sTfR, soluble transferrin receptor.

three-times weekly schedule with respect to several important clinical parameters. The primary efficacy parameter of the study was the time-adjusted area under the Hb–time curve (Hb AUC<sub>5–16</sub>). The q.w. regimen was clinically comparable to the t.i.w. regimen, as the two curves were virtually identical. Furthermore, the difference in Hb AUC<sub>5–16</sub> between the two groups did not exceed 0.6 g/dl at any time during the study. The remaining clinical parameters examined in this study (Hb nadirs, response rates and transfusion requirements) confirmed these data. In the assessment of equivalence in mean weekly epoetin doses, a difference of 21% (once-weekly to thrice-weekly dose ratio equal to 1.21) was recorded between the two treatment groups between weeks 5 and 16. This ratio remained within the prespecified equivalence range. Moreover, the observed difference could be attributed to a small portion of patients with CLL who responded quickly to epoetin beta administered thrice weekly. No difference at all (i.e. 2%) was observed in the vast majority of patients ( $n = 193$ ) with multiple myeloma or NHL.

A previous study has examined the effect of a once-weekly epoetin regimen on Hb levels, transfusion requirements and quality of life in patients with solid and haematological malignancies (Gabrilove *et al*, 2001). This study showed that a dose of 40 000 IU once weekly provided improvements in haemoglobin and quality of life similar to the conventional thrice weekly dosing ( $3 \times 10\,000$  IU). However, this study had many potential flaws (Nguyen & Trinh 2002): (a) it was non-randomized and compared the once-weekly results with those of historical, rather than parallel, control subjects receiving epoetin t.i.w.; (b) there was no adjustment for potential baseline confounding variables and for handling of the relatively large dropout rate; (c) different weekly doses of epoetin alpha (40 000 in q.w. group vs 30 000 in t.i.w. group) were compared. In contrast, the current study was randomized, and directly compared results between patients receiving identical doses of epoetin beta (30 000 IU) q.w. or t.i.w., thus producing a more robust assessment. The results are consistent with those of recent randomized trials of epoetin beta in the maintenance treatment of renal anaemia, which demonstrated that the efficacies of once

weekly and three times weekly epoetin beta regimens are equivalent (Weiss *et al*, 2000; Locatelli *et al*, 2002).

The efficacy of the once-weekly regimen is in agreement with the physiological role of Epo in erythropoiesis. In fact, Epo mainly acts as a survival factor for erythroid progenitors, which require the continual presence of small doses of the hormone to survive (Koury & Bondurant, 1990a; Kelley *et al*, 1993). In this model of erythropoiesis based on Epo prevention of programmed cell death, erythropoiesis can be substantially and steadily expanded only through preamplification of Epo-dependent progenitors (Koury & Bondurant, 1990b). When endogenous Epo levels are inappropriately low, administration of epoetin can be effective in allowing the survival of more erythroid progenitors and the generation of erythroid precursors that subsequently mature to red cells. The results of the present study indicate that this can be effectively achieved with the once-weekly subcutaneous administration of epoetin beta.

Despite the success of epoetin in treating anaemia in both the haemodialysis and cancer settings, outside the setting of uraemia, a variable portion of patients do not respond to epoetin therapy (Cazzola *et al*, 1997). Attempts have been made to identify those patients most likely to respond to therapy. In this study, the number of patients who responded to epoetin beta treatment was high in both arms (~75%). This is probably attributable to the strict inclusion criteria of the trial, whereby only patients with defective endogenous Epo production, as indicated by serum Epo levels  $\leq 100$  mU/ml, were enrolled. In clinical practice, a serum Epo level  $< 100$  mU/ml in an anaemic patient can be taken as an indicator of reduced serum Epo production and a strong predictor of response to epoetin treatment (Beguin, 2002). It must be stressed that, even in this selected population of patients with low serum Epo, this latter parameter was found to be a strong predictor of response (Table IV). This also indicates that, in patients with defective endogenous Epo production, the lower the serum Epo, the higher the likelihood of response.

Tailoring epoetin use to patients with a high probability of response, i.e. improving the prediction of response, is one of the major ways of making epoetin treatment cost-effective (Barosi & Marchetti, 2000). Therefore, in patients

with lymphoproliferative disorders, limiting epoetin administration to those who show defective endogenous Epo production represents a rational use of the recombinant hormone from both a medical (Pangalis *et al*, 2002) and community perspective (Barosi & Marchetti, 2000). In this study, for instance, about 25% of patients initially screened for serum Epo had values > 100 mU/ml (Table I) and were excluded from treatment. A small portion of patients, however, in spite of their low serum Epo levels (< 100 mU/ml), did not respond to epoetin beta: further characterization of predictors of non-response is required as this might further improve the cost effectiveness of epoetin therapy.

Incidences of adverse events during the study were similar for both regimens, and the incidence of those that could be directly related to epoetin beta was very low. More importantly, no patient enrolled in the study developed anti-Epo antibodies. It has recently been noted that some dialysis patients treated with epoetin have developed pure red cell aplasia through the production of neutralizing anti-Epo antibodies (Casadevall *et al*, 2002). This complication appears to be linked to a particular epoetin formulation (Gershon *et al*, 2002), and whether it can also occur outside nephrology is unclear at present. A close laboratory monitoring of patients receiving epoetin therapy is, therefore, recommended (Cavill & Williams, 2002).

In conclusion, epoetin beta given q.w. is comparable to the established t.i.w. regimen and, therefore, represents an effective and safe treatment for anaemia in patients with lymphoproliferative malignancy and defective endogenous Epo production. Self-administration at home of the same quantity of epoetin beta in a single weekly injection with no loss of efficacy will undoubtedly help to produce substantial cost savings (Besarab *et al*, 2002). Using this method of administration and tailoring treatment to subjects with defective endogenous Epo production represents a rational use of epoetin from a medical and a community perspective.

#### ACKNOWLEDGMENT

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#### APPENDIX

In addition to the authors of the present paper, the following investigators participated in the NeoRecormon<sup>®</sup> Once-Weekly (NOW) study: Johannes Ach (Wien), Photis Beris (Geneve), Réda Bouabdallah (Marseille), Dominique Bron (Brussels), Po-Min Chen (Taipei), Chang-Fang Chiu (Tai-chung), Guenther Derigs (Mainz), Anna Dmoszynska (Lublin), Houchingue Eghbali (Bordeaux), Gerlinde Egerer

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