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Outcomes in patients with chronic kidney disease not on dialysis receiving extended dosing regimens of darbepoetin alfa: long-term results of the EXTEND observational cohort study

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ORIGINAL ARTICLE

ABSTRACT

Background. Extended dosing of the erythropoiesis-stimulating agent (ESA) darbepoetin alfa (DA) once biweekly or monthly reduces anaemia treatment burden. This observational study assessed outcomes and dosing patterns in patients with chronic kidney disease not on dialysis (CKD-NoD) commencing extended dosing of DA.

Methods. Adult CKD-NoD patients starting extended dosing of DA in Europe or Australia in June 2006 or later were followed up until December 2012. Outcomes included haemoglobin (Hb) concentration, ESA dosing, mortality rates and receipt of dialysis and renal transplantation. Subgroup analyses were conducted for selected outcomes.

Results. Of 6035 enrolled subjects, 5723 (94.8%) met analysis criteria; 1795 (29.7%) received dialysis and 238 (3.9%) underwent renal transplantation. Mean (standard deviation) Hb concentration at commencement of extended dosing was 11.0 (1.5) g/dL. Mean [95% confidence interval (CI)] Hb 12 months after commencement of extended dosing (primary outcome) was 11.6 g/dL (11.5, 11.6) overall and was similar across countries, with no differences between subjects previously treated with an ESA versus ESA-naïve subjects, subjects with versus without prior renal transplant or diabetics versus non-diabetics. Weekly ESA dose gradually decreased following commencement of extended DA dosing and was similar across subgroups. The decrease in weekly DA dose was accompanied by an increase in the proportion of patients receiving iron therapy. Hb concentrations declined following changes in ESA labels and treatment guidelines. The mortality rate (95% CI) was 7.06 (6.68, 7.46) deaths per 100 years of follow-up. Subjects alive at study end had stable Hb concentrations in the preceding year, while those who died had lower and declining Hb concentrations in their last year.

Conclusions. Long-term, extended dosing of DA maintained Hb concentrations in patients already treated with an ESA and corrected and maintained Hb in ESA-naïve patients.

Keywords: anaemia, chronic kidney disease, darbepoetin alfa, erythropoiesis-stimulating agent, extended dosing

INTRODUCTION

Anaemia is a complication of chronic kidney disease (CKD), twice as common in patients with any stage of CKD as in the general population [1]. The introduction of erythropoiesis-stimulating agents (ESAs) to clinical practice transformed the care of patients with anaemia of CKD, including those not on dialysis (NoD), by improving and maintaining haemoglobin (Hb) concentrations, reducing transfusion requirements and improving quality of life [2, 3].

Despite these benefits, the randomized, controlled studies CHOIR, CREATE and TREAT showed an increased risk for cardiovascular (CV) morbidity and mortality end points among patients treated to high Hb targets (e.g. ≥13 g/dL) [4–6]. Thus, recommended target Hb concentrations have been lowered in expert clinical practice guidance [7, 8] and ESA labels [9, 10]. In 2008, the European labels for ESAs were changed to reflect the European Medicines Agency directive to stipulate a target Hb range of 10–12 g/dL, with a warning not to exceed 12 g/dL [10].

Less frequent dosing using longer-acting ESAs appears to reduce the burden of injections on patients, caregivers and healthcare professionals compared with short-acting agents [11]. Aranesp® (darbepoetin alfa; DA) is a longer-acting ESA with demonstrated efficacy and safety in CKD-NoD patients when administered subcutaneously (s.c.) at extended dosing intervals either once biweekly (Q2W) or once monthly (QM) [12–18]. The observational study EXTEND [an observational cohort study of EXTENDed dosing (Q2W or QM) with Aranesp® s.c. in subjects with CKD-NoD] was conducted to provide data on the real-world clinical management and outcomes of a cohort of adult CKD-NoD patients receiving DA at extended dosing intervals [11]. Although a formal hypothesis was not tested in this observational study, the premise was that these patients can be adequately treated with extended dosing of DA to reach target Hb levels according to the recommendations of international treatment guidelines. The interim 1-year analysis of the EXTEND study found that Hb concentrations were maintained in subjects already treated with ESAs before enrolment and were corrected and maintained in ESA-naïve subjects [mean (95% confidence interval, CI) Hb at Months 10–12 = 11.6 (11.6, 11.7) and 11.7 (11.7, 11.8) g/dL, respectively] [11].

The original EXTEND study protocol was amended to capture long-term data on the management of CKD across the disease spectrum, expanding on the interim results previously published [11]. This report describes final results for EXTEND on the effectiveness of DA in extended dosing, including Hb concentrations, as well as ESA dose and dosing frequency in this real-life observational study. We also report a calendar analysis of data from EXTEND performed after the interim analysis, which was designed to examine the implications of changing Hb target ranges on ESA doses and achieved Hb concentrations over time. In addition, the scarcity of long-term data on the natural history of CKD is addressed by examining outcomes for key subgroups (by country, diabetic status and kidney transplant status) and by describing rates of transition to dialysis or transplant and mortality rates in both dialysed and NoD subjects. Predictors of receipt of dialysis, and the relationship between C-reactive protein (CRP) concentration and type of dialysis access, are also explored.

MATERIALS AND METHODS

Study design and patients

Details of the EXTEND study design and a description of the subjects included in the interim analysis have been previously reported [11]. Briefly, EXTEND was a multicentre, longitudinal, non-interventional cohort study of adult (≥18 years of age) CKD patients in Europe and Australia, NoD at time of first extended dosing of DA (i.e. Q2W or QM), who initiated extended dosing on or after 1 June 2006. This start date was chosen to ensure capture of contemporary data.

As of January 2009, all subjects previously or currently (during this study) enrolled according to the original EXTEND protocol were eligible to remain in the amended study, or to re-enrol if they had already completed the original study, with the exception of those who terminated the study early or who were lost to follow-up.

Key study amendments were the extension of the observation period to the end of 2012, with extension of the study duration for individual subjects up to 6 years and an increase in the target sample size from 3500–4000 to 6000 subjects.

The amended protocol retained the primary outcome from the original protocol, mean Hb 12 months after commencement of DA extended dosing. The primary outcome was examined by subgroups of interest, namely by prior-ESA status, renal transplant status and presence or absence of diabetes, all evaluated at commencement of DA extended dosing. The influence of different variables on the Hb concentration 12 months after commencement of DA Q2W or QM was also evaluated.

Additional outcome variables included were as follows: changes in anaemia management and ESA practice patterns in CKD subjects NoD or on dialysis in relation to the new European Hb target range (i.e. 10–12 g/dL, not to exceed 12 g/dL [10]); receipt of dialysis and renal transplant in CKD subjects; mortality rates in CKD subjects NoD or post-dialysis; and Hb maintenance at all stages of disease from Stage 3 to dialysis. Prescription of iron therapy and prevalence of iron adequacy (as defined by serum ferritin >100 μg/L and/or transferrin saturation (TSAT) >20% [19]) were also evaluated. Use of iron therapy was recorded as presence or absence, administration route [oral or intravenous (IV)] and purpose (for treatment or prophylaxis), but quantitative data on iron therapy dosing were not collected, and iron usage was not mandated in the protocol of this observational study. In subgroup analyses, selected outcomes were examined by country. In addition, exploratory analyses were undertaken of CRP concentrations among subjects who received dialysis, stratified by type of dialysis access. An exploratory analysis was also performed to compare DA dose over time leading up to the last DA dose for subjects who died from CV or non-CV events and subjects who survived to study end.

Procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 as revised in 2000.

Statistical analysis

Analyses were conducted for two sets of subjects: the Full Analysis Set (FAS), comprising all eligible enrolled subjects who commenced DA Q2W or QM, and the Dialysis Analysis Set (DAS), consisting only of subjects who initiated dialysis during the follow-up period.

As this was not a hypothesis-driven study, all analyses were descriptive. Continuous variables are described using the mean, standard deviation (SD), median, quartiles and exact 95% CI, as applicable. While average Hb values are reported using arithmetic means, weekly ESA doses are reported using geometric means due to the skewed nature of the dosing data. Categorical variables are reported as the number and per cent of subjects. CRP concentrations are reported as area under the curve (AUC) per month post-dialysis, calculated for each subject as the area under the CRP–time graph divided by the number of months of available data.

The effect of covariates on the Hb concentration 12 months after commencement of DA Q2W or QM was investigated for the FAS using a general linear model. In addition to univariate modelling, multivariable modelling was performed using a stepwise procedure including variables significant at the 5% level. Variables considered in the models were age, ESA status, frequency of DA dosing, Hb concentration, renal function, serum ferritin, TSAT and weekly DA dose at commencement of extended dosing, as well as weekly dose equivalent of DA and weekly dose equivalent of epoetin-α or -β immediately prior to commencement of extended dosing.

Time to dialysis was assessed as the proportion of subjects initiating dialysis in each 3-month time period. A *post hoc* multivariable analysis of baseline predictors of initiating dialysis was conducted, which included variables found to be significant in univariate analyses. Variables considered included all those listed above for evaluating predictors of Hb concentration at 12 months, as well as albumin, creatinine, CRP, diabetes, estimated glomerular filtration rate (eGFR), fasting plasma glucose, glycated Hb, history of CV disease, adequacy of iron stores, kidney transplant, proteinuria, parathyroid hormone, serum calcium and serum phosphorus at commencement of extended dosing.

Mortality was calculated by counting deaths recorded by end of study, as well as deaths reported as occurring after study end, those recorded as fatal serious adverse events and those that were cited as the reason for discontinuation of ESA therapy (i.e. censored subjects).

For the primary outcome variable, missing Hb values were imputed by the last observation carried forward (LOCF) method up to Month 12. As a sensitivity analysis, the primary outcome variable was also analysed without imputation. For all other outcome variables, results are presented for observed data.

Data were analysed using SAS Statistical Software v9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

During the study period from June 2006 to December 2012, 6035 eligible patients were enrolled at 375 specialist nephrology centres in 18 European countries and Australia (Table 1). The first patient was enrolled in February 2007 and had 6 months of retrospective data. Of the enrolled subjects, 5723 (94.8%) met the criteria for inclusion in the FAS and 1795 (29.7%) subsequently received dialysis and were included in the DAS (Figure 1). The mean (SD) follow-up duration for patients in the FAS was 38.0 (22.8) months.

Table 1. Subject geographic distribution

Country	All enrolled subjects, *n* (%) (*N* = 6035)
France	1513 (25)
Germany	1184 (20)
Poland	392 (6)
Austria	384 (6)
UK	381 (6)
Belgium	312 (5)
Italy	308 (5)
Australia	261 (4)
The Netherlands	251 (4)
Sweden	202 (3)
Portugal	172 (3)
Hungary	150 (2)
Greece	142 (2)
Ireland	117 (2)
Czech Republic	113 (2)
Slovakia	60 (1)
Finland	49 (1)
Norway	28 (<1)
Denmark	16 (<1)

Demographic and clinical characteristics of enrolled subjects either at commencement of extended dosing or at enrolment are shown in Table 2. Subjects in the FAS were relatively evenly balanced with respect to sex (52.3% male and 47.6% female); the mean (SD) age was 67.4 (15.0) years. Nearly half of subjects (48.1%) had received ESAs before commencing DA extended dosing. A minority of subjects (10.9%) had a history of renal transplantation with functioning grafts at enrolment; 38.0% were diabetic. Subjects with a renal transplant were generally younger than those without, but demographic characteristics were otherwise similar across subgroups. At initiation of dialysis, subjects in the DAS were slightly more likely to be male (56.4%) and were slightly younger (mean age 65.4 years) than subjects in the FAS.

The most common primary aetiologies of CKD were diabetes mellitus (24.8%), hypertension-attributed (23.8%) and glomerulonephritis (12.8%). While 15.5% of subjects with renal transplants had diabetes, diabetes was the primary aetiology of CKD among only 5.8% of subjects with prior renal transplant. Predictably, diabetes was the primary aetiology of CKD among most subjects with diabetes (63.1%). Compared with the overall FAS, hypertension-attributed was the primary cause of CKD less frequently in subjects with prior renal transplant (8.2%) or diabetes (15.1%). Glomerulonephritis was the primary aetiology of CKD in a higher proportion of renal transplant recipients (29.9%) but fewer diabetics (3.9%). Most subjects had severely or very severely reduced renal function at the commencement of extended dosing (51.7% had CKD Stage 4 and 20.2% had CKD Stage 5). Fewer prior renal transplant recipients (5.6%) were in Stage 5 at the commencement of extended dosing.

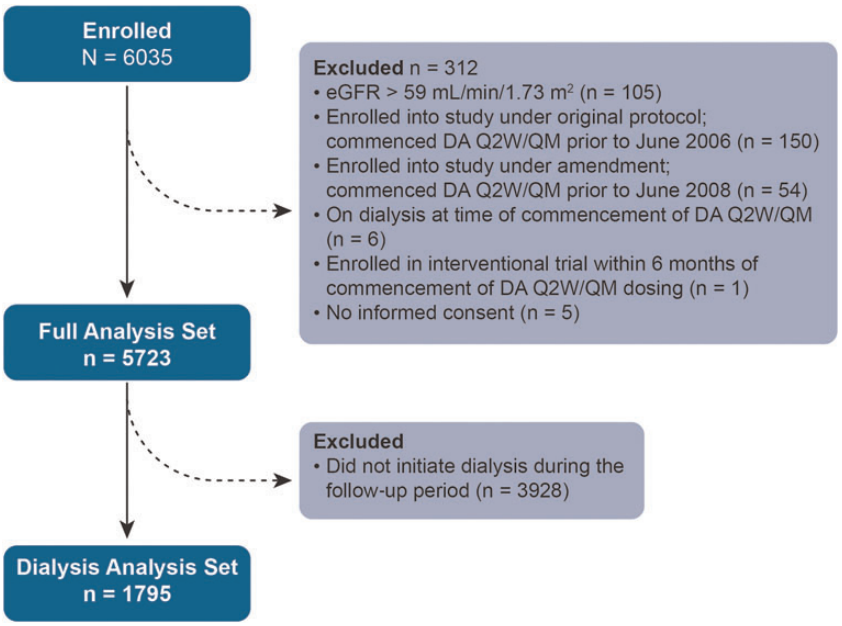

FIGURE 1: Disposition of subjects. DA, darbepoetin alfa; eGFR, estimated glomerular filtration rate; Q2W, once every 2 weeks; QM, once monthly.

Hb concentrations

While the arithmetic mean (SD) Hb concentration at commencement of extended dosing was 11.0 (1.5) g/dL, only half of subjects with Hb data (2446/4827, 50.7%) had concentrations within the range of 10–12 g/dL. As shown in Table 2, Hb at commencement of extended dosing was higher in subjects who received ESAs prior to commencing DA extended dosing compared with ESA-naïve subjects [11.7 (1.6) versus 10.2 (1.1) g/dL], but was similar across subgroups of prior renal transplant and diabetes status.

For the primary outcome, the mean (95% CI) Hb 12 months after commencement of extended dosing was 11.6 (11.5, 11.6) g/dL, based on the LOCF analysis for the FAS. Results were consistent in the sensitivity analysis with no imputation of missing values: 11.6 (11.6, 11.7) g/dL.

In the LOCF analysis, mean Hb concentrations at 12 months were similar for prior-ESA and ESA-naïve subjects [11.5 (11.5, 11.6) and 11.6 (11.6, 11.7) g/dL, respectively], and for subjects with and those without prior renal transplant [11.6 (11.5, 11.7) and 11.6 (11.5, 11.6) g/dL]. Diabetics had slightly lower Hb concentrations at 12 months than non-diabetics [11.5 (11.4, 11.5) versus 11.7 (11.6, 11.7) g/dL]. Based on the univariate analysis, lower mean Hb at Month 12 was observed for subjects whose weekly dose equivalent of epoetin-α or -β prior to commencement of DA extended dosing was above the median compared with those whose dose was at or below the median. Similarly, lower mean Hb at Month 12 was seen in subjects whose weekly dose equivalent of DA at commencement of DA extended dosing was above the median compared with subjects whose DA dose was at or below the median. Lower mean Hb at Month 12 was also observed in subjects whose Hb at commencement was below the median and/or whose renal function at commencement was Stage 4 or 5. The multivariable analysis indicated that lower mean Hb was also associated with prior ESA usage, weekly dose equivalent of DA at commencement above the median, Hb below the median at commencement and Stage 4 or 5 renal function (see Supplementary data, Table S1).

In the overall cohort, following an initial increase in the first 3 months following commencement of DA extended dosing, similar Hb concentrations were maintained long term to study completion up to 72 months after commencement of extended dosing (Figure 2A). When assessed by prior-ESA status, mean Hb concentrations showed a sharper increase following commencement of DA extended dosing in ESA-naïve subjects in need of anaemia correction compared with prior-ESA subjects (Figure 2B). Among prior-ESA subjects, at Month 3 following commencement of DA extended dosing, mean Hb concentrations exceeded the values observed from Month 6 onwards, which were similar in both prior-ESA and ESA-naïve subjects. Mean Hb concentrations were similar at all time points in subjects with and those without prior renal transplant (Figure 2C), and in subjects with and those without diabetes (Figure 2D).

The percentage of subjects with Hb concentrations above, within and below the post-2008 European target range of 10–12 g/dL before and after commencement of DA extended dosing is shown in Figure 3. The percentage of subjects with Hb below this target range was more than halved within the 3 months following commencement of extended dosing, indicating correction of low Hb concentrations in the ESA-naïve subgroup, and remained relatively stable for the remainder of follow-up. Following an initial increase in the percentage of subjects with Hb >12 g/dL, this percentage decreased from Months 4–6 onwards. The percentage of subjects with Hb concentrations within the range of 10–12 g/dL increased from 50.7% at commencement of extended dosing to 63.5% at Months 70–72.

Table 2. Subject characteristics

	FAS[a] (*n* = 5723)	ESA status		Prior renal transplant		Diabetes		
		Prior (*n* = 2752)	Naïve (*n* = 2971)	Yes (*n* = 625)	No (*n* = 5098)	Yes (*n* = 2172)	No (*n* = 2824)	Unknown (*n* = 14)
Age, years								
Mean (SD)	67.4 (15.0)	66.8 (15.1)	67.9 (14.9)	51.8 (13.3)	69.3 (14.1)	69.1 (12.1)	66.0 (16.4)	70.2 (17.9)
Median (Q1, Q3)	71.0 (59.0, 79.0)	70.0 (58.0, 78.0)	71.0 (60.0, 79.0)	52.0 (42.0, 62.0)	72.0 (62.0, 79.0)	71.0 (62.0, 78.0)	70.0 (55.0, 79.0)	76.5 (60.0, 82.0)
Sex, *n* (%)								
Female	2724 (47.6)	1319 (47.9)	1405 (47.3)	290 (46.4)	2434 (47.7)	1039 (47.8)	1336 (47.3)	6 (42.9)
Male	2993 (52.3)	1432 (52.0)	1561 (52.5)	335 (53.6)	2658 (52.1)	1130 (52.0)	1486 (52.6)	8 (57.1)
Unknown	6 (0.1)	1 (0.0)	5 (0.2)	0 (0.0)	6 (0.1)	3 (0.1)	2 (0.1)	0 (0.0)
Supposed primary aetiology of CKD, *n* (%)								
Diabetes mellitus	1417 (24.8)	663 (24.1)	754 (25.4)	36 (5.8)	1381 (27.1)	1370 (63.1)	24 (0.8)	1 (7.1)
Hypertension-attributed	1362 (23.8)	614 (22.3)	748 (25.2)	51 (8.2)	1311 (25.7)	328 (15.1)	813 (28.8)	1 (7.1)
Glomerulonephritis	733 (12.8)	382 (13.9)	351 (11.8)	187 (29.9)	546 (10.7)	84 (3.9)	552 (19.5)	2 (14.3)
Interstitial nephropathy/obstructive nephropathy	562 (9.8)	282 (10.2)	280 (9.4)	86 (13.8)	476 (9.3)	89 (4.1)	397 (14.1)	4 (28.6)
Polycystic kidney/hereditary disease	293 (5.1)	139 (5.1)	154 (5.2)	64 (10.2)	229 (4.5)	26 (1.2)	207 (7.3)	0 (0.0)
Other	700 (12.2)	336 (12.2)	364 (12.3)	128 (20.5)	572 (11.2)	135 (6.2)	430 (15.2)	1 (7.1)
Unknown	589 (10.3)	305 (11.1)	284 (9.6)	70 (11.2)	519 (10.2)	126 (5.8)	359 (12.7)	5 (35.7)
Missing	16 (0.3)	7 (0.3)	9 (0.3)	3 (0.5)	13 (0.3)	5 (0.2)	7 (0.2)	0 (0.0)
CKD stage at commencement of extended dosing, *n* (%)								
Stage 3a	295 (5.2)	148 (5.4)	147 (4.9)	89 (14.2)	206 (4.0)	101 (4.7)	155 (5.5)	2 (14.3)
Stage 3b	1283 (22.4)	619 (22.5)	664 (22.3)	236 (37.8)	1047 (20.5)	498 (22.9)	623 (22.1)	6 (42.9)
Stage 4	2959 (51.7)	1402 (50.9)	1557 (52.4)	260 (41.6)	2699 (52.9)	1193 (54.9)	1412 (50.0)	5 (35.7)
Stage 5	1155 (20.2)	567 (20.6)	588 (19.8)	35 (5.6)	1120 (22.0)	370 (17.0)	621 (22.0)	1 (7.1)
Missing	31 (0.5)	16 (0.6)	15 (0.5)	5 (0.8)	26 (0.5)	10 (0.5)	13 (0.5)	0 (0.0)
Hb at commencement of extended dosing								
N	4827	2355	2472	537	4290	1832	2410	9
Mean (SD), g/dL	11.0 (1.5)	11.7 (1.6)	10.2 (1.1)	11.1 (1.5)	10.9 (1.5)	10.9 (1.5)	11.0 (1.6)	10.8 (0.8)
Median (Q1, Q3), g/dL	10.7 (9.9, 11.9)	11.8 (10.7, 12.8)	10.2 (9.6, 10.8)	11.0 (10.1, 11.9)	10.7 (9.9, 11.9)	10.6 (9.9, 11.9)	10.7 (9.9, 11.9)	11.0 (10.4, 11.3)
Category, *n* (%)								
<10 g/dL	1268 (22.2)	317 (11.5)	951 (32.0)	121 (19.4)	1147 (22.5)	496 (22.8)	639 (22.6)	1 (7.1)
10–12 g/dL	2446 (42.7)	1019 (37.0)	1427 (48.0)	291 (46.6)	2155 (42.3)	927 (42.7)	1214 (43.0)	8 (57.1)
>12 g/dL	1113 (19.4)	1019 (37.0)	94 (3.2)	125 (20.0)	988 (19.4)	409 (18.8)	557 (19.7)	0 (0.0)
Missing	896 (15.7)	397 (14.4)	499 (16.8)	88 (14.1)	808 (15.8)	340 (15.7)	414 (14.7)	5 (35.7)
Kidney transplant status at time of enrolment, *n* (%)								
No prior transplant	5098 (89.1)	2364 (85.9)	2734 (92.0)	–	5098 (100.0)	2075 (95.5)	2416 (85.6)	11 (78.6)
Prior renal transplant	625 (10.9)	388 (14.1)	237 (8.0)	625 (100.0)	–	97 (4.5)	408 (14.4)	3 (21.4)
History of CV disease at enrolment, *n* (%)								
Yes	3282 (57.3)	1523 (55.3)	1759 (59.2)	270 (43.2)	3012 (59.1)	1429 (65.8)	1511 (53.5)	1 (7.1)
No	2263 (39.5)	1147 (41.7)	1116 (37.6)	340 (54.4)	1923 (37.7)	652 (30.0)	1263 (44.7)	4 (28.6)
Unknown	114 (2.0)	45 (1.6)	69 (2.3)	7 (1.1)	107 (2.1)	56 (2.6)	42 (1.5)	9 (64.3)
Missing	64 (1.1)	37 (1.3)	27 (0.9)	8 (1.3)	56 (1.1)	35 (1.6)	8 (0.3)	0 (0.0)
Diabetes at commencement of extended dosing, *n* (%)								
Yes	2172 (38.0)	1040 (37.8)	1132 (38.1)	97 (15.5)	2075 (40.7)	2172 (100.0)	–	0 (0.0)
No	2824 (49.3)	1349 (49.0)	1475 (49.6)	408 (65.3)	2416 (47.4)	–	2824 (100.0)	0 (0.0)
Unknown	14 (0.2)	2 (0.1)	12 (0.4)	3 (0.5)	11 (0.2)	0 (0.0)	0 (0.0)	14 (100.0)
Missing	713 (12.5)	361 (13.1)	352 (11.8)	117 (18.7)	596 (11.7)	0 (0.0)	0 (0.0)	0 (0.0)

Continued

Table 2. Continued

	FAS[a] ($n = 5723$)	ESA status		Prior renal transplant		Diabetes		
		Prior ($n = 2752$)	Naïve ($n = 2971$)	Yes ($n = 625$)	No ($n = 5098$)	Yes ($n = 2172$)	No ($n = 2824$)	Unknown ($n = 14$)
Time since initiation of ESA treatment to commencement of extended dosing, months								
N	2752	2752	–	388	2364	1040	1349	2
Mean (SD)	8.1 (9.9)	8.1 (9.9)	–	11.5 (15.2)	7.5 (8.6)	8.1 (9.8)	8.3 (10.4)	3.0 (0.0)
Median (Q1, Q3)	6.0 (3.0, 9.0)	6.0 (3.0, 9.0)	–	6.0 (4.0, 13.5)	5.0 (3.0, 8.0)	5.0 (3.0, 9.0)	6.0 (3.0, 9.0)	3.0 (3.0, 3.0)

CKD, chronic kidney disease; DA, darbepoetin alfa; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; Q2W, once every 2 weeks; QM, once monthly.
[a]Full Analysis Set (FAS), all eligible enrolled subjects who commenced DA Q2W or QM.

In subgroup analyses for subjects in France, Germany, Italy, and the UK and Ireland, at commencement of DA extended dosing, there was a trend for Hb to be higher in the UK and Ireland compared with the other countries (see Supplementary data, Figure S1).

Calendar analysis of Hb concentrations

The change in Hb concentrations over time was assessed in two ways: in terms of Hb concentrations at commencement of extended dosing according to calendar date (Figure 4A) and in terms of Hb concentrations achieved by calendar date (Figure 4B). For Hb concentrations at commencement of extended dosing, the mean (95% CI) Hb in subjects with prior ESA experience declined over calendar time, from 12.0 (11.8, 12.2) g/dL in July–September 2006 to 11.4 (11.1, 11.8) g/dL in July–September 2009, with the most notable drop occurring after June 2007. Hb concentrations in ESA-naïve subjects declined from 10.5 (10.3, 10.7) g/dL in July–September 2006 to 9.9 (9.7, 10.1) g/dL in July–September 2009.

In the analysis of Hb concentrations achieved by calendar date, the mean (95% CI) achieved Hb in subjects with prior ESA experience declined from 12.2 (12.0, 12.3) g/dL in January–March 2007 to 11.6 (11.5, 11.6) g/dL in October–December 2012. Achieved Hb in ESA-naïve subjects showed a similar trend, declining from 12.0 (11.8, 12.2) g/dL in January–March 2007 to 11.5 (11.4, 11.6) g/dL in October–December 2012.

ESA dose

Mean weekly ESA dose gradually decreased following commencement of DA extended dosing and was similar across subgroups of ESA status, renal transplant and diabetes status (Figure 2). Geometric mean (95% CI) weekly ESA dose 12 months after commencement of DA extended dosing was 14.17 (13.81, 14.53) μg/week.

In subgroup analyses, at commencement of DA extended dosing, there was a trend for DA dose to be lower in the UK and Ireland compared with France, Germany and Italy (see Supplementary data, Figure S1).

Patterns of extended dosing

A total of 2629 (45.9%) of the 5723 subjects in the FAS changed their frequency of dosing of DA in the first year following commencement of extended dosing (Table 3). The percentages of subjects switching dosing frequency were similar in prior-ESA and ESA-naïve subjects.

Switching to a different frequency of administration was more common among subjects commencing extended dosing with DA Q2W than among subjects starting with DA QM (64.6 versus 53.0%, respectively; Table 4). Among subjects who started with DA Q2W, similar percentages of prior-ESA and ESA-naïve subjects switched dosing frequency (65.2 and 64.0%, respectively), whereas among subjects who started with DA QM, more prior-ESA subjects than ESA-naïve subjects switched dosing frequency (57.8 versus 49.6%, respectively). Of the subjects who switched their dosing frequency, the most common initial switches were from Q2W to QM and from QM to Q2W.

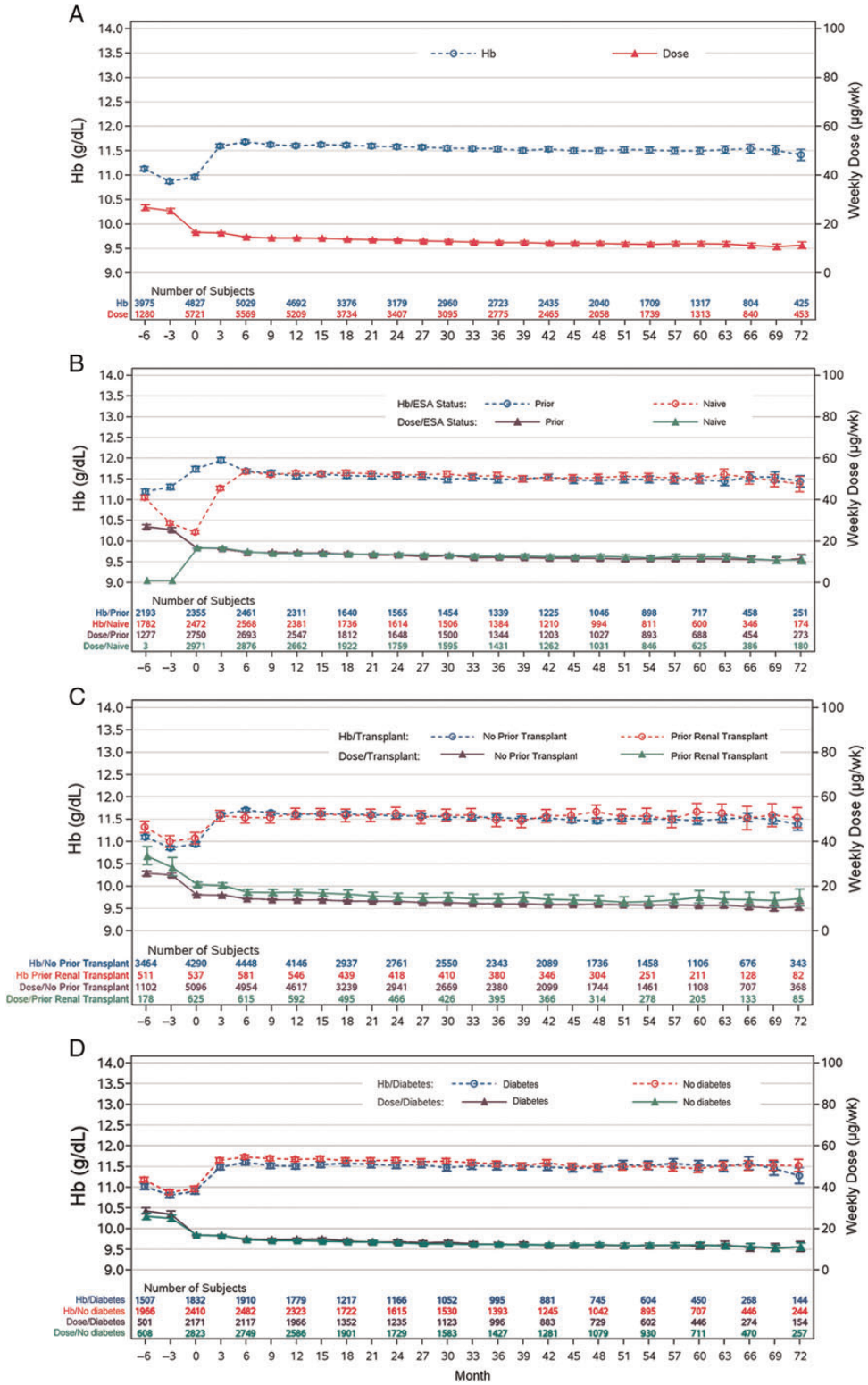

FIGURE 2: Hb concentration and weekly ESA dose in the Full Analysis Set (all eligible enrolled subjects who commenced DA Q2W or QM): (**A**) overall, (**B**) by prior-ESA status, (**C**) by prior renal transplant status and (**D**) by diabetes status. Values are arithmetic means for Hb and geometric means for ESA dose, with 95% confidence intervals. Month numbering is in relation to commencement of extended dosing. ESA, erythropoiesis-stimulating agent; FAS, Full Analysis Set; Hb, haemoglobin; Q2W, once every 2 weeks; QM, once monthly.

Iron status and iron therapy

Overall, approximately half of subjects (51%) in the FAS were iron replete at commencement of extended dosing. Among subjects with available data, the percentage of subjects with iron adequacy at commencement of extended dosing was higher in the UK and Ireland (153/267, 57.3%) and Italy (50/89,

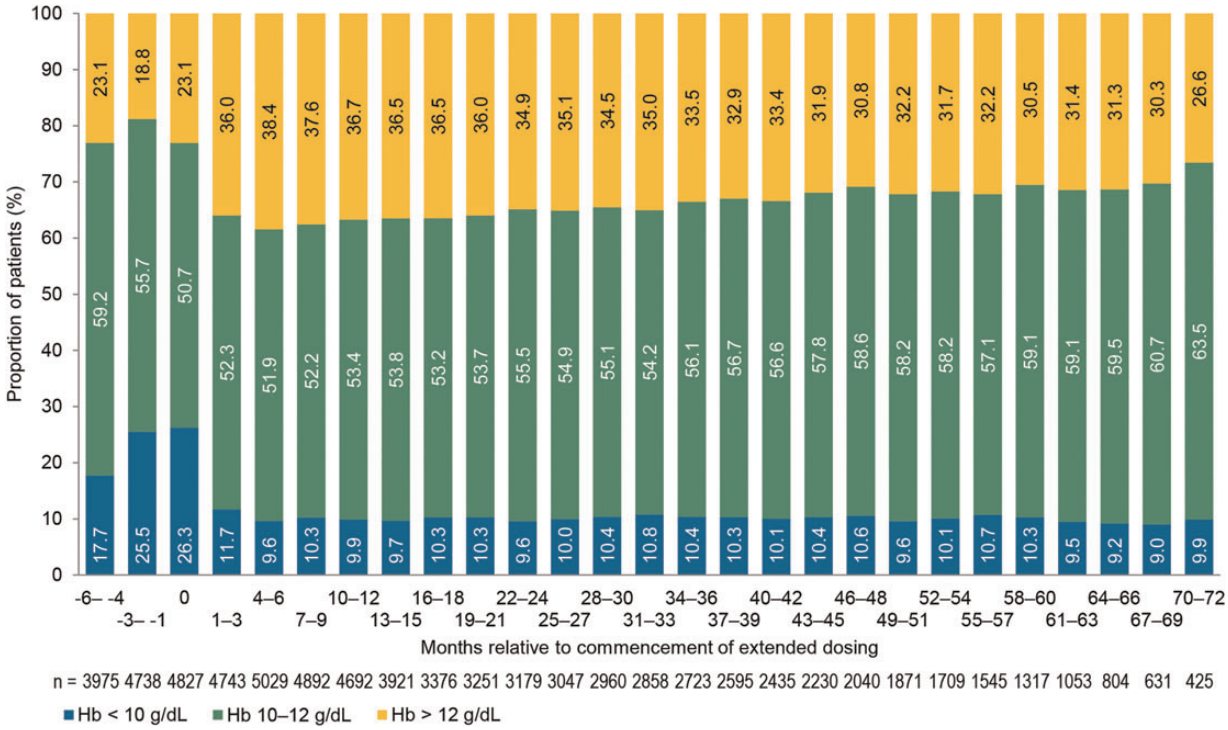

FIGURE 3: Proportion of subjects with Hb concentration above, within and below 10–12 g/dL over 3-month intervals relative to commencement of extended dosing. Hb, haemoglobin.

56.2%) than in France (330/624, 52.9%) or Germany (270/535, 50.5%). Overall in the FAS, iron adequacy declined to 48% during the first 3-month interval after commencement of extended dosing, and then increased to 56% of subjects at 4–6 months after commencement of extended dosing. The proportion of subjects with adequate iron increased over the remainder of the study, with 67% of subjects at 72 months being iron replete.

Use of iron therapy in the FAS increased from 30.9% of subjects in Months −6 to −4 prior to commencement of extended dosing to 45.8% in the 3-month period following commencement of extended dosing (Figure 5). Thereafter, during each 3-month interval during follow-up, slightly less than half of subjects in the FAS received iron therapy, with an apparent decline as sample sizes decreased towards the end of follow-up. Use of iron therapy was more common among subjects without prior renal transplant compared with subjects transplanted prior to enrolment, and among diabetics compared with non-diabetics. While iron use was more common among prior-ESA subjects before commencement of extended dosing, the percentage of subjects taking iron therapy was similar in each 3-month interval up to Months 70–72 following commencement of extended dosing. Prior to commencement of extended dosing, the UK and Ireland had a higher percentage of subjects receiving iron therapy than did France, Italy or Germany, with greater use of IV iron (see Supplementary data, Figure S2). Following commencement of extended dosing, the use of IV iron increased in all four countries.

Approximately one-third of subjects in the FAS received iron therapy in the two 3-month intervals prior to initiation of dialysis. After initiation of dialysis, the use of iron therapy increased from 49% of DAS subjects at 1–3 months after initiation of dialysis to 52% at 12 months after dialysis initiation.

Initiation of dialysis

Of the 1795 subjects who initiated dialysis during the study, 1728 (96.3%) received haemodialysis and 67 (3.7%) received peritoneal dialysis. Of the 1795 subjects who initiated dialysis, 763 (42.5%) did so during the first year following commencement of extended dosing, with the annual incidence of dialysis initiation among the remaining NoD subjects declining gradually thereafter (26.0, 15.5, 8.8, 5.7 and 1.2% in each successive year up to 6 years). In the multivariable analysis of baseline predictors of initiating dialysis, predictive factors were as follows: age, high levels of creatinine, low eGFR, low Hb, low serum calcium, high serum phosphorus, renal function at Stages 4 or 5 and prior kidney transplant (see Supplementary data, Table S2).

For the subgroup of subjects who initiated dialysis, Hb concentration and ESA dose are shown in Figure 6. Mean Hb concentration decreased during the months prior to the initiation of dialysis and remained low for the first 3-month interval following dialysis initiation, then increased and stabilized at ~11.5 g/dL. Mean weekly ESA dose was also relatively stable from Month 6 post-dialysis onwards. As expected, with a reduced sample size, wider CIs were observed around both mean Hb concentration and mean weekly ESA dose towards the end of follow-up.

Incidence of renal transplant

Among the 238 subjects who underwent renal transplant, 37 (15.5%) were transplanted in the first year following

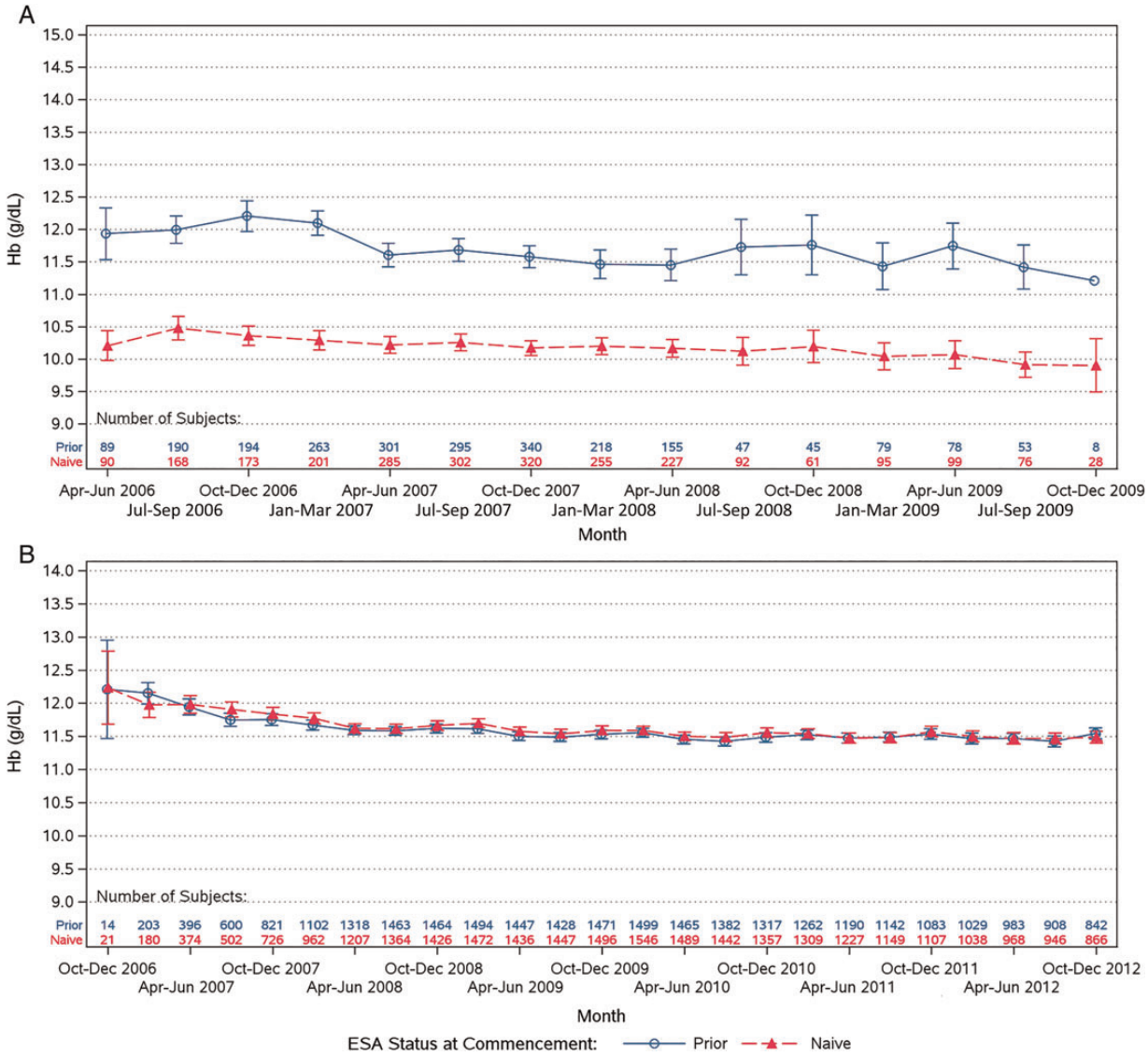

FIGURE 4: Hb at (**A**) commencement of extended dosing and (**B**) achieved by calendar date. Values are arithmetic means with 95% confidence intervals. ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

commencement of extended dosing, and the annual incidence of transplantation was 14.7, 19.3, 23.9, 18.9 and 6.3% in each successive year up to 6 years.

Mortality

A total of 1259 (22.0%) of the 5723 subjects in the FAS died in the follow-up period after commencement of extended dosing, resulting in a mortality rate (95% CI) of 7.06 (6.68, 7.46) deaths per 100 years of follow-up. These deaths comprised 618 (22.5%) prior-ESA subjects and 641 (21.6%) ESA-naïve subjects, with a similar mortality rate in both groups: 6.96 (6.44, 7.54) and 7.14 (6.61, 7.72) per 100 patient-years, respectively. The mortality rate was higher among subjects without prior renal transplant compared with those with prior transplant: 7.68 (7.26, 8.13) versus 2.99 (2.37, 3.77) per 100 patient-years, respectively. Among subjects with known diabetes status, the mortality rate after commencement of extended dosing was higher among diabetics compared with non-diabetics: 8.30 (7.62, 9.03) versus 6.12 (5.63, 6.65) per 100 patient-years, respectively. Among the 1795 subjects who initiated dialysis, the mortality rate in the period after initiation of dialysis was 13.52 (12.39, 14.75) per 100 patient-years.

Cause of death was unknown for 19.2% of subjects. Among subjects with known cause of death, CV reasons were the most common cause overall, regardless of dialysis status (see Supplementary data, Table S3). However, while CV reasons were the most common cause of death in France, Germany and Italy, in the UK and Ireland, infection was the most frequent cause of death. Subjects who survived until the end of the study had stable Hb concentrations in the year preceding end of study, while those who died had lower and declining Hb concentrations in the year preceding death, with a trend for lower Hb concentrations among subjects who died from non-CV causes compared with those who died from CV causes (see Supplementary data, Figure S3). Over the year preceding the last DA dose, the geometric mean DA dose was substantially lower in

Table 3. Number of switches of dosing frequency of DA therapy

Number of switches	Prior-ESA ($n = 2752$)	ESA-naïve ($n = 2971$)	Overall ($n = 5723$)
Within 3 months of commencement of extended dosing, *n* (%)			
0	2331 (84.7)	2496 (84.0)	4827 (84.3)
1	372 (13.5)	436 (14.7)	808 (14.1)
2	44 (1.6)	36 (1.2)	80 (1.4)
3	5 (0.2)	3 (0.1)	8 (0.1)
>3	0 (0.0)	0 (0.0)	0 (0.0)
Within 6 months of commencement of extended dosing, *n* (%)			
0	1920 (69.8)	2041 (68.7)	3961 (69.2)
1	643 (23.4)	757 (25.5)	1400 (24.5)
2	155 (5.6)	141 (4.7)	296 (5.2)
3	22 (0.8)	24 (0.8)	46 (0.8)
>3	12 (0.4)	8 (0.3)	20 (0.3)
Within 12 months of commencement of extended dosing, *n* (%)			
0	1486 (54.0)	1608 (54.1)	3094 (54.1)
1	773 (28.1)	889 (29.9)	1662 (29.0)
2	320 (11.6)	301 (10.1)	621 (10.9)
3	106 (3.9)	111 (3.7)	217 (3.8)
>3	67 (2.4)	62 (2.1)	129 (2.3)

Values are *n* (%). DA, darbepoetin alfa; ESA, erythropoiesis-stimulating agent.

Table 4. Pattern of initial switches of dosing frequency of DA therapy

Dosing frequency	Prior-ESA ($n = 2752$)	ESA-naïve ($n = 2971$)	Overall ($n = 5723$)
Q2W	2449	2552	5001
QW	598 (24.4)	493 (19.3)	1091 (21.8)
QM	661 (27.0)	822 (32.2)	1483 (29.7)
OT	337 (13.8)	318 (12.5)	655 (13.1)
No switch	853 (34.8)	919 (36.0)	1772 (35.4)
QM	303	419	722
QW	37 (12.2)	43 (10.3)	80 (11.1)
Q2W	108 (35.6)	125 (29.8)	233 (32.3)
OT	30 (9.9)	40 (9.5)	70 (9.7)
No switch	128 (42.2)	211 (50.4)	339 (47.0)

Values are *n* (%). DA, darbepoetin alfa; ESA, erythropoiesis-stimulating agent; OT, other frequency; Q2W, once every 2 weeks; QM, once monthly.

subjects who survived to study end than among those who died, and was slightly lower in the 10 months prior to the last dose among subjects who died of CV causes than among those who died from non-CV causes (see Supplementary data, Table S4).

Compared with subjects who survived to study end, those who died had lower TSAT and albumin, and higher serum ferritin and CRP levels; significantly higher CRP levels were especially prevalent among subjects who died of non-CV events (data not shown).

CRP concentration

Among subjects who initiated dialysis and had CRP measurements available ($n = 1269$), CRP concentrations post-dialysis were lower for those with arteriovenous fistulas than for subjects with other access types (see Supplementary data, Table S5). The mean (95% CI) monthly AUC CRP concentrations were lower for subjects with arteriovenous fistulas [20.61 (17.90, 23.32) mg/L] than for those with permanent venous catheters [31.46 (25.20, 37.72) mg/L], but were similar for all other pairwise comparisons of access types.

DISCUSSION

In this analysis of data from 2006 to 2012 for patients in real-life clinical practice receiving DA Q2W or QM at time of enrolment, a stable mean Hb concentration was maintained over time. Mean Hb concentrations were maintained in the prior-ESA subgroup and were corrected and maintained in the ESA-naïve subgroup. Mean achieved Hb with DA extended dosing was similar across subgroups of renal transplant and diabetes status, demonstrating that it was possible to correct and maintain Hb in patient subgroups considered to be more challenging to manage. Nearly two-thirds of subjects had Hb concentrations within the target range of 10–12 g/dL at Months 70–72 following the commencement of DA extended dosing. These effectiveness results support the efficacy findings from clinical studies of DA extended dosing in CKD-NoD patients [12–18].

The calendar analysis revealed that Hb concentrations at the commencement of DA extended dosing declined over time, with the most notable drop following the addition to the US labels for ESAs of a black-box warning regarding greater risks for death and serious CV events when administering ESAs to achieve higher versus lower Hb concentrations in the CHOIR and CREATE clinical studies (13.5 versus 11.3 g/dL and 13–15 versus 10.5–11.5 g/dL, respectively) [9]. Mean achieved Hb concentrations were maintained within the relevant targets set by the EU label applicable at each time point, and were consistent with the European Renal Best Practice (ERBP) Anaemia Working Group's position statement following publication of the TREAT study [7]. These changes suggest that clinicians modified their treatment practice to align with the revised Hb targets.

Compared with prior-ESA subjects, ESA-naïve subjects had lower Hb concentrations at commencement of extended dosing, but by the 4- to 6-month period following commencement of extended dosing, Hb concentrations in ESA-naïve subjects increased to concentrations comparable to those in prior-ESA subjects and remained similar through to the end of the study. Since the 2006 trials suggesting a safety signal regarding treating to high Hb targets, both the Hb concentration at initiation of DA extended dosing and the mean achieved Hb declined, independently of prior ESA use.

Approximately a third of subjects in the FAS (31.4%) initiated dialysis, with initiation mainly seen during the first year of the study. Initiating dialysis was associated with a transient decrease in Hb concentrations and a consequent increase in ESA doses. As could be expected, predictive factors for initiating dialysis in the multivariable analysis were age, high levels of creatinine, low eGFR, low Hb, low serum calcium, high serum phosphorus, renal function at Stages 4 or 5 and prior kidney transplant. Notably, very few subjects who initiated dialysis started peritoneal dialysis (3.7%), far lower than has been reported in countries such as Sweden, where as many as 20.6% of dialysis patients receive continuous ambulatory peritoneal dialysis (data from Swedish Renal Registry 2013). The proportion of all dialysis patients treated with this modality continues to decline in developed countries except Scandinavia [20].

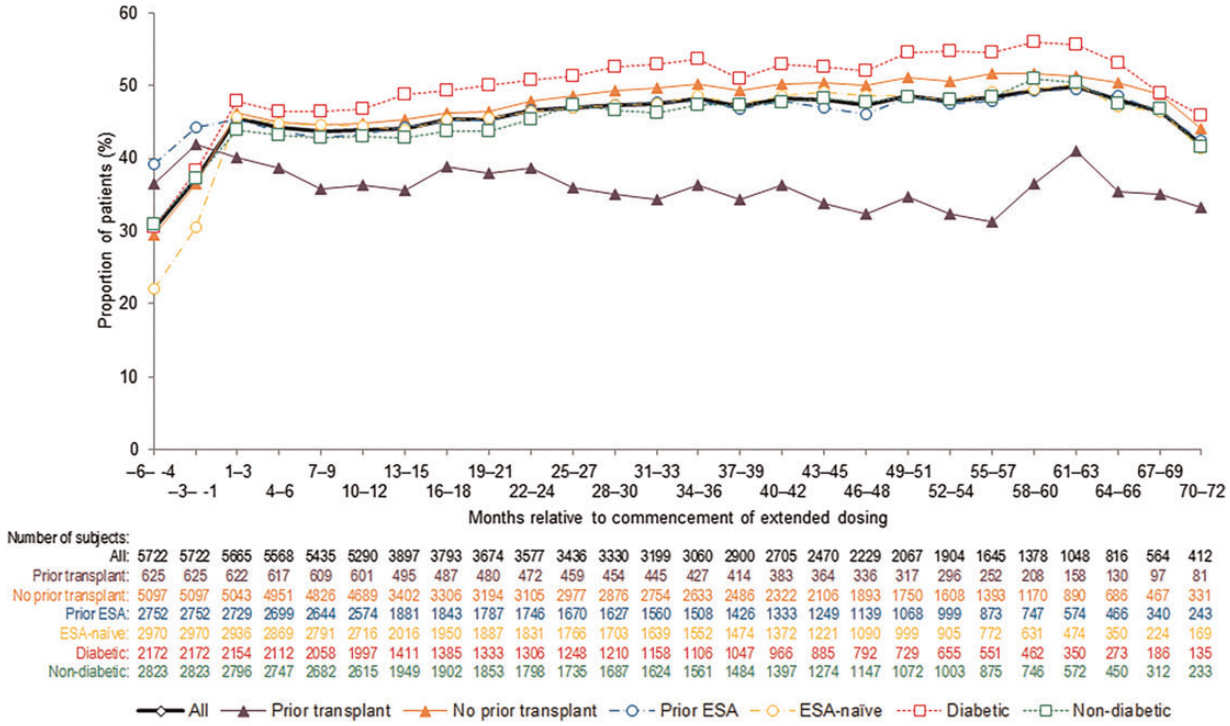

FIGURE 5: Proportion of subjects taking iron therapy relative to commencement of extended dosing. Month numbering is in relation to commencement of extended dosing. ESA, erythropoiesis-stimulating agent.

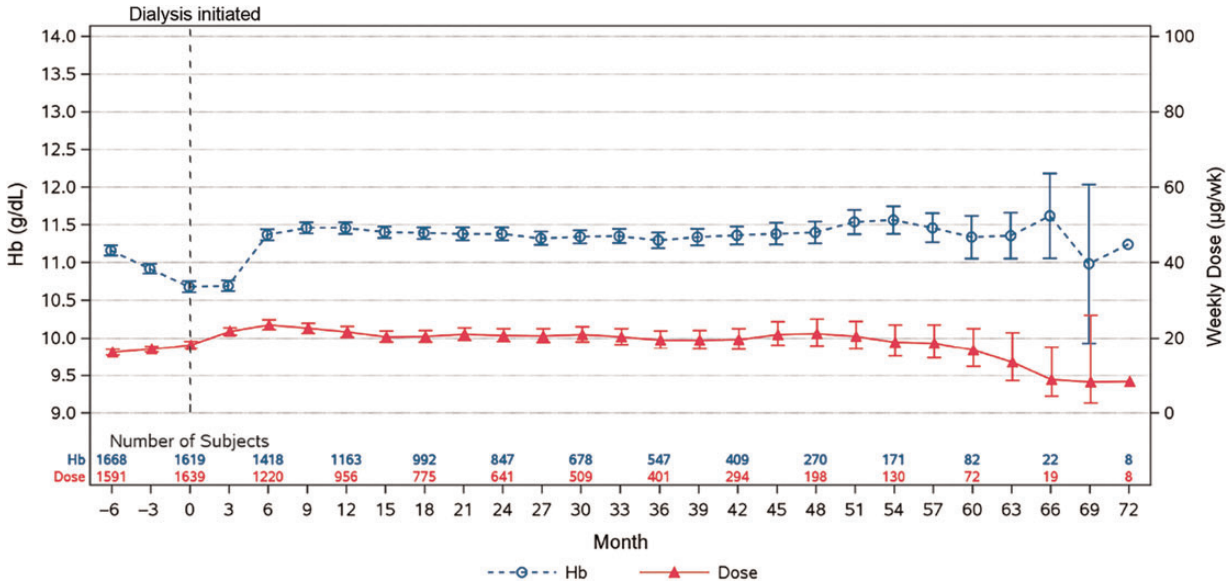

FIGURE 6: Hb concentration and weekly ESA dose at time points relative to initiation of dialysis in the Dialysis Analysis Set (subjects who initiated dialysis during the follow-up period). Values are arithmetic means for Hb and geometric means for ESA dose, with 95% confidence intervals. Month numbering is in relation to initiation of dialysis. DAS, Dialysis Analysis Set; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin.

Only 4.2% (238/5723) of the subjects in the FAS underwent renal transplant over long-term follow-up. This low observed rate of receipt of renal transplant may reflect the high median age of the study cohort (71 years), which can be expected to be a population at increased risk for infection [21] and CV complications [22]. These factors can make transplant procedures inappropriate for many patients who would otherwise be considered for receipt of a graft.

Overall, nearly one-half of subjects received iron supplements, with less use among those with prior renal transplant and non-diabetics. Approximately one-half of subjects were classified as iron inadequate and thus appropriate candidates for iron therapy according to the 2004 ERBP guidelines [23] and the 2009 ERBP position statement on anaemia management in patients with CKD [24]. Meanwhile, recommendations for iron therapy have again been revised since 2012 [25, 26], but

these revised recommendations could not have influenced treatment of the EXTEND population. Prior to commencement of extended dosing, the percentage of subjects receiving iron therapy was higher in the UK and Ireland than in France, Italy or Germany, with a higher percentage of subjects receiving IV iron. Correspondingly, the percentage of subjects with iron adequacy at commencement of extended dosing was higher in the UK and Ireland than in France or Germany (but not higher than in Italy). This observation could at least in part explain the observed trend for higher Hb values at commencement of DA extended dosing in the UK and Ireland, despite lower DA dose, compared with other countries.

CV reasons were the most common cause of death overall and in most countries, regardless of dialysis status. However, subgroup analysis revealed that in the UK and Ireland, infection was a more frequent cause of death than CV reasons, without an obvious reason detectable for this finding.

In accordance with previous data [27, 28], stable Hb concentrations in the year preceding end of study were predictive of better survival, while subjects who died had lower and declining Hb concentrations in the year preceding death. Interestingly, we observed a trend for lower Hb concentrations among those subjects who died from non-CV causes compared with those who died from CV causes. Higher CRP and serum ferritin levels among subjects who died before study end may be interpreted as evidence for inflammation (although elevated CRP may have reflected progression of non-specific inflammation associated with uraemia). Since infection was the most common non-CV cause of death, these observations underline the connection between infection and diminished ESA response [29].

Although we were unable to explain with certainty the lower mortality rate among patients with prior renal transplant, we speculate that study subjects enrolled with a prior transplant were a selected subgroup with a generally better prognosis; the fact that a patient is on a transplant list (or has undergone transplantation already) may be associated with better health and/or younger age, compared with a patient who is not listed for transplantation.

As elevated serum CRP is indicative of infection or inflammation [25], CRP concentrations post-dialysis revealed that infection was also more prominent in subjects who initiated dialysis and whose vascular access modality was either catheter or synthetic fistula rather than arteriovenous fistula. This observation is also consistent with previous findings [30], and underlines the need for arteriovenous fistula to be the preferred access modality.

While DA dosing frequency changes were common, among those subjects who switched dosing frequency, a minority changed to weekly DA dosing (34% of switching subjects who commenced DA Q2W and 21% of switching subjects who commenced DA QM). These results suggest that while most patients commencing DA extended dosing are able to remain on an extended dosing regimen, more frequent dosing may be adopted according to clinical need.

Although the EXTEND study has a number of strengths, most notably a large sample size of CKD-NoD patients treated in clinical practice with no protocol-defined interventions, it is also subject to limitations. The study may be prone to selection bias since subjects had already been deemed suitable to receive ESA at an extended dosing interval; thus, the cohort is not representative of the wider population of CKD-NoD patients. There is also the potential for geographic bias since ~45% of subjects were enrolled at centres in two countries, France and Germany. Finally, as with any observational, uncontrolled study, it is not possible to determine causality in any of the relationships observed, since the results were not compared with a within-study control group of subjects not receiving DA extended dosing.

In conclusion, these long-term data from the EXTEND study support the proposition that CKD-NOD patients with anaemia can be adequately treated with extended dosing of DA to reach and maintain Hb concentrations recommended in treatment guidelines.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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AUTHORS' CONTRIBUTIONS

J.A. contributed to study design; M.F. contributed to study conception and study design; N.M. performed the statistical analysis; all authors contributed to data interpretation, and the drafting, revision and final approval of the manuscript.

CONFLICT OF INTEREST STATEMENT

J.-C.G. has received lecture fees, consultancy fees and travel funding from Amgen. J.A., M.F. and N.M. are employees of Amgen with Amgen stock ownership. M.G.S. has received grants and travel funding from Amgen, Janssen and Roche. K.C. has received travel funding from Amgen and lecture fees from Alexion. S.D.G. reports no potential conflicts of interest. A.G. has received consultancy fees and travel funding from Amgen, and has served on Advisory Boards for Amgen. H.H. has received lecture fees from Amgen, MSD, GSK and AstraZeneca, and has received travel funding from Amgen. I.K. has

received lecture fees from Amgen, Abbot, Boehringer-Ingelheim, EGIS (Hungary), MSD, Richter (Hungary) and Sandoz; has served on Advisory Boards for Amgen, Abbot, EGIS (Hungary), MSD, Richter (Hungary) and Sandoz and has received travel funding from Amgen, EGIS (Hungary) and MSD. G.W. has received lecture fees and travel funding from Amgen and Roche, and consultancy fees from Amgen. C.W. has received grants from Otsuka and Roche. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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