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Every-Other-Week Darbepoetin Alfa in the Correction and Maintenance of Haemoglobin Levels in Elderly Patients with Chronic Kidney Disease:

Post Hoc Subanalysis of Data from Two Clinical Trials

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Abstract

Background: Anaemia is a common complication of chronic kidney disease (CKD) and is associated with increased rates of mortality and diminished quality of life in patients with CKD. Although extended dosing with darbepoetin alfa, an erythropoiesis-stimulating agent (ESA), has been shown to be effective in maintaining haemoglobin (Hb) levels in CKD patients, little information is published on the use of darbepoetin alfa in the correction and maintenance of Hb levels in elderly CKD patients naive to ESA therapy.

Objective: This *post hoc* subanalysis of data from two clinical trials was conducted to investigate the efficacy and safety profile of *de novo* every-other-week (q2w) darbepoetin alfa in elderly patients with CKD-associated anaemia (not on dialysis), as compared with that of a younger (aged <65 years) patient cohort.

Methods: This analysis was based on data obtained from two open-label, single-arm, multicentre studies of similar design. Patients were aged ≥18 years and naive to previous ESA therapy. Darbepoetin alfa administration was initiated at 0.75 µg/kg and titrated according to individual patient requirements to achieve and maintain Hb levels between 11.0 and 13.0 g/dL. The proportion of patients who achieved the primary endpoint, Hb ≥11.0 g/dL (study 1), and an Hb level between 11.0 and 13.0 g/dL (study 2) at weeks 4, 8 and 12 weeks and at the end of the study were determined. The results of this subanalysis were stratified by age (<65, 65–74 and ≥75 years).

Results: A total of 203 patients were enrolled in the two studies; 60% were female, 84 (41%) were aged <65 years, 57 (28%) were aged 65–74 years and 62 (31%) were aged ≥75 years. The proportion of patients who achieved Hb levels of ≥11.0 g/dL in study 1 and 11.0–13.0 g/dL in study 2 at week 20 were 93%, 96% and 92%, respectively, for the three age groups. Weight-adjusted q2w darbepoetin alfa doses were similar between the age groups and stable throughout

the study period. The mean (standard deviation) Hb levels at week 21 were 12.0 (1.2), 12.7 (1.1) and 12.6 (1.0) g/dL in subjects aged <65, 65–74 and ≥75 years, respectively. The median (standard error) time to reach the primary endpoint was 5.0 (4.7), 5.0 (5.7) and 5.0 (5.7) weeks for subjects aged <65 years, 65–74 years and ≥75 years, respectively. The safety profiles of q2w darbepoetin alfa in both the older and younger age-groups were consistent with those expected for patients with CKD not receiving dialysis.

Conclusions: The results of this study suggest that ESA-naïve subjects aged <65, 65–74 and ≥75 years of age with CKD (not receiving dialysis) who received q2w darbepoetin alfa were able to achieve and maintain Hb levels at 11.0–13.0 g/dL. The *de novo* q2w treatment regimen with darbepoetin alfa described in the present report may help optimize anaemia management in CKD-associated anaemia patients, including those in the older adult population.

Background

Chronic kidney disease (CKD) is often associated with several debilitating co-morbidities.^[1] Anaemia, a common complication of CKD, frequently develops as a result of a decrease in the ability of the kidneys to produce the glycoprotein hormone erythropoietin^[2,3] and occurs relatively early during the progression of CKD.^[4,5]

Data from the 1999–2004 National Health and Nutrition Examination Survey (NHANES) report show that the incidence of CKD in the ≥70-year age group is much higher than that in those aged 20–39 years.^[6] The prevalence of CKD shows an age-related increase among elderly long-term care residents.^[7–9] The occurrence of both CKD and anaemia in the elderly is associated with a higher risk of mortality than either CKD or anaemia alone.^[10] Furthermore, anaemia of CKD may also be associated with conditions such as decreased physical performance and muscular strength, recurrent falls, decreased quality of life and adverse clinical outcomes such as increased cardiovascular disease and hospitalizations.^[11–20] Correction of anaemia of CKD in the elderly may improve clinical outcomes;^[21,22] however, prospective studies are required to demonstrate this.

Erythropoiesis stimulating agents (ESAs) have facilitated decreases in blood transfusion rates and have become an integral part of anaemia management. Darbepoetin alfa is an ESA that has a similar mechanism of action to recombinant human erythropoietin (rHuEPO);^[23,24] however, darbepoetin alfa has a unique molecular structure that affords it a longer serum half-life than rHuEPO.^[23] Thus, darbepoetin alfa can be administered at extended dosing intervals. In the US, every-other-week (q2w) administration of darbepoetin alfa has been approved by the US Food and Drug Administration (FDA) for the correction and maintenance of haemoglobin (Hb) levels in anaemic subjects with chronic renal failure. However, little information has been published on correcting and maintaining Hb levels with q2w darbepoetin alfa specifically in elderly subjects with CKD (not receiving dialysis) previously naïve to ESA therapy (ESA-naïve). The purpose of this combined *post hoc* analysis of two studies was to compare the efficacy and safety profile of q2w darbepoetin alfa in ESA-naïve elderly subjects with CKD with that in younger subjects with CKD.

Methods

Study Design

This is a *post hoc* subanalysis of data from two combined studies that have been individually reported elsewhere.^[22,25] The studies were open-label, multicentre, clinical trials conducted in the US and Australia and had similar designs and objectives. The objective of both studies was to evaluate the safety profile and efficacy of darbepoetin alfa, administered *de novo* q2w, in correcting and maintaining Hb levels at >11.0 g/dL (study 1) or 11.0–13.0 g/dL (study 2) in ESA-naïve CKD subjects not receiving dialysis.

The study design of both trials is shown in figure 1. The studies had a 2-week baseline period, followed by a treatment period (18 weeks for study 1 and 23 weeks for study 2) and an end-of-study assessment period (week 21 for study 1 and week 25 for study 2). Subjects received subcutaneous (SC) q2w darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, CA, USA) initiated at 0.75 µg/kg. Darbepoetin alfa doses were rounded to the nearest unit dose of 20, 30, 40, 50, 60, 80, 100, 150, 200 or 300 µg (study 1) or 10, 15, 20, 30, 40, 50, 60, 80 or 100 µg (study 2). Darbepoetin alfa doses were adjusted appropriately to achieve and maintain Hb levels in the target range of 11.0–13.0 g/dL. The target range was similar to ranges previously reported in ESA trials^[22,26] and was consistent with clinical practice at the time the study was designed. Levels of Hb were determined on a q2w basis: for study 1, adjustments were made based on the most recent available Hb levels; for study 2, adjustments were made on the basis of two consecutive Hb levels. If the patient's Hb level was <11.0 g/dL, the darbepoetin alfa dose was increased to the next higher dose. If Hb was >13.0 and ≥14.0 g/dL, the darbepoetin alfa dose was adjusted to the next lower dose. If Hb was >14.0 g/dL, darbepoetin alfa administration was suspended until Hb levels decreased to <13.0 g/dL and then resumed at the next lower dose. Additionally, in study 2, the darbepoetin alfa dose was reduced to the next lower unit dose if the rate of increase in Hb level in a 2-week period was >1.0 g/dL. To ensure that patients were iron replete, iron therapy was encouraged and was administered according to established clinical procedures. Concomitant medications were permitted during the studies.

The study protocol, subject information and informed consent forms were approved by the Institutional Review Board/Independent Ethics Committee for each study centre. The studies were conducted according to the principles of FDA regulations and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines. Written informed consent was obtained from all subjects participating in each of the trials prior to the performance of any study-specific procedures.

Study Subjects

Subjects enrolled in these studies were ≥18 years of age, had a diagnosis of CKD, were not receiving or scheduled to receive dialysis for the duration of the study period, and had an estimated glomerular filtration rate (eGFR) of ≥15 mL/min/1.73 m² and ≤60 mL/min/1.73 m² (study 1) or a creatinine clearance of <40 mL/min (study 2). Additionally, subjects were required to have a mean Hb level of <11.0 g/dL based on two screening/baseline visits, serum vitamin B₁₂ and folate levels above the lower limit of the normal range, and transferrin saturation (TSAT) levels of ≥15% (study 1) and ≥20% (study 2).

Subjects were excluded from the study if they had received ESA therapy within a 12-week period prior to study enrolment, were recipients of (or anticipated/scheduled to receive) a kidney transplant, had uncontrolled hypertension (a diastolic blood pressure determination of >110 mmHg or systolic blood pressure >180 mmHg during screening) or had undergone major surgery within 12 weeks prior to enrolment. Subjects who had the following cardiac conditions were also excluded: acute myocardial ischaemia, hospitalization for congestive heart failure, or myocardial infarction within 12 weeks before enrolment for study 1, and congestive heart failure (New York Heart Association functional class III or IV) for study 2. Additional exclusion criteria included severe hyperparathyroidism (parathyroid hormone level >1500 pg/mL), clinical evidence of malignancy and/or treatment with chemotherapy/radiotherapy other than basal cell or squamous cell carcinoma of the skin and cervical intraepithelial neoplasia, systemic haematological disease, currently taking antibacterial therapy for systemic infection, or being pregnant or lactating. Any subject who tested positive for HIV or hepatitis B surface antigen or who received red blood cell (RBC) transfusions within 8 weeks before enrolment was also excluded.

Study Endpoints

The primary endpoint was the proportion of subjects who achieved an Hb level of ≥ 11.0 g/dL at any study week except for week 1 for study 1, or an Hb level within the range of 11.0–13.0 g/dL at any study week for study 2. Secondary endpoints for both studies included patient Hb levels and darbepoetin alfa doses over the course of the study. Safety endpoints included the frequency of adverse events (AEs) and their possible relationship to darbepoetin alfa treatment.

Study Assessments

Hb levels, AEs and vital signs were evaluated at baseline, at the time of each administration of darbepoetin alfa, and at the end-of-study visit (weeks 21 and 25 for study 1 and study 2, respectively). Specific dose levels of darbepoetin alfa, adjusted according to the individual patient's weight and Hb levels, were recorded at the time of each administration event. A number of options are available for the measurement of bioavailable iron; TSAT was the specific index utilized in the present study. Other laboratory assessments included levels of albumin, ALT, AST, platelets and white blood cells at screening/baseline, week 7 and at the end-of-study visit (weeks 21 and 25 for study 1 and study 2, respectively). Validated anti-erythropoietin antibody bioassays were performed before the start of darbepoetin alfa therapy and also post-treatment and included radioimmune precipitation screening assay (study 1 only) and Biacore® biosensor immunoassays.

Statistical Analysis

Efficacy and safety analyses were performed using data from subjects who received at least one dose of darbepoetin alfa. The proportions of subjects who achieved the target Hb level (≥ 11 g/dL for study 1 and 11.0–13.0 g/dL for study 2) were assessed at weeks 4, 8, 12, 16 and 20. Darbepoetin alfa doses were also assessed at baseline and at week 19 (the last week at which dose information was available for both studies). Exploratory analyses were also conducted for subjects who had at least one Hb level >13.0 or >14.0 g/dL at any time during the study. Efficacy and safety results were stratified by age-group, i.e. <65 , 65–74 and ≥ 75 years.

Descriptive statistics presented include means and standard deviations (SDs), medians and inter-quartile ranges (25th [Q1] and 75th [Q3] percentiles) for continuous variables, and count and percentage for categorical variables. The Kaplan-Meier method was used to calculate the proportion of subjects who achieved an Hb response and the arithmetic method was used to calculate the time to achieve an Hb response. Median darbepoetin alfa doses are reported together with Hodges-Lehmann's distribution-free 95% confidence intervals (CIs). All eGFR levels were calculated using the Modification of Diet in Renal Disease 4-variable equation.^[27] Statistical tests of ANOVA and repeated measures analyses for continuous variables, or chi-squared (χ^2) test for categorical variables were performed to compare results among the three age-groups (i.e. <65 , 65–74 and ≥ 75 years). The Kaplan-Meier log-rank test was used to test for age-group differences in Hb response rates. A statistically significant difference among the three age-groups was supported if the p-value was <0.05 . SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) software was used for all statistical analyses.

Results

Subject Demographics and Baseline Characteristics

A total of 203 subjects enrolled in the two studies; 84 (41%) were aged <65 years, 57 (28%) were aged 65–74 years and 62 (31%) were aged ≥ 75 years. Of these, 69 (82%), 51 (89%) and 52 (84%) subjects in the three age groups, respectively, completed the study (table I).

The primary reason for termination from the study was initiation of dialysis treatment (9 [11%] subjects aged <65 years, 3[5%] aged 65–74 years and 2 [3%] aged ≥75 years).

Subject demographics and baseline characteristics are presented in table II. Females (60%) and Whites (56%) were in the majority. Approximately 59% of the patient population was aged ≥65 years. In general, subjects aged ≥75 years weighed less than the younger age groups. Mean (SD) subject weights were 87.0 (23.3), 80.5 (18.2) and 72.4 (15.5) kg for subjects aged <65, 65–74 and ≥75 years, respectively; differences between the age groups were statistically significant ($p < 0.0001$). Mean (SD) baseline Hb levels were 9.9 (0.7), 9.8 (0.7) and 10.0 (0.6) g/dL for subjects aged <65, 65–74 and ≥74 years, respectively. Mean (SD) baseline eGFR was 24.5 (13.0), 27.9 (13.7) and 27.6 (12.0) mL/min/1.73 m² for the three age groups, respectively. Mean (SD) TSAT levels were 25.9% (6.9%), 25.7% (15.9%) and 26.8% (10.9%) for the three age groups, respectively. Baseline Hb, eGFR and TSAT levels were not significantly different among the three age groups. Most of the subjects were categorized as having stage 3 or stage 4 kidney disease (National Kidney Foundation/Kidney Disease Outcomes Quality Initiative [NKF/KDOQI] classification^[28]). The most common causes of CKD were diabetes mellitus (43%, 56% and 35% of subjects aged <65, 65–74 and ≥75 years, respectively) and hypertension (23%, 25% and 42% of subjects aged <65, 65–74 and ≥75 years, respectively). At screening, iron therapy was administered to 83 (41%) subjects. Intravenous iron was administered to 5 (6%), 0 (0%) and 5 (8%) subjects aged <65, 65–74 and ≥75 years, respectively. Oral iron was administered to 27 (32%), 20 (35%) and 26 (42%) subjects aged <65, 65–74 and ≥75 years, respectively.

Efficacy Results

Hb results are shown in table III. Of the subjects who received at least one dose of darbepoetin alfa, a total (standard error [SE]) of 93% (3%), 96% (3%) and 92% (4%) of patients aged <65, 65–74 and ≥75 years, respectively, had achieved the primary endpoint at week 20 of the study. Mean (SD) Hb levels at week 21 were 12.0 (1.2), 12.7 (1.1) and 12.6 (1.0) g/dL in subjects aged <65, 65–74 and ≥75 years, respectively, with a mean (SD) change of 2.1 (1.3), 2.8 (1.3) and 2.5 (1.1) g/dL, respectively, from baseline. Once corrected, Hb levels remained stable over the course of the studies in all age groups (figure 2). The median (SE) time to achieve the primary endpoint was 5.0 (4.7), 5.0 (5.7) and 5.0 (5.7) weeks for subjects aged <65, 65–74 and ≥75 years, respectively (table III).

At least one Hb level >13.0 or >14.0 g/dL, respectively, was evaluated in 37 (44%) and 17 (20%) of subjects aged <65 years, 28 (49%) and 12 (21%) of subjects aged 65–74 years and 35 (56%) and 19 (31%) of subjects aged ≥75 years. For subjects who had an Hb >13.0 or >14.0 g/dL, respectively, the median time for Hb levels to return to ≤13.0 g/dL was 4 and 8 weeks for subjects aged <65 years, 5 and 8 weeks for subjects aged 65–74 years, and 6 and 6 weeks for subjects aged ≥75 years.

Darbepoetin Alfa Dosage

The mean (SD) q2w darbepoetin alfa doses at week 1 were 64.5 (18.2), 60.7 (15.0) and 58.4 (24.3) µg/q2w for subjects aged <65, 65–74 and ≥75 years, respectively. Mean and median q2w darbepoetin alfa doses differed significantly among the three age groups during the evaluation period ($p = 0.0452$; see table IV). The median (Q1, Q3) q2w darbepoetin alfa dose at week 19, which was the last week for which dose information was available from both studies, was 65 (40, 100), 60 (30, 100) and 45 (20, 80) µg/q2w for the three age groups, respectively. The lower dose observed in the older age-groups was attributed primarily to the lower mean weight of the older age groups compared with subjects in the <65-year age group. No significant differences were observed between the three age groups when

darbepoetin alfa doses were adjusted for weight ($p = 0.6436$). Mean weight-adjusted q2w darbepoetin alfa doses were relatively stable throughout the study period (table IV).

Treatment Safety and Adverse Events

AEs in subjects who received at least one dose of q2w darbepoetin alfa are reported in table V. A total of 66 (79%), 47 (100%) and 48 (77%) subjects aged <65, 65–74 and ≥ 75 years, respectively, were reported to have an AE by the study investigator. Treatment-related AEs were reported in 5 (6%), 4 (9%) and 4 (6%) subjects aged <65, 65–74 and ≥ 75 years, respectively. Serious AEs occurred in 22 (26%) subjects aged <65 years, 15 (32%) subjects aged 65–74 years and 17 (27%) subjects aged ≥ 75 years (table V). None of the serious AEs were considered treatment related by the study investigator.

Six participants died during the study; one subject (aged <65 years) for unknown reasons, three subjects (two aged 65–74 years, one aged ≥ 75 years) from myocardial infarction, one (aged ≥ 75 years) from pulmonary oedema and one (aged ≥ 75 years) from acute renal failure. No deaths were considered to be related to darbepoetin alfa treatment.

Exploratory analysis of subjects who had at least one Hb measurement >13.0 or >14.0 g/dL indicated that 30 (81%) and 14 (82%) subjects aged <65 years, 22 (79%) and 8 (67%) subjects aged 65–74 years, and 26 (74%) and 13 (68%) subjects aged ≥ 75 years, respectively, reported at least one AE (table VI). In general, the specific types and frequencies of AEs in these subjects were similar to the AEs in subjects who never had an Hb measurement >13.0 or >14.0 g/dL.

There were no clinically relevant changes in mean laboratory values and mean vital signs over the course of the study. All bioassay tests for neutralizing antibodies to darbepoetin alfa were negative. Iron therapy was administered to 140 (69%) subjects. Intravenous iron was administered to 15 (18%), 9 (16%) and 7 (11%) subjects aged <65, 65–74 and ≥ 75 years, respectively. Oral iron was administered to 41 (49%), 29 (51%) and 39 (63%) subjects aged <65, 65–74 and ≥ 75 years, respectively.

One subject (1%) aged <65 years, 4 subjects (7%) aged 65–74 years and 5 subjects (8%) aged ≥ 75 years received one RBC transfusion. One subject (1%) aged <65 years received two RBC transfusions, and 1 subject (1%) aged <65 years and 1 subject (2%) aged 65–74 years received ≥ 3 RBC transfusions. Mean (SD) TSAT levels at week 21 were 25.1% (10.4%) in subjects aged <65 years, 24.1% (9.6%) in subjects aged 65–74 years and 32.8% (18.5%) in subjects aged ≥ 75 years, respectively.

Antihypertensive treatments, such as angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) and ACE inhibitors are commonly used in the treatment of CKD patients. Information on these pharmacological interventions was collected in both studies. In brief, 61 (72.6%), 37 (64.9%) and 39 (62.9%) of subjects aged <65, 65–74 and ≥ 75 years, respectively, were taking ACE inhibitors or ARBs. The proportion of subjects in each age group taking either ACE inhibitors or ARBs was found to be not significantly different at the 5% level ($p = 0.4053$). Platelet counts, expressed as mean $\times 10^9/L$ (SD), were 259.87 (86.65), 243.46 (70.52) and 223.03 (81.56) for subjects aged <65, 65–74 and ≥ 75 years, respectively, and were significantly different ($p = 0.0287$) between the three age groups. Additional laboratory measurements, such as ALT, ASP and white blood cell counts, however, indicated no statistically significant differences between the three age groups.

Overall, the safety profile reported for subjects aged 65–74 years and ≥ 75 years was comparable with the safety profile for subjects aged <65 years and consistent with that expected of patients with CKD not receiving dialysis.

Discussion

Darbepoetin alfa administered q2w has been shown to be an effective treatment for anaemia in CKD patients not receiving dialysis. However, although numerous reports have described q2w dosing with darbepoetin alfa,^[22,26,29,30] these analyses have not focused on an elderly cohort previously naive to ESA therapy. To our knowledge, the present report is the first analysis describing the response of an elderly population to de novo q2w administration of darbepoetin alfa.

Both patients who are naive to ESA therapy^[22,26] and patients who were previously treated^[29] have been shown to achieve and/or maintain target Hb levels with q2w darbepoetin alfa. Previous reports have also indicated that Hb levels in elderly subjects with CKD can be maintained with once-monthly darbepoetin alfa administration.^[21,31] This is the first report that describes use of q2w darbepoetin alfa for the correction and maintenance of Hb levels in ESA-naive elderly subjects with CKD not receiving dialysis.

The study described here is the *post hoc* analysis of the combined data from Suranyi et al.^[22] and Silver et al.^[25] The results indicate that a total of 93%, 96% and 92% of ESA-naive elderly patients with CKD (not receiving dialysis) aged <65, 65–74 and ≥75 years, respectively, met the study objectives of achieving and maintaining Hb levels at ≥11 g/dL (study 1) or between 11.0 and 13.0 g/dL (study 2) while taking q2w darbepoetin alfa; these results were similar to those seen in younger subjects with CKD-associated anaemia. Furthermore, the results also suggest that the q2w darbepoetin alfa dosing requirements were similar among subjects aged <65, 65–74 and ≥75 years. The safety profile in subjects aged 64–75 and ≥75 years was similar to that in subjects aged <65 years. The safety profile was also consistent with CKD patients not receiving dialysis. AEs that were considered treatment-related occurred infrequently, and there were no serious AEs that were considered to be treatment related (tables V and VI).

Management of anaemia and identification of optimal Hb target ranges are controversial areas of clinical research,^[32,33] and the risk-benefit ratio of ESA use is the focus of active ongoing study.^[34–41] The current NKF/KDOQI guidelines recommend an Hb target in the range of 11.0–12.0 g/dL, and not to exceed 13.0 g/dL.^[28] The present study had a target range of 11.0–13.0 g/dL.

In the subanalysis of these studies, doses were titrated accordingly when Hb levels were <11.0 or >13.0 g/dL, or were suspended when Hb levels were >14.0 g/dL. Exploratory analysis summarizing the AEs in patients with Hb >13.0 or >14.0 g/dL indicated that the AEs were similar in incidence and severity to those in patients who did not have Hb >13.0 g/dL. However, care must be taken in interpreting these results as the studies were not designed to assess Hb variability or outcomes associated with an Hb level outside the range specified by the studies.

It is also worth mentioning that there are limitations to the statistical analyses presented here. For example, the original two studies comprising this *post hoc* subanalysis were not individually intended or designed to compare the efficacy and safety of darbepoetin alfa between age groups.

Darbepoetin alfa treatment administered q2w may provide greater convenience for elderly individuals, who frequently have multiple comorbidities requiring multiple medications. Initiating anaemia-correction treatment with q2w darbepoetin alfa and maintaining Hb levels with q2w administration can provide a dosing schedule that may be useful for elderly CKD anaemia subjects. Thus, this treatment regimen may help enhance the management of anaemia in community-dwelling and long-term care elderly patients.

Conclusions

The results of this study indicate that *de novo* q2w darbepoetin alfa is a well tolerated and effective treatment for correcting anaemia in older patients with CKD not receiving dialysis.

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Fig. 1.
Design of studies. **Hb** = haemoglobin; **q2w** = every other week.

Fig. 2.
Mean (SD) haemoglobin (Hb) level over time. **a** Includes only subjects from study 2. **n** = number of patients who had Hb levels measured at the specified week.

Table I

Subject disposition

Variable	Age group (y)		
	<65	65–74	≥75
Subjects enrolled (n)	84	57	62
Subjects who completed study [n (%)]	69 (82)	51 (89)	52 (84)
Subjects who discontinued study [n (%)]	15 (18)	6 (11)	10 (16)
dialysis initiated	9 (11)	3 (5)	2 (3)
death	1 (1)	2 (4)	2 (3)
adverse event ^a	1 (1)	1 (2)	2 (3)
lost to follow-up	3 (4)	0 (0)	0 (0)
noncompliance	0 (0)	0 (0)	2 (3)
administrative decision	1 (1)	0 (0)	1 (2)
other	0 (0)	0 (0)	1 (2)

^a Adverse events were not treatment related.

Table II

Subject demographics and baseline characteristics

Variable	Age group (y)		
	<65 (n = 84)	65–74 (n = 57)	≥75 (n = 62)
Gender [n (%)]			
Female	47 (56)	44 (77)	30 (48)
Race [n (%)]			
White	37 (44)	30 (53)	46 (74)
Black	37 (44)	17 (30)	11 (18)
Other	10 (12)	10 (18)	5 (8)
Age (y)			
Mean (SD)	51.0 (10.2)	68.9 (2.7)	80.9 (4.4)
Weight (kg) ^a			
n	84	57	61
Mean (SD)	87.0 (23.3)	80.5 (18.2)	72.4 (15.5)
Hb level (g/dL)			
n	84	57	62
Mean (SD)	9.9 (0.7)	9.8 (0.7)	10.0 (0.6)
TSAT (%)			
n	78	54	60
Mean (SD)	25.9 (6.9)	25.7 (15.9)	26.8 (10.9)
Median (Q1, Q3)	25.0 (21.3, 29.6)	21.2 (18.1, 25.0)	24.6 (19.7, 30.0)
eGFR (mL/min/1.73²) ^b			
n	84	56	61
Mean (SD)	24.5 (13.0)	27.9 (13.7)	27.6 (12.0)
Stages of CKD [n (%)] ^c			
n	84	57	62
Stage 2	0 (0)	1 (2)	1 (2)
Stage 3	27 (32)	18 (32)	22 (35)
Stage 4	40 (48)	28 (49)	33 (53)
Stage 5	17 (20)	9 (16)	6 (10)
Primary cause of CKD [n (%)]			
n	84	57	62
Diabetes mellitus	36 (43)	32 (56)	22 (35)
Hypertension	19 (23)	14 (25)	26 (42)
Glomerulonephritis	6 (7)	4 (7)	0 (0)
Polycystic kidney disease	2 (2)	1 (2)	0 (0)
Other	20 (24)	6 (11)	12 (19)
Unknown	1 (1)	0 (0)	2 (3)

CKD = chronic kidney disease; eGFR = estimated GFR; GFR = glomerular filtration rate; Hb = haemoglobin; Q = quartile; TSAT = transferrin saturation.

^aDifferences in weight between the three age groups were statistically significant ($p < 0.0001$).

^beGFR estimation calculated using the Modification of Diet in Renal Disease equation.^[27]

^cStage 2 CKD defined as GFR of 60–89 mL/min/1.73 m², stage 3 CKD defined as GFR of 30–59 mL/min/1.73 m², stage 4 CKD defined as GFR 15–29 mL/min/1.73 m², stage 5 CKD defined as GFR 0–14 mL/min/1.73 m².

Table III

Haemoglobin (Hb) levels for subjects who received at least one dose of darbepoetin alfa

Variable	Age group (y)			p-Value
	<65 (n = 84)	65-74 (n = 57)	≥75 (n = 62)	
Hb levels (g/dL)				0.37 ^a
n	68	52	53	
at wk 21 [mean (SD)]	12.0 (1.2)	12.7 (1.1)	12.6 (1.0)	
change from baseline to wk 21 [mean (SD)]	2.1 (1.3)	2.8 (1.3)	2.5 (1.1)	
Cumulative percentage (SE) of subjects with Hb levels of 11.0-13.0 g/dL (study 2) or ≥11 g/dL (study 1)				0.78 ^b
by wk 4	39 (5)	25 (6)	34 (6)	
by wk 8	74 (5)	63 (6)	74 (6)	
by wk 12	82 (4)	90 (4)	82 (5)	
by wk 16	92 (3)	96 (3)	90 (4)	
by wk 20	93 (3)	96 (3)	92 (4)	
Median (SE) time to Hb response (wk)	5.0 (4.7)	5.0 (5.7)	5.0 (5.7)	

SE = standard error.^a p-Value refers to age differences over all timepoints, not just wk 21.^b Log rank test/Kaplan-Meier method testing for age differences in time to Hb response.

Table IV

Every-other-week (q2w) darbepoetin alfa doses at weeks 1 and 19

Age group (y)	Variable	Week 1		Week 19	
		darbepoetin alfa dosage (µg/q2w) ^{a,b}	weight-adjusted darbepoetin alfa dosage (µg/kg/q2w) ^{a,c}	darbepoetin alfa dosage (µg/q2w) ^{a,b}	weight-adjusted darbepoetin alfa dosage (µg/kg/q2w) ^{a,c}
<65 (n = 84)	n	84	84	72	72
	Mean (SD)	64.5 (18.2)	0.7 (0.07)	70.0 (58.2)	0.8 (0.6)
	Median (Q1, Q3)	65 (50, 80)	0.7 (0.7, 0.8)	65 (40, 100)	0.7 (0.5, 0.9)
	95% CI of the mean	60, 70	0.73, 0.76	50, 75	0.63, 0.82
65–74 (n = 57)	n	57	57	54	54
	Mean (SD)	60.7 (14.98)	0.8 (0.05)	66.7 (53.2)	0.8 (0.57)
	Median (Q1, Q3)	60 (50, 80)	0.8 (0.7, 0.8)	60 (30, 100)	0.8 (0.4, 1.0)
	95% CI of the mean	55, 65	0.74, 0.76	50, 80	0.59, 0.89
≥75 (n = 62)	n	62	60	54	54
	Mean (SD)	58.4 (24.31)	0.8 (0.29)	56.7 (64.8)	0.7 (0.67)
	Median (Q1, Q3)	55 (50, 60)	0.8 (0.7, 0.8)	45 (20, 80)	0.6 (0.3, 1.0)
	95% CI of the mean	50, 55	0.74, 0.77	35, 60	0.51, 0.8

Q = quartile.

^a p-Values are the repeated measures analysis for age differences in dosage over the duration of the study.

^b p = 0.0452.

^c p = 0.6436.

Table VSummary of adverse events (AEs)^a

Type of AE	Age group (y)		
	<65 (n = 84)	65–74 (n = 47)	≥75 (n = 62)
All AEs	66 (79)	47 (100)	48 (77)
life-threatening AEs	2 (2)	1 (2)	0 (0)
serious AEs	22 (26)	15 (32)	17 (27)
Treatment-related AEs	5 (6)	4 (9)	4 (6)
treatment-related serious AEs	0 (0)	0 (0)	0 (0)
AEs leading to withdrawal	1 (1)	1 (2)	2 (3)
Deaths during study ^{b,c}	1 (1)	2 (4)	3 (5)

^a All data are given as no. (%).^b Includes deaths occurring within 30 days of last dose of darbepoetin alfa.^c No deaths were considered treatment related.

Adverse events (AEs) in subjects with haemoglobin (Hb) levels >13 or >14 g/dL.^a

^z All data are given as no. (%).