Randomized Evaluation of efficacy and safety of ferric carboxymaltose in Patients with iron deficiency Anaemia and Impaired Renal function (REPAIR-IDA): rationale and study design

Lynda A. Szczech1,2, David B. Bregman3,4, Robert A. Harrington2,5, David Morris6, Angelia Butcher3, Todd A. Koch3, Lawrence T. Goodnough7, Myles Wolf8 and Jane E. Onken2

1Renal Division, Department of Medicine, Duke University Medical Center, Durham, NC, USA, 2Duke Clinical Research Institute, Durham, NC, USA, 3Luitpold Pharmaceuticals, Inc., Valley Forge, PA, USA, 4Department of Pathology, Albert Einstein College of Medicine, Bronx, NY, USA, 5Cardiology Division, Department of Medicine, Duke University Medical Center, Durham, NC, USA, 6WebbWriters, Durham, NC, USA, 7Departments of Pathology and Medicine, Stanford University School of Medicine, Stanford, CA, USA and 8University of Miami Miller School of Medicine, Miami, FL, USA

Correspondence and offprint requests to: Lynda A. Szczech; E-mail: szcze001@mc.duke.edu

Abstract

Background. Patients with iron deficiency anaemia (IDA) in the setting of non-dialysis-dependent chronic kidney disease (NDD-CKD) may benefit from treatment with intravenous (IV) iron. Ferric carboxymaltose (FCM) is a novel IV iron formulation designed to permit larger infusions compared to currently available IV standards such as Venofer® (iron sucrose).

Methods. The primary objective of REPAIR-IDA is to estimate the cardiovascular safety and efficacy of FCM (two doses at 15 mg/kg to a maximum of 750 mg per dose) compared to Venofer® (1000 mg administered as five infusions of 200 mg) in subjects who have IDA and NDD-CKD. REPAIR-IDA is a multi-centre, randomized, active-controlled, open-label study. Eligible patients must have haemoglobin (Hgb) ≤ 11.5 g/dL and CKD defined as (1) GFR < 60 mL/min/1.73 m^2 on two occasions or (2) GFR < 90 mL/min/1.73 m^2 and either evidence of renal injury by urinalysis or elevated Framingham cardiovascular risk score. Two thousand and five hundred patients will be randomized to FCM or Venofer® in a 1:1 ratio. The primary efficacy endpoint is mean change in Hgb from baseline to the highest observed Hgb between baseline and Day 56. The primary safety endpoint is the proportion of subjects experiencing at least one of the following events: death due to any cause, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization or medical intervention, arrhythmias, hypertension or hypotension during the 120 days following randomization.

Conclusion. REPAIR-IDA will assess the efficacy and safety of two 750-mg infusions of FCM compared to an FDA-approved IV iron regimen in patients with NDD-CKD at increased risk for cardiovascular disease.

Keywords: kidney disease; intravenous iron; iron deficiency anaemia

Introduction

Anaemia is a leading cause of morbidity and impaired quality of life associated with chronic kidney disease (CKD). The multifactorial pathogenesis of anaemia in CKD involves inadequate erythropoietin production, excessive blood loss from frequent laboratory evaluations, iron-restricted erythropoiesis, inflammation and shortened red blood cell (RBC) survival [1–5]. While the definition of the diagnosis of anaemia varies across studies, ~1% of patients with a GFR of ~60 mL/min/1.73 m^2, 9% of patients with a GFR of ~30 mL/min/1.73 m^2 and 33 and 67% of men and women with a GFR of ~15 mL/min/1.73 m^2, respectively, met the criteria for anaemia defined as haemoglobin (Hgb) < 12 g/dL for men or < 11 g/dL for women [6]. An estimated 26 million Americans have CKD [7]. Given that ~50% of CKD patients are anaemic [8] and 50% of those have iron deficiency, iron deficiency contributes to anaemia in roughly 6 million American CKD patients [9].

The therapeutic approach to iron deficiency anaemia (IDA) in patients with CKD has undergone significant changes since the approval of erythropoiesis-stimulating agents (ESAs) in 1989. While the product labelling for ESAs has always stressed the necessity to replete iron stores, the clinical importance of attaining adequate iron stores prior to the initiation of ESAs is gaining increased recognition. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin Beta (CREATE) and Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trials demonstrated that
excessive use of ESAs is associated with serious adverse cardiovascular events including congestive heart failure (CHF), stroke and death [10–12]. These findings underscore the importance of appropriately replenishing iron stores as the primary therapeutic strategy for treating IDA in the presence of CKD followed by optimizing ESA dose and RBC response while minimizing cardiovascular side effects.

It is often challenging to sufficiently replenish iron deficits with oral iron due to poor absorption and gastrointestinal side effects. Thus, intravenous (IV) iron is a cornerstone of iron therapy in CKD [13]. Iron dextran (Dexferrum® and INFeD®) may be administered in high doses (1000 mg or more) because of their stable iron–carbohydrate formulation, but risk of anaphylactic reactions can limit their use [14]. Newer iron formulations such as iron sucrose (Venofer®) and iron gluconate (Ferrlecit®) are not associated with anaphylactic reactions but must be administered in lower doses because they have a less stable iron–carbohydrate formulation. The free iron that may accumulate in the blood before it is incorporated into the reticuloendothelial system might result in potential labile iron reaction (hypotension, gastrointestinal symptoms and pain in the back or chest) [15]. In contrast, ferumoxytol (Feraheme®) is a recently approved iron formulation with a stable iron–carbohydrate (modified dextran) formulation that permits rapid administration of up to two 510-mg doses with minimal risk of labile iron reactions [16]. Post-marketing safety experience will be informative since clinical trials excluded patients with a history of iron or multiple drug allergies [17].

Ferric carboxymaltose (FCM) is a stable non-dextran–iron formulation that permits the uptake of iron by the reticuloendothelial system without the release of free iron [18]. It is approved in Europe for the treatment of IDA when oral iron preparations are ineffective or cannot be used. The efficacy and safety of doses of up to 1000 mg in patients with heavy uterine bleeding or post-partum IDA have been documented in Phase II and III trials [18–22]. The Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial provided evidence that FCM can improve symptoms and functional capacity in patients with CHF and iron deficiency [23]. This 24-week trial of 459 patients with New York Heart Association (NYHA) Class II or III CHF showed that correcting iron deficiency with FCM significantly improved NYHA class, 6-min walk distance and patient global assessment compared to placebo. Deaths and adverse events were similar in the FCM and placebo arms. Given these encouraging results, REPAIR-IDA is being undertaken to assess efficacy and safety in CKD patients with IDA who are at high risk for adverse cardiovascular events.

### Trial design and methods

REPAIR-IDA was designed by Luitpold Pharmaceuticals and the Duke Clinical Research Institute (DCRI). All members of the Steering Committee (SC) reviewed the final version of the protocol. Approximately 300 centres in
Table 2. Subject inclusion and exclusion criteria

Inclusion criteria
1. Male or female subjects ≥18 years of age and able to give informed consent.  
2. Chronically impaired renal function as defined by these criteria:  
   a. GFR < 60 mL/min/1.73 m² on two measurements during the screening period (using the MDRD calculation)  
   OR  
   b. GFR < 90 mL/min/1.73 m² on two measurements during the screening period AND EITHER  
   1. Kidney damage as indicated by abnormalities in composition of urine (as documented in the subjects medical history)  
   OR  
   2. Elevated risk of cardiovascular disease (Category 2 or 3) based on the Framingham Model (see Table 1).  
3. Screening visit central laboratory Hgb ≥ 11.5 g/dL.  
   • There will be two screening central labs drawn within 7 days of each other: the average of the Hgb values determined during these draws must be ≤ 11.5 g/dL and the two values must be within 0.7 mg/dL of each other.  
4. Screening ferritin ≤ 100 ng/mL or ≤ 300 when TSAT is ≤ 30%.  
5. If on an ESA a stable dose (±20%) for 4 weeks prior to randomization.

Exclusion criteria
1. Known hypersensitivity reaction to any component of FCM or Venofer®.  
2. Previously randomized in a clinical study of FCM  
3. Requires dialysis for treatment of CKD OR is being considered for initiation of dialysis during the time period of this trial.  
4. No evidence of iron deficiency.  
5. During the 10-day period prior to the first screening visit (or anytime until randomization) has been treated with IV iron.  
6. During the 30-day period prior to screening or during the study period has or will be treated with a RBC transfusion, radiotherapy and/or chemotherapy.  
7. During the 30-day period prior to screening or during the study period has or will require a surgical procedure that necessitates general anaesthesia (other than vascular access surgery).  
8. Any non-viral infection.  
9. Aspartate aminotransferase or alanine aminotransferase at screening as determined by central labs >1.5 times the upper limit of normal (ULN).  
10. Known positive hepatitis with evidence of active disease.  
11. Received an investigational drug within 30 days of screening.  
12. Alcohol or drug abuse within the past 6 months.  
13. Haemochromatosis or other iron storage disorders.  
14. Estimated life expectancy of <6 months or, for cancer patients, an Eastern Cooperative Oncology Group (ECOG) Performance Status >1.

The ECOG Performance Status is defined as follows
0. Fully active, able to carry on all pre-disease activities without restriction.  
1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.  
2. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.  
3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.  
15. Any other laboratory abnormality, medical condition or psychiatric disorder which, in the opinion of the investigator, would put the subject at risk or may result in the subject being unable to comply with study requirements.  
16. Pregnant or sexually active female subjects who are of childbearing potential and who are not willing to use an acceptable form of contraception (s/p tubal ligation or otherwise incapable of pregnancy, hormonal contraceptives, spermicide plus barrier or intrauterine device).

Study design
REPAIR-IDA is a multi-centre, randomized, active-controlled, open-label study that compares the safety and efficacy of IV FCM vs IV Venofer® in subjects who have IDA and CKD (Figure 1). Major inclusion criteria are Hgb ≤ 11.5 g/dL and CKD defined as (1) GFR < 60 mL/min/1.73 m² or (2) GFR < 90 mL/min/1.73 m² and either evidence of renal injury by urinalysis or elevated Framingham cardiovascular disease risk score (Tables 1 and 2). Subjects will be stratified by baseline Hgb (≤ 9, 9.1–10.0, ≥10.1 g/dL), baseline cardiovascular risk [have a history of myocardial infarction (MI), stroke or CHF (yes or no)], erythropoietin use (yes/no) and CKD stage as per the National Kidney Foundation Outcome Quality Initiative (KDOQI) stage of CKD (2, 3–4 or 5) [24] and randomized in a 1:1 ratio to receive either IV FCM or IV Venofer. The FCM group will receive two doses of FCM at 15 mg/kg to a maximum of 750 mg per dose for a maximum total dose of 1500 mg. The Venofer group will receive five doses of Venofer® 200 mg for a total dose of 1000 mg.

Study visits
Subjects will be screened twice (between Days −14 and −1, inclusive) and randomized with administration of first
4. Unstable angina requiring hospitalization

Unstable angina requiring hospitalization will be defined as ischaemic symptoms meeting the following criteria:

1. LASTING ≥ 10 min and considered to be myocardial ischaemia on final diagnosis

2. Requiring unscheduled visit to a healthcare facility and overnight admission (does not include chest pain observation units)

3. At least one of the following:
   - New dynamic ECG changes
   - Ischaemia evidence on stress testing with or without cardiac imaging
   - Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery

5. CHF requiring hospitalization or medical intervention

CHF events will meet the following criteria:

1. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12-h stay (or a date change if the time of admission/discharge is not available).

2. Clinical manifestation of CHF including at least one of the following: New or worsening: dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, oedema, pulmonary basilar crackles, jugular venous distension or radiological evidence of worsening heart failure.

3. Additional/increased therapy
   - IV treatment with diuretic, inotrope or vasodilator therapy
   - OR
   - Mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function) or the use of ultrafiltration, haemofiltration or dialysis that is specifically directed at treatment of heart failure.

6. Arrhythmia will be defined as any symptomatic deviation from normal sinus rhythm experienced by the subject that results in an evaluation by a healthcare provider. The evaluation may include a physical exam during an outpatient visit, an ECG or a hospital admission. Arrhythmias may include any conduction abnormality, atrioventricular heart block, prolongation of QTc interval, supraventricular/nodal arrhythmia, vasovagal episode, ventricular arrhythmia or other cardiovascular arrhythmia.

7. Hypertension

- During the observation period immediately following study drug administration, hypertension will be defined as an increase in systolic blood pressure ≥ 20 mmHg that results in a value >180 mmHg or an increase in diastolic blood pressure ≥ 15 mmHg that results in a value >105 mmHg.

- Following the release of a subject from the study visit during which they are receiving medication, hypertension will be defined as requiring an unscheduled outpatient healthcare visit, a hospital admission or a change in medical therapy (e.g. administration of antihypertensives) in conjunction with the objective criteria a rise in blood pressure (an increase in systolic blood pressure ≥ 20 mmHg that results in a value ≥ 180 mmHg or a increase in diastolic blood pressure ≥ 15 mmHg that results in a value ≥ 105 mmHg).

8. Hypotension

- During the observation period immediately following study drug administration, hypotension will be defined as a decrease in systolic blood pressure ≥ 20 mmHg that results in a value < 90 mmHg or a decrease in diastolic blood pressure ≥ 15 mmHg that results in a value < 50 mmHg.

- Following the release of a subject from the study visit during which they are receiving medication, hypotension will be defined as requiring an unscheduled outpatient healthcare visit, a hospital admission or a change in medical therapy (e.g. fluid/volume repletion, holding of antihypertensives) in conjunction with the objective criteria a decrease in blood pressure (a decrease in systolic blood pressure ≥ 20 mmHg that results in a value < 90 mmHg or a decrease in diastolic blood pressure ≥ 15 mmHg that results in a value < 50 mmHg).

*There will be two baseline blood pressure values utilized to determine if the hypotension or hypertension endpoint has been met. The first baseline is the pre-dose blood pressure from the Day 0 visit. The second baseline is the blood pressure from the most recent (i.e. the latest) study visit. If an iron infusion occurred at that visit, the pre-infusion value will be used to calculate the second baseline.

dose of study drug on Day 0. Treatment visits will occur on Days 3, 7, 11 and 14. Subjects randomized to FCM will receive treatments on Days 0 and 7; subjects randomized to Venofer will receive treatment on five consecutive visits starting on Day 0. Sitting heart rate and blood pressure will be assessed before, immediately following and 30 min af-
ter iron administration while being monitored for serious acute reactions to IV iron such as hypersensitivity or bioactive iron reactions [15,18]. Additional study visits will occur on Days 28, 56, 90 and 120 to assess efficacy and safety.

Additional IV iron dosing
Subjects may receive additional IV iron after Day 56 at the discretion of the investigator [e.g. Hgb < 11 g/dL and either ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) is ≤30%]. Subjects in the FCM group will receive a single dose of FCM, 750 mg (15 mg/kg). Subjects in the Venofer group will receive an additional one- to four-dose course of Venofer, 200 mg (200–800 mg total). No additional iron may be administered between the Day 90 and the Day 120 visits.

Withdrawal and intervention
Any subject who wishes to withdraw from the study may do so at any time without the need to justify their decision. The investigator may withdraw a subject from the trial at any time if it is felt to be in the best interest of the subject.

Intervention is defined as an increase in erythropoietin for any reason (Days 0–56), a blood transfusion or the use of IV or oral iron outside of the protocol. Subjects found to take <30 mg/day of oral iron will not be excluded from subsequent efficacy and safety evaluations but must discontinue the iron supplements at the time it is discovered.

Study objective and primary endpoints
The overall objective of this study is to compare the cardiovascular safety and the efficacy of FCM to Venofer® in subjects with IDA and CKD. The primary efficacy endpoint will be the mean change from baseline to the highest observed Hgb at any time point between baseline and Day 56. The primary safety endpoint will be the proportion of subjects experiencing at least one component of the primary composite safety endpoint following the first dose of study drug. The composite safety endpoint includes all-cause death, non-fatal MI, non-fatal stroke, unstable angina requiring hospitalization, CHF requiring hospitalization or medical intervention, arrhythmia and hypertension or hypotension (Table 3). All potential endpoints will be adjudicated by the DCRI CEC.

Secondary efficacy endpoints include the proportion of subjects achieving an increase in Hgb of ≥1 g/dL any time between baseline and Day 56 or intervention and the mean changes from baseline to the highest observed ferritin and TSAT values any time between baseline and Day 56 or time of intervention. Additional secondary endpoints include the mean change in Hgb, ferritin and TSAT from baseline to the pre-dosing value on Day 7. Secondary safety measures include the number of deaths and reported adverse events as well as the incidence of significant clinical laboratory abnormalities and vital signs (e.g. hypotension or hypertension).

Statistical considerations
Sample size rationale
Based on results of the CHOIR study [12] as well as the Sponsor’s Phase III database for FCM, ~4% of subjects are expected to experience one or more of the events comprising the primary composite safety endpoint. The difference between FCM and Venofer in the proportion of subjects experiencing the primary composite safety endpoint will be assessed with a 95% two-sided confidence interval (CI) constructed with the normal approximation to the bi-
nominal with continuity correction. Using this approach, a sample size of 1250 patients per group will provide evidence of equivalent cardiovascular risk for FCM and Venofer if the 95% CI includes zero. The precision of the estimated treatment group difference can be measured by the width of its 95% CI; decreasing width indicates increasing precision. Figure 2 illustrates that increases in precision of the estimated difference are minimal beyond 1250 subjects per treatment group. The width for event rates of 2, 4 and 8% are provided.

This sample size provides >95% power to demonstrate non-inferiority with a 95% two-sided CI (based on normal distribution) and a non-inferiority margin of 0.2 g/dL for the difference between FCM and Venofer in the mean increase from baseline to the highest observed Hgb any time between baseline and Day 56 or the time of intervention.

Analysis populations

The safety population will consist of all subjects who received a dose of randomized treatment. All safety analyses will be performed with the safety population. The primary population for evaluating all efficacy endpoints will be the intent-to-treat population, defined as subjects from the safety population who have at least one post-baseline Hgb assessment and have a stable (±20%) ESA dose (or are not using ESA) for 4 weeks before randomization.

Efficacy analyses

The non-inferiority of FCM to Venofer for the primary efficacy endpoint (the mean change from baseline to the highest observed Hgb any time between baseline and Day 56) will be assessed with the 95% two-sided CI (based on normal distribution, assuming equal variances). For the secondary endpoint of the proportion of subjects achieving an increase in Hgb of ≥1 g/dL any time between baseline and Day 56 or time of intervention, the treatment difference (FCM vs Venofer) will be estimated with a 95% two-sided CI based on the normal approximation for the binomial distribution, using continuity correction. Non-inferiority will be concluded if the lower limit of the two-sided CI is ≥-0.075. Similar methods will be used for other efficacy endpoints.

Safety analyses

The difference between FCM and Venofer in the proportion of subjects experiencing the primary composite safety endpoint will be assessed with a 95% two-sided CI constructed with the normal approximation to the binomial with continuity correction.

The number and percentage of subjects who report treatment-emergent adverse events will be summarized for each treatment group. Time to the first event comprising the primary composite safety endpoint will be summarized with the Kaplan–Meier approach. The number and percentage of subjects with potentially clinically significant abnormal results will be summarized for clinical laboratory analytes and vital signs.

Key efficacy and safety data (including a tally of the composite endpoint events) will be reviewed at least every 6 months. No statistical adjustments for interim analyses or multiple endpoints will be made.

Exploratory biomarker measurement: FGF23

Fibroblast growth factor 23 (FGF23) is a phosphorus- and vitamin D-regulating hormone that is secreted by osteocytes. Increased secretion of FGF23 stimulates phosphaturia, inhibits parathyroid hormone secretion and decreases circulating levels of 1,25-dihydroxyvitamin D. In syndromes of primary FGF23 excess, increased FGF23 causes hypophosphataemia, calcitriol deficiency and rickets [25]. In contrast, CKD is a state of secondary FGF23 excess in which the elevated FGF23 is thought to be an appropriate compensation that helps maintain normal serum phosphate levels by augmenting fractional excretion of phosphate. However, increased FGF23 levels at the outset of dialysis are independently associated with increased subsequent risk of mortality [26]. The clinical and prognostic significance of FGF23 elevation in pre-dialysis CKD patients is less clear. Baseline FGF23 will, therefore, be measured in all participants using the Immutopics C-terminal assay [27]. This measurement will be correlated with baseline characteristics and trial outcomes in exploratory analyses.

Administration of FCM is associated with transient asymptomatic drops in serum phosphate. For example, in a clinical trial of patients treated with FCM due to IDA secondary to heavy uterine bleeding, the incidence of serum phosphate reductions below 2 mg/dL was 70% (normal value ∼2.5–4.5 mg/dL) [22]. The incidence of values
<2 mg/dL was 8–8.5% in two trials of patients being treated with FCM for post-partum anaemia (data on file). Nadir serum phosphate occurred at ~14 days after administration of FCM, with return to baseline after an additional 14–18 days. Another recent trial of eight patients receiving an IV iron marketed in New Zealand that is very similar to FCM showed a post-treatment decrease in serum phosphate that was caused by a significant increase in FGF23 [28]. The latter study suggests that the mechanism through which IV iron induces hypophosphataemia is increased FGF23. Therefore, in addition to measuring FGF23 at baseline in all participants in the current study, plasma FGF23 levels will also be assessed in ~40 patients in each treatment arm at screening and on Days 7, 14, 28 and 56. Serum phosphate will be assessed in all patients at these treatment visits. Associations between FGF23 levels, baseline characteristics and trial outcomes will be assessed as well as rates of change in FGF23 across the treatment groups in a series of exploratory analyses.

Governance committees

Steering Committee

The SC consists of four to six members including the chair, as well as representation of the sponsor. The functions of the SC will include (1) reviewing and approving the protocol and the statistical analysis plan, (2) decisions regarding continuation of the study based on recommendations from the DSMB and other available information and (3) drafting the manuscript describing the main study results (Table 4).

Data and Safety Monitoring Board

The DSMB is composed of approximately five senior academic individuals with expertise in cardiology, neurology, nephrology, haematology and/or statistics. The DSMB will evaluate interim analyses of the data after the first ~500 patients have been enrolled and regularly thereafter.

Adjudication by the Clinical Events Classification Committee

A CEC Committee will review and adjudicate each suspected endpoint event while blinded to the treatment allocation in this study. The CEC for this trial consists of nephrologists, cardiologists, neurologists or physicians with clinical expertise and prior adjudication experience from the DCRI or other academic institutions. A more senior group of qualified scientists from the DCRI and other academic institutions will prepare the definitions of endpoints and instructions for interpretation and provide ongoing oversight to the CEC members for this trial to ensure that events are adjudicated in consistent fashion over time. Detailed composite endpoint definitions are provided in Table 3.

Discussion

This trial will evaluate the safety and efficacy of FCM among patients with IDA and CKD. Patients with CKD are at elevated risk for cardiovascular disease events and the severity of anaemia has been associated with the magnitude of cardiovascular risk. Given the safety concerns raised in the treatment of anaemia with ESAs [11,12], some have suggested that an ESA dose-sparing approach to anaemia could mitigate this risk [29]. Increased use of IV iron is one of the most efficacious strategies to decrease ESA dose [30,31]. Therefore, the need for iron supplements that are safe is paramount. The power afforded by the 2500 patient sample size should enable this trial of FCM to document the safety and efficacy profile of FCM. Prior iron studies have demonstrated haemodynamic changes associated with IV iron administrations. However, no randomized studies have been undertaken to provide direct comparison across specific iron preparations. This trial will randomize patients to FCM or Venofer, allowing, for the first time, a comparison of two preparations to assess this relative safety.

The upcoming change in the manner in which the centres for Medicare and Medicaid services pays for haemodialysis further emphasizes the critical need for comparative safety data between different iron preparations in CKD patients [32]. Under the proposed final rule, medications to treat anaemia will no longer be billed separately but instead will be included in a single composite payment. Given the relative cost of ESAs compared to IV iron, the greatly reduced reimbursement under the new rule and the cost effectiveness of IV iron over an increase in ESA dose [33], it is likely that IV iron will be used as a frequent ESA-sparing strategy in the near future.

While the trial will be open label, there are several reasons why it will yield unbiased results. First, the composite safety endpoint will be adjudicated by a committee blinded to the treatment allocation. In addition, ascertainment of potential endpoint events will occur via pre-specified triggers on the case report forms so as to minimize the likelihood of differential ascertainment between treatment arms. The primary efficacy endpoint is the objective measure of Hgb, determined via automated laboratory analysis. Lastly, CHOIR and CREATE [10,12] utilized open-label designs and ultimately provided evidence that higher-dose regimens were not preferable to lower-dose regimens, which was not the result anticipated by the sponsors.

The management of anaemia is undergoing evolution. Because of adverse outcomes in trials of ESAs in patients with CKD [11,12] as well as changes in reimbursement for care in patients with ESRD, substantial shifts in the management of anaemia, particularly in outpatients, are expected to occur. Comparative safety data across IV iron products from well-designed randomized trials such as REPAIR-IDA are critical for guiding the informed clinical management of anaemia in CKD.


References

7. Morbidity and mortality weekly report. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5608a2.html (27 January 2010, date last accessed) 2010
10. Shander A, Spence RK, Auerbach M. Can intravenous iron therapy meet the unmet needs created by the new restrictions on erythropoietin stimulating agents? Transfusion 2009

Received for publication: 26.3.10; Accepted in revised form: 29.3.10