An observational cohort study of extended dosing (once every 2 weeks or once monthly) regimens with darbepoetin alfa in patients with chronic kidney disease not on dialysis: the EXTEND study

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Abstract

Background. Darbepoetin alfa (DA) has been shown to be an effective treatment of anaemia in patients with chronic kidney disease (CKD) not on dialysis (NoD). EXTEND is an observational study assessing the effectiveness of DA administered once biweekly (Q2W) or monthly (QM) in a general CKD-NoD population.

Methods. Adult CKD-NoD patients starting DA Q2W/QM treatment in June 2006 or later were eligible. Retrospective and/or prospective data including haemoglobin levels and erythropoiesis-stimulating agent (ESA) dosing were collected for 6 months before and 12 months after DA initiation. Mean Hb levels were calculated every 3 months, and ESA dose was converted to a geometric mean weekly DA equivalent dose and summarized monthly.

Results. Data from 4278 patients showed that patients receiving ESA treatment before DA Q2W/QM initiation had a mean (95% confidence interval) Hb level of 11.9 g/dL (11.8–12.0 g/dL) at initiation and 11.6 g/dL (11.6–11.7 g/dL) at Months 10–12, with mean ESA dose of 22 μg/week (21–23 μg/week) prior to initiation, 16 μg/week (15–16 μg/week) at initiation and 16 μg/week (15–16 μg/week) at Month 12. In ESA-naive patients, Hb levels increased from 10.3 g/dL (10.2–10.3 g/dL) at initiation to 11.7 g/dL at Months 4–6 and were maintained at a mean level of 11.7 g/dL (11.7–11.8 g/dL) at Months 10–12, with mean ESA dose of 16 μg/week (16–17 μg/week) at initiation and 16 μg/week (16–17 μg/week) at Month 12. In the 85% of patients receiving DA at extended intervals (Q2W or less frequently) at Month 12, 12 patients (0.3%) experienced DA-related adverse reactions.

Conclusion. DA Q2W/QM was an effective treatment of anaemia in the general CKD-NoD patient population and a dose increase was not required in patients switching from a previous ESA regimen.

Keywords: anaemia; chronic kidney disease; darbepoetin alfa; erythropoiesis-stimulating agent

Introduction

Erythropoiesis-stimulating agents (ESAs) improve and maintain haemoglobin (Hb) levels in patients with anaemia and chronic kidney disease (CKD) not on dialysis (NoD) and reduce the need for red blood cell (RBC) transfusions [1]. Recently, anaemia management strategies have explored extended dosing intervals with ESAs [2–5], possibly allowing for more flexible dosing, improving convenience for patients and physicians and reducing waste (e.g. syringes) [6–8].

Studies in CKD-NoD patients have demonstrated the efficacy and safety of darbepoetin alfa (DA) administered once biweekly (Q2W) or once monthly (QM) to partially correct and/or maintain Hb levels [2–5, 9, 10]. However, few studies have assessed the effectiveness of extended dosing strategies in routine practice. Interpretation of results from trials in CKD-NoD patients is limited by patient selection, whereas the general CKD-NoD population is a spectrum of patients that differ by disease state and includes many with significant comorbidities [11–13]. Furthermore, renal anaemia management guidelines and ESA labels have been changed over the last few years since randomized controlled studies demonstrated no clinical benefit and even showed increased risk for some clinical outcomes when treating CKD-NoD patients with ESAs to high Hb targets (e.g. 13.5 g/dL) [14–19]. In Europe, the recommended Hb target in ESA labels was decreased from >11 g/dL (upper limit ≤14 g/dL) to a range of 10–12 g/dL in 2008.

More data are needed to better characterize the CKD-NoD population receiving ESA therapy. We describe the interim analysis of EXTEND, an ongoing observational study of CKD-NoD patients receiving DA subcutaneously (SC) at extended dosing intervals (Q2W or QM) to treat anaemia, with a primary objective of assessing the effectiveness of DA Q2W/QM. The original protocol which required follow-up of patients for up to 12 months after DA initiation was amended to allow the follow-up of patients for a longer period through disease progression, including the need for dialysis.

Materials and methods

Study design and patients

EXTEND is a multicentre, longitudinal observational cohort study. Patients ≥18 years of age, NoD, with an estimated glomerular filtration rate (eGFR) of ≤59 mL/min/1.73m^2 (CKD Stages 3–5) were eligible if treatment with DA Q2W/QM SC was initiated on June 2006 or later. Patients were enrolled in Europe and Australia and treated according to local standard medical practice. Use of other ESA regimens (DA at other dosing frequencies or other ESA types) prior to initiation of DA Q2W/QM was allowed, but patients enrolled in an interventional study 6 months before or at any time after initiation were ineligible. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Hb levels, ESA type, dose, frequency and route, relevant medical history, medications and laboratory measures were collected retrospectively for up to 6 months prior to DA Q2W/QM initiation and retrospectively or prospectively for up to 12 months after. Data on hospitalizations, DA-related adverse drug reactions (ADRs) (as identified by the treating physician) and referral information were also collected. Primary end points were

achievement of Hb level >11 g/dL and absolute Hb level 12 months post-initiation. The secondary end points were Hb concentrations over time, anaemia practice patterns, patient characteristics and patient safety.

Statistical analysis

A sample size of 3500–4000 patients was estimated to ensure that the primary end points could be calculated with sufficient precision for subgroups of interest that represent the heterogeneity of the CKD-NoD population. Assuming an Hb SD of 1.4 g/dL, the 95% confidence interval (CI) widths for a subgroup that represented 5% of a study population of 3500 patients were estimated to be 14.8% for the proportion of patients with Hb >11 and 0.41 g/dL for mean Hb level. For a study population of 4000 patients, the corresponding 95% CI widths were estimated to be 13.8% and 0.39 g/dL, respectively.

Analyses are descriptive and, unless otherwise stated, were carried out using the full analysis set (FAS) as observed and consisted of patients who received at least one dose of DA Q2W/QM with no imputation for missing data. For this interim analysis, the FAS as observed was restricted to patients who had 12 months of data available or who withdrew from the study and for whom all critical data queries relating to Hb and dose were resolved at the time of analysis. Overall cohort data are presented and subgroups stratified by prior ESA history—prior use of an ESA or non-use (ESA naive) within 6 months of initiating DA Q2W/QM. Mean Hb levels were calculated for 3-month intervals. ESA dose was calculated for 1-month intervals and normalized to a geometric mean (log transformation) weekly equivalent due to the impact of non-normal data distribution on the arithmetic mean. Epoetin alfa/beta doses were converted from IU to μg using the conversion factor 200 IU:1 μg per the DA label. To explore the sensitivity of the primary analysis of the primary end points to missing data, a predefined sensitivity analysis of primary end points also used the FAS with the last observation carried forward (LOCF), in which missing Hb data in a 3-month window were replaced with the previously available 3-month Hb values (with no imputation from pre-initiation to post-initiation).

The study sponsor conducted all statistical analyses with SAS/STAT software (version 8.2; SAS Institute Inc., Carey, NC). Authors had access to all clinical data outputs and were fully involved in formulating the analyses and questions of interest.

Results

The FAS comprised 4278 patients enrolled at 342 centres in 18 European countries and Australia. Due to outstanding critical data queries relating to Hb and ESA dose, 148 patients were not included in the analysis. Extended dosing with DA was initiated at Q2W for 3749 patients (88%) and at QM for 527 (12%) patients; dose frequency data were missing for 2 patients. Twelve months of data were available for 2836 patients (66%), ≥9 to <12 months of data were available for 1151 patients (27%) and <9 months of data were available for 291 patients (7%). Reasons for dropout were patient no longer treated at clinic, consent withdrawal, kidney transplant, death and other reasons not categorized. Protocol violations included initiation of DA Q2W before June 2006 (36 patients), initiation of DA at Q2W or less frequently prior to the recorded initiation date (95 patients) and Stage 1 or 2 CKD (30 patients).

Table 1 summarizes patient characteristics at initiation of extended dosing. The mean (±SD) patient age was 67.4 (±15.0) years. Most patients (51%) enrolled were in Stage 4 CKD, and 19% of patients enrolled were in Stage 5 CKD. Common CKD aetiologies were diabetes mellitus (25%) and hypertension (24%). The prevalence of type 2 diabetes mellitus was 32% and cardiovascular disease was 58%. ESAs were used previously by 48.7% of patients, while 51.3% were ESA naive. Patients in both subgroups had similar characteristics.

Haemoglobin levels and ESA dose

ESA dose data for the two subgroups are presented in Figure 1. In the prior ESA subgroup, mean Hb increased before initiation and continued to increase immediately after initiation, then decreased and stabilized at around the 7- to 9-month interval. The proportion of patients with Hb levels >11 g/dL was 1288/1802 (71%) at initiation and 1307/1865 (70%) for Months 10–12. Increasing Hb levels corresponded to a reduction in the geometric mean weekly ESA dose at initiation compared with pre-initiation dosing with no dose penalty in the post-initiation period.

In the ESA-naive subgroup, the mean Hb level decreased before initiation, increased after initiation, then stabilized around the 7- to 9-month period. The post-initiation Hb level increase resulted in an increase in the proportion of patients with Hb levels >11 g/dL from 342/1842 (19%) at initiation to 1359/1885 (72%) for Months 10–12. After initiation, the geometric mean weekly ESA dose was stable.

In the FAS population, the mean Hb for Months 10–12 was 11.67 g/dL (95% CI, 11.63–11.71 g/dL) with a geometric mean weekly dose of 15.9 μg (95% CI, 15.5–16.3

μg). Haemoglobin levels were >11 g/dL in 2666/3750 (71%) of patients for Months 10–12. Haemoglobin data from the FAS-LOCF sensitivity analysis were comparable to the primary analysis with no imputation with a mean Hb level of 11.64 g/dL (95% CI, 11.60–11.68 g/dL) for Months 10–12 with 2945/4221 (70%) of patients having Hb levels >11 g/dL. Overall, 93% of patients remained in the study beyond 9 months and 11% of data were imputed in the LOCF analysis.

Results were generally consistent across countries, although differences were observed for mean Hb levels at initiation and geometric mean weekly ESA dose. The analysis by country was limited by small sample sizes.

Anaemia treatment patterns

Before initiation of DA Q2W/QM, most patients (70%) in the prior ESA subgroup had been receiving DA QW, 8% had been receiving DA at other dosing intervals and 18 and 3% had been receiving epoetin beta and alfa, respectively. After initiation, some patients required modification to the ESA dosing regimen (Table 2). For Months 7–12, 43% of

Table 1. Patient characteristics at initiation of DA Q2W/QM[a,b]

	Overall (N = 4278)	Prior ESA (n = 2085)	ESA naive (n = 2193)
Age, mean (±SD), years	67.4 (±15.0)	66.6 (±15.2)	68.2 (±14.8)
Sex			
Female	2066 (48)	1018 (49)	1048 (48)
Male	2208 (52)	1066 (51)	1142 (52)
Unknown	4 (<1)	1 (<1)	3 (<1)
Race/ethnicity			
White	3221 (75)	1586 (76)	1635 (75)
Black	16 (<1)	9 (<1)	7 (<1)
Asian	46 (1)	23 (1)	23 (1)
Other	28 (1)	18 (1)	10 (<1)
Unknown	967 (23)	449 (22)	518 (24)
CKD stage			
Stage 1[c]	2 (<1)	1 (<1)	1 (<1)
Stage 2[c]	28 (1)	13 (1)	15 (1)
Stage 3	1082 (25)	530 (25)	552 (25)
Stage 4	2203 (51)	1056 (51)	1147 (52)
Stage 5	819 (19)	423 (20)	396 (18)
Missing	144 (3)	62 (3)	82 (4)
Primary aetiology of CKD			
Hypertension	1023 (24)	450 (22)	573 (26)
Glomerulonephritis	561 (13)	309 (15)	252 (11)
Diabetes mellitus	1055 (25)	502 (24)	553 (25)
Interstitial nephropathy/obstructive nephropathy	397 (9)	211 (10)	186 (8)
Tumours	41 (1)	20 (1)	21 (1)
Polycystic kidney/hereditary disease	217 (5)	105 (5)	112 (5)
Unknown aetiology	461 (11)	235 (11)	226 (10)
Other	523 (12)	253 (12)	270 (12)
Prior history of diabetes			
Type I	209 (5)	101 (5)	108 (5)
Type II	1385 (32)	672 (32)	713 (33)
Unknown type	27 (1)	10 (<1)	17 (1)
No history	2600 (61)	1277 (61)	1323 (60)
Unknown	57 (1)	25 (1)	32 (1)
Prior history of cardiovascular disease			
Yes	2477 (58)	1158 (56)	1319 (60)
No	1683 (39)	869 (42)	814 (37)
Unknown	118 (3)	58 (3)	60 (3)
Haemoglobin, mean (±SD), g/dL	11.08 (1.57)	11.90 (1.57)	10.29 (1.10)

[a]Q2W, once every 2 weeks; QM, once monthly.
[b]Number of patients (%) unless noted otherwise.
[c]Protocol violations.

A

B
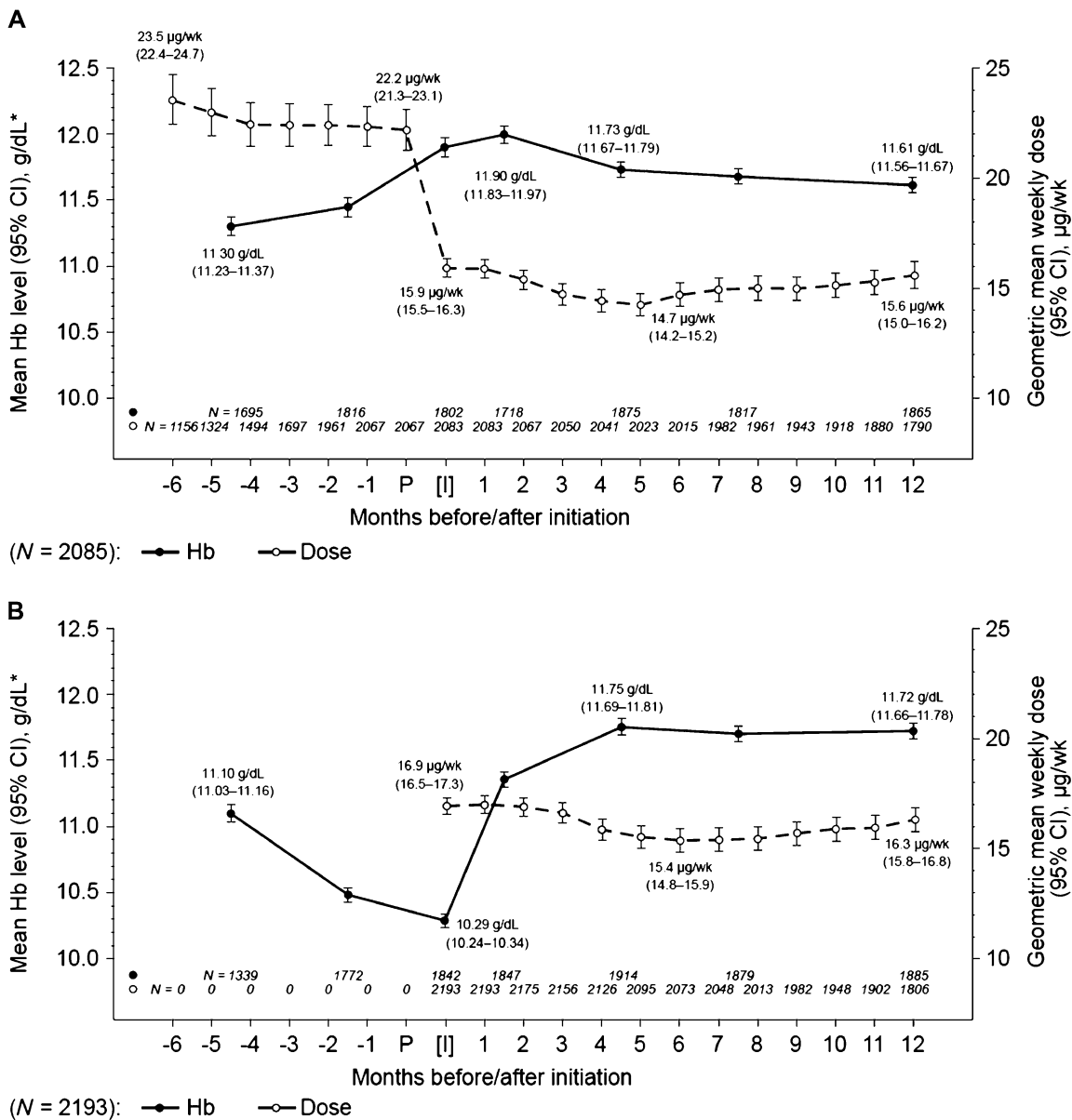
Fig. 1. Haemoglobin and ESA dose. Mean haemoglobin and geometric mean weekly equivalent ESA dose before and after initiation of DA Q2W/QM in the (A) prior ESA subgroup and (B) ESA-naive subgroup. Error bars represent the 95% CI. [I], initiation of DA Q2W/QM; P, immediately prior to initiation. *Hb level defined as single closest value ±45-day analysis time window except at initiation (–8-week analysis time window) and Months 10–12 (–90 to +20 day time window); no imputation for missing data.

patients in the prior ESA subgroup required 1–2 dose changes, 28% required 1–2 dose frequency changes, while 52% required no modifications. Similar dose modification requirements were observed in the ESA-naive subgroup during the post-initiation period. Dosing data at 12 months from 3595 patients showed the following DA frequencies: 51% Q2W, 28% QM, 11% QW, 5% once tri-weekly and 2% at other frequencies. About 3% had switched to other ESA types. Route of administration was SC for 95% of patients and intravenously for 5%.

Within the prior ESA subgroup, iron use ranged from 42 to 46% of patients throughout the study (Figure 2), whereas iron use in the ESA-naive subgroup increased from pre-initiation (range, 21–30%) to post-initiation (range, 44–45%). Trans-

ferrin saturation and serum ferritin levels, from a limited number of patients, remained satisfactory in both subgroups; although decreases were observed for the 3-month average before initiation in the prior-ESA subgroup with mean levels of 21.7% and 199 µg/L, respectively, and for the 3-month average after initiation in the ESA-naive subgroup with mean levels of 21.8% and 194 µg/L, respectively.

RBC transfusions were infrequent in both subgroups (Figure 3). In the prior ESA subgroup, the tri-monthly transfusion rate ranged from 2 to 4%. There was an increase in RBC transfusions pre-initiation in the ESA-naive subgroup, from 3% (Months −6 to −4) to 6% (Month −3 to initiation). Post-initiation, the tri-monthly transfusion rate ranged from 1 to 3%.

Table 2. Post-initiation dose and dose frequency changes after initiation of DA Q2W/QM[a]

	Prior ESA		ESA naive	
	1–6 months ($n = 2085$)	7–12 months ($n = 1983$)	1–6 months ($n = 2193$)	7–12 months ($n = 2048$)
Injection dose or frequency changes, n (%)				
No changes	1066 (51)	1032 (52)	1055 (48)	1069 (52)
1–2 changes	900 (43)	865 (44)	1041 (47)	868 (42)
≥3 changes	119 (6)	86 (4)	97 (4)	111 (5)
Injection dose changes, n (%)				
No changes	1094 (52)	1043 (53)	1082 (49)	1089 (53)
1–2 changes	879 (42)	858 (43)	1018 (46)	856 (42)
≥3 changes	112 (5)	82 (4)	93 (4)	103 (5)
Frequency changes, n (%)				
No changes	1457 (70)	1400 (71)	1485 (68)	1484 (72)
1–2 changes	599 (29)	558 (28)	685 (31)	534 (26)
≥3 changes	29 (1)	25 (1)	23 (1)	30 (1)

[a]Q2W, once every 2 weeks; QM, once monthly.

Adverse drug reactions

DA-related ADRs were reported in 12 patients and included 17 different preferred terms as follows: dizziness, headache (x2), hypersensitivity, hypertension (x4), influenza, leukopoenia, malaise, puncture site reaction, phlebitis, rash (x2), tachycardia and vertigo. Serious ADRs were pancreatic carcinoma and subdural haematoma (one patient for each), with no causal relationship established. There were no reports of antibody-mediated pure RBC aplasia.

Hospitalizations

Post-initiation, 1346/4278 (31%) patients were hospitalized, with a tri-monthly hospitalization rate ranging from 10 to 12% (Table 3), and an infrequent admission to the intensive care unit. Reasons for hospitalization included planned surgery and infection. The tri-monthly incidence of hospitalization for stroke remained <1%.

Renal replacement therapy

The mean eGFR declined during the pre- but not the post-initiation periods. Mean eGFR, excluding patients who had a significant eGFR decline and progressed to dialysis, was 26 mL/min/1.73m^2 (95% CI, 25−26 mL/min/1.73m^2) for Month −6, 24 mL/min/1.73m^2 (95% CI, 24−25 mL/min/1.73m^2) at initiation and 24 mL/min/1.73m^2 (95% CI, 23−24 mL/min/1.73m^2) for Month 12 (Figure 4). However, the rate of starting renal replacement therapy (RRT) post-initiation was stable, ranging from 3.5 to 3.7% per 3-month interval. During the 12 months after initiation, a total of 598 patients (14.1%) started RRT with rates of 2.1% (23/1082), 9.9% (219/2203) and 41.3% (338/819) for CKD Stages 3, 4 and 5, respectively.
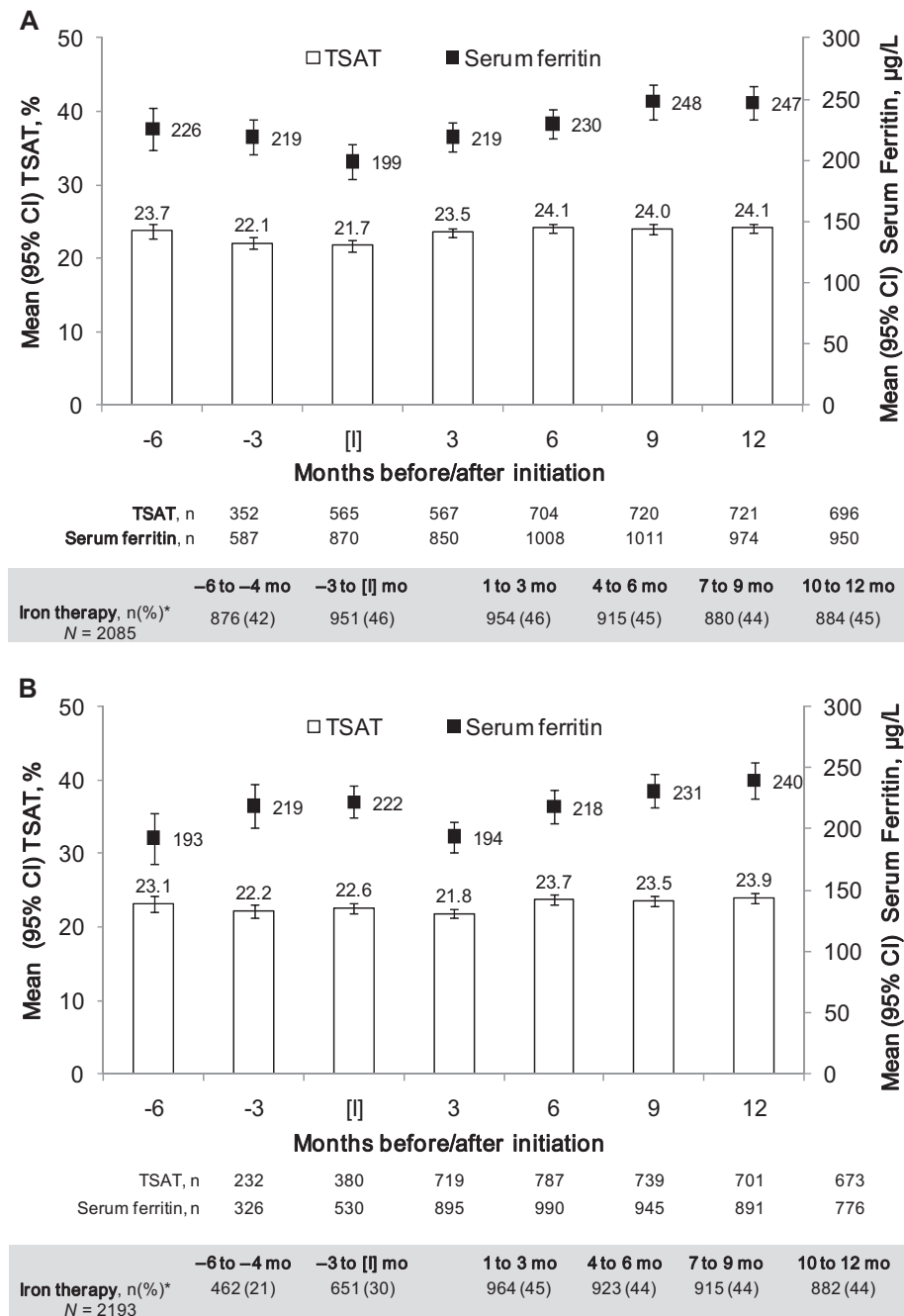
Treatment discontinuations

During the 12-month post-initiation period, 368 patients (9%) discontinued ESA treatment due to death [157 patients (4%)], kidney transplant [17 patients (1%)] or other reasons [192 patients (4%)]; no reason was specified for 2 patients (<1%).

Discussion

Interim analysis of the EXTEND observational study indicates that treatment of CKD-NoD patients with DA Q2W/QM was effective for the partial correction and/or maintenance of Hb levels, with no indication of safety issues. Mean Hb levels were maintained in the prior ESA subgroup and were corrected and maintained in the ESA-naive subgroup. Both the DA Q2W and QM regimens were well tolerated as DA-related ADRs were infrequent, but data limitations preclude any definitive interpretation. Changes to ESA dose and dose frequency were required for some patients. Most patients were receiving DA Q2W/QM at Month 12, with a doubling in the proportion of patients receiving DA QM (from 12 to 28%), which may reflect patients initiating DA Q2W then switching to QM dosing. Some patients switched to different ESA regimens.

Despite the limitations of observational data, some trends in this analysis are noteworthy. In the prior ESA subgroup, the increasing Hb levels prior to initiation and the corresponding drop in ESA dose at initiation likely reflect a common practice among nephrologists in Europe to initiate extended dosing with ESA in order to modify the total ESA dose, particularly in patients who demonstrate a good response to initial ESA treatment. Most patients were receiving DA QW prior to initiation and initiated extended dosing with DA at the Q2W frequency. Changes to both the dose and dose frequency were observed after initiation and illustrate the use of flexible dosing by clinicians. Maintaining stable Hb levels in CKD patients can be challenging as a number of patient-related factors and intercurrent events such as hospitalizations [20–22] may affect Hb stability [13, 20, 23, 24].

DA Q2W/QM initiation was associated with a decrease in RBC transfusion requirements in the ESA-naive subgroup. The highest transfusion rate in this subgroup corresponded to a trend of decreasing Hb levels in the pre-initiation period. The tri-monthly transfusion rate in the 3 months prior to initiation was 6% compared with a lower rate of 3% in the first 3 months after initiation. While a causal relationship cannot be established in an observational study, these data are consistent with the literature [1, 18, 25].

A

	−6 to −4 mo	−3 to [I] mo	1 to 3 mo	4 to 6 mo	7 to 9 mo	10 to 12 mo
Iron therapy, n(%)* N = 2085	876 (42)	951 (46)	954 (46)	915 (45)	880 (44)	884 (45)

B

	−6 to −4 mo	−3 to [I] mo	1 to 3 mo	4 to 6 mo	7 to 9 mo	10 to 12 mo
Iron therapy, n(%)* N = 2193	462 (21)	651 (30)	964 (45)	923 (44)	915 (44)	882 (44)

Fig. 2. Iron therapy and iron parameters. Patients receiving iron therapy in tri-monthly intervals before and after the initiation of DA Q2W/QM in the (**A**) prior ESA and (**B**) ESA-naive subgroups and the mean levels for transferrin saturation and serum ferritin. *Denominator does not include patients with missing data. [I], initiation of DA Q2W/QM; TSAT, transferrin saturation.

The types of DA-related ADRs reported were consistent with those in the literature [2, 5, 18]. The low ADR rates suggest that treatment was well tolerated, but this may also be related to under-reporting [26]. Although some studies have indicated an increased risk of pancreatic carcinoma with ESA treatment in certain cancer patients [27], such a relationship cannot be established with the current data.

During the post-initiation period, 14% of patients started RRT, 31% were hospitalized and 4% died (based on reason for discontinuing ESA treatment). These outcomes appear to be consistent with other observational studies in CKD-NoD populations. However, EXTEND was not designed as an outcomes study. Moreover, definitive comparisons cannot be made because of differences in study design and patient populations [28–33]. In this interim analysis, hospitalization and mortality data did not go beyond the 12-month post-initiation period, were not captured in a systematic manner that allows in-depth analysis and lacked detail.

Nevertheless, mortality and morbidity data obtained from this study are of clinical interest, particularly in view

of results from the Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial and the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT). In both trials, ESA treatment to high Hb targets was linked with adverse outcomes [15, 18].

In CHOIR, CKD-NoD patients (Stage 3/4) were randomized to achieve an Hb target of 13.5 versus 11.3 g/dL with epoetin alfa treatment and followed for 3 years. Compared with patients in the low Hb target arm, patients in the high Hb target arm were at greater risk for the primary composite outcome of death, myocardial infarction, hospitalization for congestive heart failure and stroke [hazard ratio (HR), 1.34; 95% CI, 1.03–1.74] [15]. There was no significant difference between treatment arms for death from any cause (7.3 versus 5.0%, respectively; P = 0.07), incidence of stroke (1.7% in each arm) or RRT (21.7 versus 18.7%, respectively; P = 0.15).
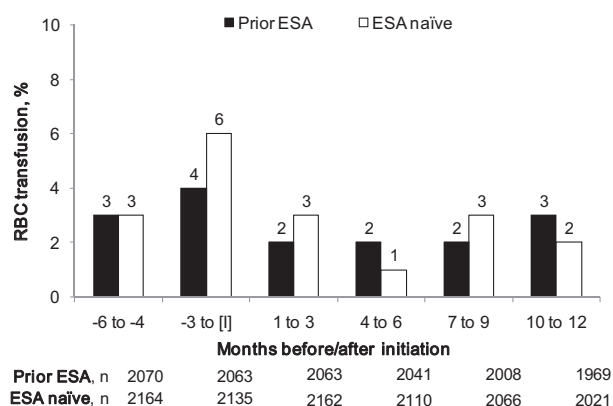
Fig. 3. RBC transfusions. Transfusions before and after the initiation of DA Q2W/QM in the prior ESA and ESA-naive subgroups. [I], initiation of DA Q2W/QM.

In TREAT, diabetic CKD-NoD (Stage 3/4) patients were randomized to receive DA treatment to achieve an Hb target of 13 g/dL versus a placebo control with rescue DA if the Hb was <9 g/dL and a return to placebo after Hb was ≥9 g/dL. Patients were followed for up to 48 months. While there was no difference between treatment arms for the primary cardiovascular composite and renal composite end points, a significant increase in the incidence of stroke was seen in the interventional arm compared with the control arm (5 versus 2.6%; HR, 1.92; 95% CI, 1.38–2.68). Death from any cause did not differ between the treatment arms (20.5 versus 19.5%, respectively; P = 0.48) nor did progression to end-stage renal disease (16.8 versus 16.3%, respectively; P = 0.83).

Although of clinical interest, any comparison of morbidity and mortality data of EXTEND to these randomized controlled trials must be qualified. Observational and clinical trial data in patients with renal anaemia have not correlated well [34], and there are important differences in the treatment goals of these studies. EXTEND was a non-interventional study with patients treated according to the standards of the participating centres, including those for Hb targets, rather than the restrictions set by the protocol of an interventional study.

While conclusions from comparisons of the outcomes data are limited, it is noteworthy that ESA dosing appeared to be much lower in EXTEND than in both CHOIR and TREAT. For 3501 patients receiving DA (any dosing schedule) at 12 months in EXTEND, the geometric mean weekly dose was 15.7 µg, arithmetic mean weekly dose was 21.1 µg and the median was 15.0 µg. The mean weekly epoetin alfa dose in the CHOIR study was 11 215 IU (~56 µg) in the high Hb target arm and 6276 IU (~31 µg) in the low Hb target arm [15]. During TREAT, the median monthly dose was 176 µg (~41 µg/week) in the

Table 3. Hospitalizations after initiation of DA Q2W/QM for the overall cohort (N = 4278)[a]

	Months after initiation			
	1−3 (n = 4299)	4−6 (n = 4161)	7−9 (n = 4084)	10−12 (n = 3992)
Patients hospitalized, n (%)	509 (12)	477 (11)	496 (12)	441 (11)
Admitted to ICU[b]	29 (6)	40 (8)	43 (9)	40 (9)
No. of hospitalizations	618	589	608	537
Primary reason, n (%)				
Ischaemic heart disease	21 (<1)	28 (1)	29 (1)	23 (1)
Peripheral vascular disease	19 (<1)	16 (<1)	14 (<1)	10 (<1)
Hyperkalaemia	8 (<1)	7 (<1)	4 (<1)	1 (<1)
Infection	82 (2)	75 (2)	106 (2)	76 (2)
Congestive heart failure	17 (<1)	22 (1)	19 (<1)	19 (<1)
Arrhythmia	9 (<1)	3 (<1)	9 (<1)	11 (<1)
Stroke	4 (<1)	8 (<1)	4 (<1)	10 (<1)
Haemorrhage	19 (<1)	18 (<1)	18 (<1)	18 (<1)
Convulsions	2 (<1)	1 (<1)	3 (<1)	0 (0)
Fractures	12 (<1)	7 (<1)	10 (<1)	9 (<1)
Electrolyte disorders	15 (<1)	12 (<1)	23 (1)	15 (<1)
Planned surgery	107 (3)	126 (3)	110 (3)	106 (2)
Others	230 (5)	209 (5)	202 (5)	187 (4)
Unknown	2 (<1)	2 (<1)	1 (<1)	3 (<1)
Duration, median (Q1, Q3)	6.0 (3.0, 11.0)	7.0 (3.0, 13.0)	7.0 (3.0, 12.0)	7.0 (4.0, 13.5)

[a]ICU, intensive care unit; Q1 lower quartile; Q3, upper quartile; Q2W, once every 2 weeks; QM, once monthly.
[b]Denominator is number of patients hospitalized.
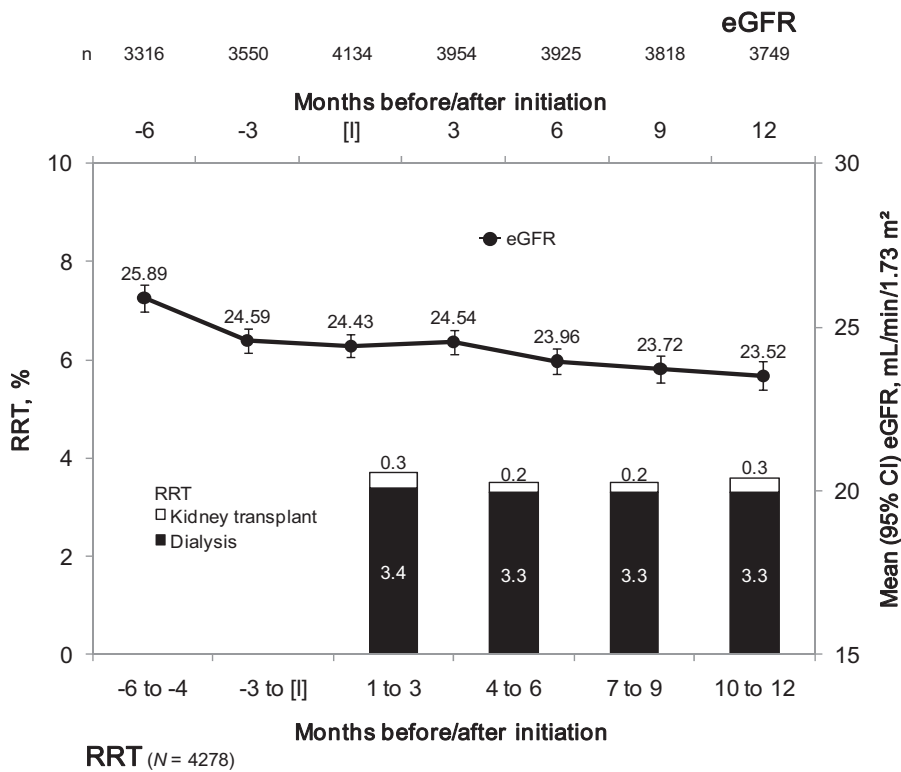
Fig. 4. Renal function and RRT. eGFR in the overall cohort before and after the initiation of DA Q2W/QM and the rate of RRT after initiation. [I], initiation of DA Q2W/QM.

interventional arm and 0 μg in the placebo arm [18]. Although we have no definitive explanation for this discrepancy, it may be indicative of a lower comorbidity level and less ESA resistance in the EXTEND patients.

Other limitations of this study are acknowledged, including confounding by indication for subgroup comparisons and selection criteria for patients. Patients were required to have initiated DA Q2W/QM at one of the participating centres, which limits the generalizability of the data. For example, the increasing Hb levels in the prior ESA subgroup pre-initiation and low dosing requirements post-initiation is likely to reflect a population of patients who were responding well to ESA treatment. Also, important regulatory changes occurred during the course of the study in 2008 that altered the Hb target for patients with renal anaemia, which may have confounded data. Analyses of the potential impact of the regulatory and guidelines changes on clinical practice patterns will be considered in subsequent reports of EXTEND.

The design of the study allowed for a mixture of retrospective and prospective data to be collected for each subject and allowed the amount of retrospective data to vary among subjects. To assess the possible impact of this, a sensitivity analysis was conducted by splitting subjects into subgroups according to when they enrolled relative to the observation period, but this analysis was confounded by time. Subjects with a large amount of retrospective data tended to have been enrolled early in the study when the higher Hb targets were in place, whereas subjects with few retrospective data were generally enrolled later, when lower Hb targets were in place. The distribution of the number of Hb values per subject was explored, and no differences were found between the time periods when data were collected retrospectively and prospectively.

Missing data can also be a limitation of observational studies. Missing Hb data at a particular time point may be attributable to subjects having withdrawn from the study or to a lack of available Hb values in the 3-month time window (because of the observational nature of the data collection). The number of subjects providing Hb data at each time point is shown in Figure 1 and was fairly stable over time. The overall dropout rate during the 12 months of the study was low, and 3987 (93%) of subjects in this analysis contributed at least 9 months of data post-DA Q2W/QM initiation. A sensitivity analysis of the primary end points imputed 11% of data using the LOCF method, and the results were consistent with the primary analysis.

Despite these limitations, EXTEND provides valuable data for a large CKD-NoD population in routine practice. Subgroup analyses are planned, and long-term follow-up will provide more data on transition to dialysis. This is particularly relevant in view of the results from the 3-year Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta (CREATE) trial, which assessed the safety and efficacy of treating CKD-NoD (eGFR 15–35 mL/min/1.73m^2) patients to an Hb target of 13–15 g/dL with epoetin beta versus a target of 10.5–11.5 g/dL [14]. Although there was no significant difference between the treatment arms for the primary composite end point of cardiovascular events, time to dialysis was significantly shorter in the high Hb target group (P = 0.03) with a median weekly ESA dose of 5000 IU (~25 μg). Additional analyses of EXTEND will provide data

from longer follow-up and will help to better characterize the progression of CKD in this cohort of patients.

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