SYNOPSIS

Name of Sponsor: Amgen Ltd., Cambridge, United Kingdom

Name of Finished Product: Aranesp®

Name of Active Ingredient: Darbepoetin alfa (formerly known as NESP)

Title of Study: A Study to Evaluate the Efficacy of Converting from Intravenous or Subcutaneous rHuEPO to Intravenous Darbepoetin Alfa (Aranesp®) in Subjects with Chronic Kidney Disease Receiving Haemodialysis

Investigators and Study Centres: Treatment Period 1 of this study was conducted at 26 study centres in Europe (Czech Republic, Poland, and Hungary), 1 of which (401) was closed during Treatment Period 1 because of significant noncompliance with International Conference on Harmonisation for Good Clinical Practice (ICH GCP) regulations/guidelines.

Publication(s): Rutkowski B, Bitterova Z, Ferenczi S, et al. Effectiveness of Converting from Intravenous (iv) or Subcutaneous (sc) Recombinant Human Erythropoietin (rHuEPO) to IV Darbepoetin Alfa (DA) in End Stage Renal Disease (ESRD) Patients (Pts) on Hemodialysis (HD). Poster #TH-PO380, presented at the American Society of Nephrology, Renal Week 2006.

Study Period: Treatment Period 1. 17 May 2005 (first subject enrolled) to 26 April 2006 (the date of the last subject assessment for which data are included in this report)
Treatment Period 2. 01 November 2005 (first subject enrolled) to 05 October 2006 (last visit/last assessment).

Development Phase: 3b

Objectives:

Primary

The primary objective of Treatment Period 1 was to demonstrate that switching subjects receiving haemodialysis with a baseline haemoglobin ≥ 10 g/dL and ≤ 13 g/dL from either subcutaneous (SC) or intravenous (IV) rHuEPO to IV darbepoetin alfa results in a mean haemoglobin > 11.0 g/dL.

The primary objective of Treatment Period 2 was to demonstrate that switching subjects with a haemoglobin > 11.0 g/dL and ≤ 13 g/dL from once-weekly to once-every-2 weeks IV administration of darbepoetin alfa maintains the mean haemoglobin at > 11.0 g/dL.

Secondary

The secondary objectives of Treatment Period 1 were the following:

- to determine the proportion of subjects with a mean haemoglobin > 11.0 g/dL
- to determine the mean change in haemoglobin between Screening/baseline and Evaluation Period 1.
- to assess the safety of switching subjects to IV darbepoetin alfa once-weekly dosing by measurement of adverse events and laboratory parameters

The secondary objectives of Treatment Period 2 were the following:

- to determine the proportion of subjects with a mean haemoglobin > 11.0 g/dL
- to determine the mean change in haemoglobin between Evaluation Period 1 (weeks 21 to 24) and Evaluation Period 2 (weeks 45 to 48)
- to determine the proportion of subjects with a mean haemoglobin level maintained within -1.0 to +1.5 g/dL of the haemoglobin in Evaluation Period 1

- to assess the safety of darbepoetin alfa once every 2 weeks by measurement of adverse events and laboratory parameters

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Methodology: This multi-centre, open-label, non-randomised study enrolled subjects with chronic kidney disease who were receiving dialysis and stable doses of SC or IV rHuEPO 2 or 3 times a week. Enrolled subjects were switched to once weekly IV darbepoetin alfa dosing for 24 weeks (Treatment Period 1). Eligible subjects from Treatment Period 1 entered Treatment Period 2 and were switched to IV darbepoetin alfa dosing once every 2 weeks for a further 24 weeks. Subjects were divided into 2 groups according to route of rHuEPO administration (IV or SC) at study entry. Efficacy was assessed during the final 4 weeks of each treatment period (ie, the evaluation periods [weeks 21 to 24 and 45 to 48]).

Number of Subjects Planned: Two hundred subjects were planned for Treatment Period 1, with a minimum of 70 subjects in each of the rHuEPO groups. Approximately 120 subjects were planned for Treatment Period 2 based on the expected completion rate of Treatment Period 1 and fulfillment of criteria for enrollment into Treatment Period 2.

Number of Subjects Enrolled: Two hundred three subjects were enrolled in the study. However, 1 study centre that enrolled subjects subsequently was closed during Treatment Period 1 as a result of significant ICH GCP noncompliance. Therefore, the principal analyses of efficacy for Treatment Period 1 of the study excluded data from the 16 subjects enrolled at this centre, and 187 subjects were considered enrolled into the study for the purposes of the principal efficacy analyses. Data for these 187 subjects are presented below.

Sex: 79 (42%) women, 108 (58%) men
Mean (standard deviation [SD]; range) Age: 57.9 (15.3; 21 to 87) years
Ethnicity (Race): 186 white, 1 other

Ninety-seven subjects enrolled in Treatment Period 2. Demographic data for these subjects are presented below.

Sex: 42 (43%) women, 55 (57%) men
Mean (standard deviation [SD]; range) Age: 58.9 (13.9; 25 to 84) years
Ethnicity (Race): 96 (99%) white, 1 (1%) other

Diagnosis and Main Criteria for Eligibility: Subjects eligible for Treatment Period 1 were ≥ 18 years of age, diagnosed with chronic disease and receiving haemodialysis for at least 3 months prior to screening, receiving stable doses of rHuEPO administered SC or IV 2 or 3 times weekly, had mean screening haemoglobin concentrations of 10.0 to 13.0 g/dL and adequate iron stores (serum ferritin ≥ 100 µg/L or transferrin saturation ≥ 20%), and had no treatment with SC epoetin alfa in the 12 months before screening. Subjects eligible for Treatment Period 2 had completed Treatment Period 1, were receiving a stable once-weekly dose of IV darbepoetin alfa during Evaluation Period 1 (weeks 21 to 24), had haemoglobin concentrations > 11.0 and ≤ 13.0 g/dL and adequate iron stores at week 24 of Treatment Period 1, and had not received a red blood cell transfusion during study weeks 16 to 24.

Investigational Product, Dose and Mode of Administration: Darbepoetin alfa was provided as a clear, colorless, sterile protein solution in pre-filled syringes containing unit doses of 10, 15, 20, 30, 40, 50, 60, 80, 100,150, or 300 µg. For Treatment Period 1, the starting once-weekly dose of darbepoetin alfa was determined by each subject's total weekly dose of rHuEPO at baseline and was based on an initial conversion factor of 200:1 (units/week rHuEPO: µg/week darbepoetin alfa). For Treatment Period 2, the starting dose (once every 2 weeks) of darbepoetin alfa was twice the weekly dose prescribed during Evaluation Period 1 (weeks 21 to 24). During each treatment period, the dose of darbepoetin alfa was adjusted to achieve and/or maintain a subject's haemoglobin concentration within a target range of > 11.0 to ≤ 13.0 g/dL.

Duration of Treatment: Each study treatment period was 24 weeks, resulting in a total treatment duration of 48 weeks.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was administered in this study.

Study Endpoints

Primary Efficacy:

Treatment Period 1

- mean haemoglobin during Evaluation Period 1 (weeks 21 to 24)

Treatment Period 2

- mean haemoglobin during Evaluation Period 2 (weeks 45 to 48)

Secondary Efficacy:

Treatment Period 1

- the proportion of subjects with a mean haemoglobin > 11.0 g/dL during Evaluation Period 1
- change in haemoglobin between Screening/baseline and Evaluation Period 1
- dose and frequency of darbepoetin alfa administration during Treatment Period 1

Treatment Period 2

- the proportion of subjects with a mean haemoglobin > 11.0 g/dL during Evaluation Period 2
- change in haemoglobin between Evaluation Period 1 (as baseline for Treatment Period 2) and Evaluation Period 2
- the proportion of subjects with a change between the haemoglobin level during Evaluation Period 1 (as baseline for Treatment Period 2) and the haemoglobin level during Evaluation Period 2 within the inclusive range of -1.0 to +1.5 g/dL
- dose and frequency of darbepoetin alfa administration during Treatment Period 2

Exploratory Efficacy:

Treatment Period 1

- the proportion of subjects with a mean haemoglobin > 11.0 g/dL and ≤ 13.0 g/dL during Evaluation Period 1
- the proportion of subjects with a baseline haemoglobin ≤ 11.0 g/dL who achieve a mean haemoglobin > 11.0 g/dL during Evaluation Period 1 with no increases in darbepoetin alfa dose or dose frequency during weeks 1 to 24

Treatment Period 2

- the proportion of subjects with a mean haemoglobin > 11.0 g/dL and ≤ 13.0 g/dL during Evaluation Period 2

Safety:

For Treatment Periods 1 and 2 separately:

- subject incidence and severity of adverse events
- subject incidence of red blood cell transfusions
- laboratory parameters and vital signs

Statistical Methods:

Primary analyses of efficacy were performed using the Full Analysis Set, which was defined for Treatment Period 1 as all subjects who were enrolled into Treatment Period 1 via the interactive voice response system (IVRS) and received at least 1 dose of IV darbepoetin alfa during Treatment Period 1, and was defined for Treatment Period 2 as all subjects who were enrolled into Treatment Period 2 via the IVRS and received at least 1 dose of IV darbepoetin alfa during Treatment Period 2. Secondary analyses of efficacy used the Evaluation Analysis Set, which was defined for Treatment Period 1 as all subjects in the Full Analysis Set who had at least 1 haemoglobin measurement taken during the evaluation period (weeks 21 to 24) and who did not receive any darbepoetin alfa doses via the SC route of administration during Evaluation Period 1, and was defined for Treatment Period 2 as all subjects in the Full Analysis Set

(Treatment Period 2) who had at least 1 haemoglobin measurement taken during Evaluation Period 2 (weeks 45 to 48) and who did not receive any darbepoetin alfa doses at a frequency of more than once every other week during Evaluation Period 2. Safety analyses were performed using the Safety Analysis Set, which was equivalent to the Full Analysis Set for each treatment period. Because Centre 401 was closed as a result of significant ICH GCP noncompliance, all analyses were performed both with and without data from Centre 401. The principal analyses of efficacy excluded data from Centre 401, whereas the principal analyses of safety included data from Centre 401. Data from Treatment Periods 1 and 2 were analyzed separately.

Efficacy
The primary endpoint analysis for each treatment period presented the mean haemoglobin level during the evaluation period together with its 95% confidence interval. Analysis of variance was conducted for Treatment Period 1 to determine the effect of baseline characteristics on the mean haemoglobin level during Evaluation Period 1. Secondary endpoints were summarised using descriptive statistics, including means and their 95% confidence intervals, medians, standard deviations, quartiles, and range for continuous endpoints and proportions and their 95% confidence intervals for categorical endpoints.

Safety
The subject incidence of each adverse event was tabulated by preferred term, severity, and relationship to treatment. The subject incidence of red blood cell transfusions also was tabulated. Laboratory results and vital signs were summarised using descriptive statistics. Darbepoetin alfa dose and frequency during the study also were summarised. The proportion of subjects developing anti-erythropoietic protein antibodies was calculated.

Summary of Results:

Subject Disposition: Treatment Period 1: Two hundred three subjects were enrolled in the study, all of whom received ≥ 1 dose of investigational product. All of these subjects were included in the principal analyses of safety for Treatment Period 1. However, as noted above, 1 study centre (401) that enrolled subjects was closed during Treatment Period 1 as a result of significant ICH GCP noncompliance. Therefore, the principal efficacy analyses for Treatment Period 1 excluded data from the 16 subjects enrolled at Centre 401, and 187 subjects (77 [41%] rHuEPO SC, 110 [59%] rHuEPO IV) were considered enrolled into the study for the purposes of the principal analyses of efficacy for Treatment Period 1. Overall, 172 (92%; 71 [92%] rHuEPO SC, 101 [92%] rHuEPO IV) of the 187 subjects completed Treatment Period 1.

Treatment Period 2: Ninety-seven of the subjects who had completed Evaluation Period 1 were subsequently enrolled in Treatment Period 2; 90 (93%) subjects completed the study. Seven subjects withdrew for reasons that included death (n=3), adverse events (n=2), kidney transplant (n=1), and noncompliance (n=1; evaluation period).

Efficacy Results:

Treatment Period 1:

Note that the following discussion presents results of the principal efficacy analyses that excluded Centre 401.

One hundred eighty-seven subjects (77 [41%] rHuEPO SC, 110 [59%] rHuEPO IV) were included in the Full Analysis Set used in the primary analyses of efficacy for Treatment Period 1. Of these subjects, 172 (71 [92%] rHuEPO SC, 101 [92%] rHuEPO IV) were included in the Evaluation Analysis Set used in secondary analyses of efficacy.

In the overall efficacy results, the mean (95% confidence interval [CI]) haemoglobin concentration during Evaluation Period 1 (weeks 21 to 24) (the primary efficacy endpoint) was 12.0 (11.9, 12.2) g/dL. The percentage of subjects in the Full Analysis Set who had a haemoglobin concentration > 11.0 g/dL increased from 61% (95% CI: 54%, 68%) at baseline to 83% (95% CI: 77%, 88%) during Evaluation Period 1. The mean (95% CI) change in haemoglobin concentration between baseline and Evaluation Period 1 for all subjects in the Full Analysis Set was 0.70 (0.52, 0.88) g/dL. The geometric mean (95% CI) weekly darbepoetin alfa

dose for all subjects in the Full Analysis Set was 28.4 (26.4, 30.5) µg/week at baseline (defined as the first weekly dose administered) and 27.9 (24.7, 31.5) µg/week during Evaluation Period 1, representing a geometric mean change (95% CI) of –2% (-11%, 8%).

Results of analyses of the primary and secondary efficacy endpoints for the Evaluation Analysis Set were generally similar to those for the Full Analysis Set.

In exploratory analyses, 70% (95% CI: 63%, 77%) of subjects in the Full Analysis Set had a mean haemoglobin concentration > 11.0 g/dL and ≤ 13.0 g/dL during Evaluation Period 1. Thirty-four percent (95% CI: 23%, 46%) of subjects in the Evaluation Analysis Set who had a baseline haemoglobin concentration ≤ 11.0 g/dL achieved a mean haemoglobin concentration > 11.0 g/dL during Evaluation Period 1 with no increases in darbepoetin alfa dose or dose frequency during weeks 1 to 24 when missing doses were counted as no increase in dose or frequency. Results were similar when missing doses were imputed as a dose increase or an increase in dosing frequency (32% [95% CI: 22%, 45%].

When the overall efficacy results were evaluated by subjects' prior rHuEPO route of administration, results were similar between the rHuEPO SC and IV groups in all outcome variables.

Primary and Secondary Efficacy Results (Treatment Period 1)

	Switched from rHuEPO SC (N=77)	Switched from rHuEPO IV (N=110)	Total (N=187)
Primary Efficacy			
Evaluation haemoglobin level - g/dL			
Mean (SD)	11.9 (1.2)	12.1 (1.0)	12.0 (1.1)
95% CI	11.6, 12.2	11.9, 12.2	11.9, 12.2
Secondary Efficacy			
Evaluation haemoglobin level > 11.0 g/dL			
n (%)	61 (79)	95 (86)	156 (83)
95% CI, %	68, 88	79, 92	77, 88
Change in haemoglobin concentration between baseline and evaluation			
Mean (SD)	0.72 (1.31)	0.69 (1.21)	0.70 (1.25)
95% CI	0.42, 1.02	0.47, 0.92	0.52, 0.88
Darbepoetin alfa dose - µg/week			
Baseline			
Geometric mean	29.5	27.6	28.4
95% CI	26.4, 33.1	25.1, 30.3	26.4, 30.5
Evaluation			
n	70	101	171
Geometric mean	30.6	26.2	27.9
95% CI	24.9, 37.5	22.5, 30.5	24.7, 31.5
% Change from baseline to evaluation			
n	70	101	171
Geometric mean	6	-7	-2
95% CI	-11, 26	-17, 5	-11, 8
Median	0	0	0

In summary, the results of the efficacy analyses for Treatment Period 1 suggest that mean haemoglobin concentrations of > 11.0 g/dL can be achieved (for subjects who entered the study with a haemoglobin concentration ≤ 11g/dL) or maintained (for subjects who entered the study with a haemoglobin concentration > 11g/dL) in subjects who convert from rHuEPO administered IV or SC 2 or 3 times per week to darbepoetin alfa administered IV once weekly.

Treatment Period 2:

The mean haemoglobin level during the evaluation period was maintained at above 11.0 g/dL with a mean (95% CI) haemoglobin level of 11.1 g/dL (10.9, 11.4). This was lower than the mean (95% CI) haemoglobin level at baseline (ie, Treatment Period 1 evaluation period) which was 12.1 (12.0, 12.2) g/dL.

The percentage (95% CI) of subjects with a mean haemoglobin > 11.0 g/dL during the evaluation period was 56% (45%, 66%). The mean (95% CI) change in haemoglobin from baseline to the evaluation period was a decrease of -0.96 g/dL (-1.20, -0.71).

Geometric mean (95% CI) weekly darbepoetin alfa dose, was 26.8 µg (23.5, 30.5) at baseline (using the first dose in Treatment Period 2) and 34.5 µg (29.2, 40.8) at evaluation, representing an increase of 30% (16%, 45%). The median change in weekly dose was an increase of 25%. Geometric mean (95% CI) weekly weight-adjusted darbepoetin alfa dose was 0.36 µg/kg/wk (0.32, 0.42) at baseline and 0.47 µg/kg/wk (0.39, 0.56) at evaluation. Results were similar when baseline dose was calculated using the last dose in Treatment Period 1.

Of the 91 subjects with dosing data during the evaluation period, 27 (30%) had no change in weekly dose from baseline to evaluation, 9 (10%) had a dose decrease and the remaining 55 (60%) had a dose increase. Dose increases of up to 50% were seen in 25 subjects (27%); increases >50% to 100% were seen in 15 subjects (16%); and increases of >100% in 15 subjects (16%).

The percentage (95% CI) of subjects with a change in haemoglobin from baseline to the evaluation period within the range -1.0 g/dL to +1.5 g/dL was 52% (41%, 62%). Of the remaining 48% (47 subjects), the majority had a change in haemoglobin less than -1.0 g/dL (46 of 47 subjects).

Results indicate that mean haemoglobin can be maintained above 11.0 g/dL when converting from once weekly to once every other week darbepoetin alfa in this patient population; however, there was an overall decrease in mean haemoglobin level from baseline to evaluation accompanied by an overall increase in dose.

Safety Results:

Treatment Period 1

Ninety-three subjects in the rHuEPO SC group and 110 subjects in the rHuEPO IV group received ≥ 1 dose of darbepoetin alfa and were included in the principal analysis of safety (including Centre 401). Of these subjects, 83 [89%] in the rHuEPO SC group and 92 [84%] in the rHuEPO IV group had ≥ 1 adverse event during Treatment Period 1. Most adverse events in both groups were mild to moderate in severity. The most commonly reported adverse events overall were muscle spasms, headache, hypertension, procedural hypertension, procedural hypotension, and blood pressure increased. Treatment-related adverse events were reported for 3 (3%) subjects in the rHuEPO SC group and 12 (11%) subjects in the rHuEPO IV group.

Five (2%) subjects (1 [1%] rHuEPO SC, 4 [4%] rHuEPO IV) died; none of the deaths were considered treatment-related by the investigator. Serious adverse events were reported for 25 (27%) subjects in the rHuEPO SC group and 26 (24%) subjects in the rHuEPO IV group; of these, 3 subjects (1 [1%] rHuEPO SC, 2 [2%] rHuEPO IV) had serious adverse events that were considered treatment-related by the investigator (rheumatoid arthritis and hypertension, arteriovenous graft thrombosis, and arteriovenous fistula thrombosis). Two (1%) subjects (both rHuEPO SC) withdrew from the study due to an adverse event (decreased haemoglobin; catheter-related complication [both considered to be serious and unrelated to investigational product]).

Forty (20%) subjects had a haemoglobin excursion (haemoglobin concentration > 14.0 g/dL) during Treatment Period 1, with a similar percentage of subjects in the rHuEPO SC and IV groups having an excursion (18% and 21%, respectively). Approximately half of these subjects had a single excursion. From the start of the titration period out to week 7, relatively few excursions

were noted (≤ 2 excursions at each visit; 0 at week 1); thereafter, there were generally no less than 4 excursions noted at each visit. Of the 40 subjects with any haemoglobin excursion > 14 g/dL, 11 (of 40; 28%) had values that remained in excess of 13 g/dL for the duration of their participation in the study (rHuEPO SC, 5 subjects; rHuEPO IV, 6 subjects), including 1 subject in the rHuEPO SC group who had a serious adverse event of polycythaemia (range of haemoglobin elevations for this subject: 16.5 to 17.3 g/dL). Overall, the median time to return to a haemoglobin level of ≤ 13 g/dL (after the first value > 14 g/dL) was 4 weeks (range: 1 to 16 weeks; quartiles: 3 and 7 weeks). Twelve (6%) subjects (6 in each rHuEPO group) had ≥ 1 adverse event within 28 days after a haemoglobin excursion. The events were all mild to moderate. In addition to the event of polycythaemia, an adverse event of tendon injury (rHuEPO SC group) was reported as being serious. None of the events were considered related to darbepoetin alfa by the investigator.

Overall, 48 (24%) subjects (27% rHuEPO SC, 21% rHuEPO IV) had at least 1 haemoglobin increase ≥ 2.0 g/dL, 25 (12%) subjects (15% rHuEPO SC, 10% rHuEPO IV) had an increase ≥ 2.5 g/dL, and 14 (7%) subjects (9% rHuEPO SC, 5% rHuEPO IV) had an increase ≥ 3.0 g/dL over any 4-week period during the study. The mean (SD) maximum haemoglobin increase over any 4-week period during the study was similar for the rHuEPO SC and IV groups (1.66 [0.83] and 1.61 [0.89] g/dL, respectively).

Mean clinical laboratory values and mean vital signs did not change notably over the course of the study in either rHuEPO group.

Eighteen (9%) subjects tested positive for binding antibodies before dosing (4 subjects in the rHuEPO SC group; 14 subjects in the rHuEPO IV group): 6 subjects with antibody response to darbepoetin alfa; 5 subjects with antibody response to epoetin alfa; and 7 subjects with an antibody response to both. All tests in the bioassay for neutralizing antibodies were negative at baseline (pretreatment) and week 24 [end of Treatment Period 1].

Treatment Period 2

Ninety percent of the subjects in Treatment Period 2 experienced at least 1 adverse event, with the most common events being muscle spasms, headache, procedural hypertension, and procedural hypotension. Only 3 subjects had adverse events that were considered by the investigator to be treatment related (thrombosis in device [2 subjects] and procedural hypertension [1 subject]).

During Treatment Period 2, 4 (4%) subjects died, 26 (27%) subjects experienced serious adverse events, and 2 (2%) subjects withdrew from the study prematurely due to adverse events; none of these events was considered to be related to the investigational product. The majority of serious adverse events were classified within the body systems of infections and infestations (8%), cardiac disorders (6%), and injury, poisoning and procedural complications (5%). Only 3 serious adverse events were reported for more than 1 subject: pyrexia, arteriovenous fistula thrombosis, and thrombophlebitis were reported for 2 subjects each.

Seven (7%) subjects in Treatment Period 2 had haemoglobin excursions (concentrations > 14 g/dL). Of these subjects, most (4 subjects) had single excursions; there were ≤ 2 haemoglobin excursions noted at each visit in Treatment Period 2 (with the exception of week 48; n=3 excursions). The mean (95% CI) percentage of haemoglobin values > 14.0 g/dL per subject was 1.5% (-0.5%, 3.4%). Of the 7 subjects with haemoglobin excursions, 3 (43%) had values that remained in excess of 13 g/dL for the duration of their participation in the study. Overall, the median time to return to a haemoglobin level of ≤ 13 g/dL (after the first value > 14 g/dL) was 5 weeks (range: 1 to 22 weeks; quartiles: 3 to 5 weeks). All 7 subjects completed the study.

Changes in haematology or chemistry laboratory results from baseline to the end of Treatment Period 2 were otherwise not clinically meaningful. Of the 87 subjects who had antibody results available, 7 had tested positive for binding, non-neutralizing anti-erythropoietic antibodies at both the end of Treatment Period 1 (week 24) and at week 48 (1 anti-darbepoetin alfa, 3 epoetin alfa, 3 with antibody response to both). Two subjects, both in the rHuEPO IV group, who had tested positive for antibodies at week 24 subsequently tested negative at week 48. No subjects

developed an anti-erythropoietic antibody response during Treatment Period 2 (ie, no one had negative binding assay results at week 24, but positive binding assay results at week 48). All subjects tested in the bioassay for neutralizing antibodies were negative at week 48.

In summary, the safety profile of darbepoetin alfa in this study was consistent with that expected for patients with chronic kidney disease who are receiving haemodialysis.