An Open-label, Multicentre, Randomised, 3-arm Study to Investigate the Comparative Efficacy and Safety of Intravenous Ferric Carboxymaltose (Ferinject® High- and Low-dosage Regimens) versus Oral Iron for the Treatment of Iron Deficiency Anaemia in Subjects with Non-dialysis-dependent Chronic Kidney Disease

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* To evaluate the long-term efficacy of FCM (using targeted ferritin levels to determine dosing) or oral iron to delay and/or reduce erythropoiesis stimulating agent (ESA) use and/or other anaemia management options in NDD-CKD subjects with iron...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Iron and trace metal metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON39180

Source
ToetsingOnline

Brief title
The FIND-CKD Trial

Condition

- Iron and trace metal metabolism disorders
- Renal disorders (excl nephropathies)

Synonym
iron deficiency anaemia in subjects with non-dialysis-dependent chronic kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: Vifor Pharma - Vifor (International) Inc.
Source(s) of monetary or material Support: Vifor pharma

Intervention

Keyword: chronic kidney disease, iron deficiency anaemia

Outcome measures

Primary outcome

* Time to the initiation of other anaemia management (e.g., ESA or transfusion)

using Kaplan-Meier survival analyses.

Secondary outcome

* Cumulative ESA requirement over the study period.

* Percentage of subjects requiring transfusion at anytime during the study.

* Cumulative iron requirements and number of iron administrations over the

study period.

Study description

Background summary

Chronic kidney disease (CKD) is a progressive loss of renal function over a period of months or years with recognised complications including anaemia and

cardiovascular disease [1,2]. Anaemia (moderate to severe) contributes to much of the morbidity and impaired quality of life (QoL) associated with CKD and patients often suffer from fatigue, angina, decreased exercise tolerance, congestive heart failure, dizziness, and poor appetite [3]. Based on recent assessments, it is estimated that over two-thirds of CKD patients are anaemic for periods of up to 12 months before dialysis [4].
It has been further hypothesised that the anaemia may be, at least in part, due to iron deficiency. Data from Fishbane, et al [5] showed that up to 59% of men and 73% of women are iron deficient whilst Gotloib, et al [6] conducted a smaller study of CKD patients and demonstrated that 46 of 47 with haemoglobin (Hb) <12 g/dL had no evidence of iron deposits in the bone marrow.
Macdougall [7] has recently reported that iron deficiency in CKD is due to a combination of the following:
* Reduced intake of dietary iron;
* Impaired absorption of iron from the gastrointestinal (GI) tract due to hepcidin over activity;
* Medication like omeprazole or phosphate binders.
Anaemia in CKD is traditionally managed by a combination of erythropoiesis stimulating agents (ESAs) and iron therapy, although the relative contribution of each strategy remains unclear. Questions regarding the balance between ESAs and iron therapy have arisen following 2 recent developments: (i) safety concerns regarding ESAs, particularly high dose; and (ii) a new hypothesis suggesting that enhanced thrombogenicity with ESAs may be due to an iron deficiency causing increased platelet counts [8].
Iron therapies include oral and intravenous (IV) preparations. The absorption of oral iron is poor with more adverse effects and often poor compliance. Whilst many preparations exist for IV administration of iron, the profiles, total iron that may be infused and the duration for infusion, differ substantially. Recently, new products such as ferric carboxymaltose (FCM) permit higher doses of iron to be delivered in shorter periods of time.
Whilst anaemia may also be managed using transfusions these should be avoided in order to minimise the risk of human leukocyte antigens sensitisation [9].

Study objective

* To evaluate the long-term efficacy of FCM (using targeted ferritin levels to determine dosing) or oral iron to delay and/or reduce erythropoiesis stimulating agent (ESA) use and/or other anaemia management options in NDD-CKD subjects with iron deficiency anaemia (IDA).

Study design

Open-label, multicentre, randomised, 3-arm design study to assess the use of FCM (using targeted ferritin levels to determine dosing) or oral iron to delay and/or reduce ESA use in NDD-CKD subjects with IDA.
Post an initial screening period (up to 4 weeks) eligible subjects will be

randomised (1:1:2) to 1 of the following 3 treatment arms for a period of 52 weeks.
a) High dosage (1,000 mg of iron) regimen of intravenous FCM targeting a ferritin level of 400-600 mcg/L.
b) Low dosage (200 mg of iron) regimen of intravenous FCM targeting a ferritin level of 100-200 mcg/L.
c) Daily oral iron (200 mg elemental iron).
Within the first 8 weeks (after the first dose of iron therapy), subjects should not initiate an ESA transfusion, or any other treatment for managing haemoglobin (Hb) level. After this initial 8-week period, if the Hb falls below 10 g/dL, additional treatment(s) for managing anaemia should be implemented per institutional practice to achieve and maintain Hb within applicable guideline ranges. Other therapies are also permitted.
Randomisation will be stratified by country.

Intervention

Arm A: FCM - High Dose
Day 0: 1,000 mg iron as FCM (subjects *66 kg to be dosed with 500 mg on Days 0 and 7).
Week 4-52 (dosing every 4 weeks ±4 days with last dose on Week 48): 1,000 mg iron as FCM (subjects *66 kg to be dosed with 500 mg at day of visit and 500 mg 1 week later) when ferritin is <200 mcg/l. If ferritin level is between 200 and <400 mcg/l a dose of 500 mg iron as FCM is to be administered. No dose to be administered if ferritin level is *400 mcg/l.
Arm B: FCM - Low Dose
Day 0: 200 mg iron as FCM.
Week 4-52 (dosing every 4 weeks ±4 days with last dose on Week 48): 200 mg iron as FCM when ferritin is <100 mcg/l. No dose to be administered if ferritin level is *100 mcg/l.
For both Arm A and Arm B, Ferinject dosing only to be initiated if transferrin saturation (TSAT) <40%. For subjects with TSAT >35% from a prior assessment (completed >10 days prior to planned Ferinject administration day) dosing must be withheld until TSAT confirmed as <40%.
Arm C: Daily Oral Iron
Week 0-52: 200 mg elemental iron/day orally.
Full dosing details and administration method for FCM are described in the protocol body.

Study burden and risks

Nausea is the most commonly reported side effect (occurs in about 3.1% of patients). Other known side effects which may occur during FCM administration or after having received FCM, include:
- Common (occurs in 1 to 10% of patients receiving FCM): headache, dizziness, high blood pressure (hypertension), nausea, and/or injection site reactions.

- Uncommon (occurs in 0.1 to 1% of patients receiving FCM): (mild) allergic reaction (hypersensitivity), sensation of pain (paraesthesia), a change in your taste sensation (dysgeusia), high heart rate (tachycardia), low blood pressure (hypotension), redness in the face (flushing), difficulty breathing (dyspnea), vomiting, upset stomach (dyspepsia), abdominal pain, constipation, diarrhea, itching (pruritus), hives (urticaria), redness of the skin (erythema), rash, muscle, joint and/or back pain (myalgia and arthralgia), muscle spasm, fever (pyrexia), tiredness(fatique), chest pain, swelling of the hands and/or the feet (oedema peripheral), pain and/or chills.
- Rare (occurs in 0.01% to 0.1% of patients receiving FCM): severe allergic reactions (anaphylactoid reactions), shivering (rigors) and/or malaise.

As part of the continuing post-marketing surveillance of FCM, the following serious adverse reactions have been observed: fainting (syncope and/or loss of consciousness), dizziness (vertigo), anxiety, face, neck and throat swelling (angioedema and/or face oedema), redness of the skin (dermatitis), being pale (pallor) and severe throat and airway tightness (bronchospasm).

Changes in liver function tests, such as an increase in enzymes called alanine aminotransferase (occurring in 1 to 10% of patients receiving FCM), aspartate aminotransferase, gamma-glutamyl transferase, blood lactate dehydrogenase, and blood alkaline phosphatase (all occurring in 0.1 to 1% of patients receiving FCM). Moreover, a transient decrease in a mineral called blood phosphate has also been observed in 1 to 10% of patients receiving FCM.

The most commonly reported adverse reactions to oral iron (ferrous sulphate) are constipation, darkened or green stools, diarrhea, nausea, upset stomach, stomach, loss of appetite, vomiting and hypersensitivity reactions.

Some known risks related to the blood drawing procedure, although rare, include pain, bleeding, dizziness, fainting, a bruise or infection (phlebitis) at the injection site. It is unknown if the study medication causes any damage to unborn children or nursing infants, therefore female patients must not be pregnant of breastfeeding.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. At least 18 years of age.;2. NDD-CKD subjects with an estimated glomerular filtration rate (eGFR) *60 ml/min/1.73 m2 using modification of diet in renal disease (MDRD) calculation.;3. NDD-CKD subjects with an eGFR loss *12 ml/min/1.73 m2 per year and a predicted eGFR *15 ml/min/1.73 m2 in 12 months. The eGFR loss, defined as *12 mL/min/1.73 m2 per year, should be based on at least 2 appropriately representative values over at least 4 weeks prior to randomisation, ideally 3 values over at least 3 months. If this predicted eGFR decline is *12 mL/min/1.73 m2 per year then subject may be included (*).
The predicted eGFR of *15 mL/min/1.73 m2 in 12 months should be estimated based on previous eGFR values.
If more than 3 eGFR values are available in the 2-year time period prior to randomisation, the predicted eGRF at 12 months should be calculated using 3 appropriately representative values (which will also be recorded in the case report form (CRF)).
4. Any single Hb between 9 and 11 g/dL within 4 weeks of randomisation. Note: A value taken as part of routine medical care may be used.;5. Any single serum ferritin <100 mcg/L or <200mcg/L with TSAT <20% within 4 weeks of randomisation. Note: Measurements taken as part of routine medical care may be used.;6. ESA naïve (no exposure in last 4 months prior to randomisation).;7. Females of child-bearing potential must have a negative pregnancy test (using any medically acceptable assessment) prior to randomisation.;8. Before any study-specific procedure, the appropriate written informed consent must be obtained.;(*) Criterion number 3 is aimed to minimise the likelihood that study participants go on to terminal renal failure (eGFR <15 ml/min/1.73 m2) during the study.

Exclusion criteria

1. History of acquired iron overload.;2. Known hypersensitivity reaction to any component of ferrous sulphate or FCM. Note: subjects with hypersensitivity to other forms of iron will be permitted to participate.;3. Documented history of discontinuing oral iron products due to significant gastrointestinal distress.;4. Screening TSAT >40%.;5. Known active infection, C-reactive protein >20 mg/l, clinically significant overt bleeding, active malignancy (i.e., clinical evidence of current malignancy or not in stable remission for at least 5 years since completion of last treatment with exception of basal cell or squamous cell carcinoma of the skin, and cervical intraepithelial neoplasia).;6. History of chronic alcohol abuse (alcohol consumption >40 g/day).;7. Chronic liver disease and/or screening alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range.;8. Active human immunodeficiency virus/acquired immunodeficiency syndrome OR active hepatitis B or C virus infection (known positive serology to HIV antibodies OR hepatitis B antigen, hepatitis C antibody with clinical signs of active hepatitis).
9. Anaemia due to reasons other than iron deficiency (e.g., haemoglobinopathy). Subject with treated Vitamin B12 or folic acid deficiency are permitted.;10. Intravenous iron and/or blood transfusion in previous 30 days prior to screening (or during the screening period).;11. Oral iron therapy at doses >100 mg/day dosing must be discontinued at least 1 week prior to randomisation. If patient has received this therapy for greater than 3 months (at doses >100 mg/day) then subject is not eligible. Note: Ongoing use of multivitamins containing iron are permitted.;12. Immunosuppressive therapy that may lead to anaemia e.g., cyclophosphamide, azathioprine, mycophenolate mofetil, etc. Note: Steroid therapy is permitted. ;13. Currently requiring renal dialysis.;14. Anticipated dialysis or transplant during the study.;15. Anticipated need for surgery that may result in significant bleeding (>100 ml).;16. Currently suffering from chronic heart failure New York Heart Association (NYHA) Class IV.;17. Poorly controlled hypertension (>160 mmHg systolic pressure or >100 mmHg diastolic pressure).;18. Acute coronary syndrome or stroke within the 3 months prior to screening.;19. Currently suffering from concomitant, severe psychiatric disorders or other conditions which, in the opinion of the Investigator, make;participation unacceptable.;20. Subject is not using adequate contraceptive precautions. Adequate contraceptive precautions are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomised partner.;Non-childbearing potential includes being surgically sterilised at least 6 months prior to the study or post menopausal, defined as amenorrhea for at least 12 months.;21. Subject of child-bearing potential is evidently pregnant (e.g., positive human chorionic gonadotropin test) or is breast feeding.;22. Body weight <35 kg.;23. Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(ies), or subject is receiving other investigational agent(s).;24. Subject will not be available for follow-up assessment.;25. Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-06-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ferinject®
Generic name:	Ferric carboxymaltose (FCM)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Plastufer®
Generic name:	Ferro sulphate monohydrate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	03-06-2010
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2011
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-10-2012
Application type:	Amendment
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Approved WMO Date:	23-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-015579-28-NL
CCMO	NL30126.029.10