A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Patients Admitted for Acute Heart Failure (Affirm-AHF)

Published: 29-11-2016
Last updated: 12-04-2024

Primary Objective(s)* To evaluate, relative to placebo, the effect of intravenous (IV) FCM on repeated heart failure (HF) hospitalisations and cardiovascular (CV) death.Secondary Objective(s)* To evaluate, relative to placebo, the effect of IV FCM...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49709

Source
ToetsingOnline

Brief title
Study to compare use of FCM with placebo in patients with AHF and ID

Condition

- Other condition
- Heart failures

Synonym
Acute heart failure with iron deficiency; Sudden insufficiency of cardiac function associated with low iron content of the blood

Health condition

Iron Deficiency

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Deficient, Failure, Heart, Iron

Outcome measures

Primary outcome

Primary Endpoint

* The composite of recurrent HF hospitalisations and CV death up to 52 weeks

after randomisation

Secondary outcome

The secondary endpoints will evaluate, relative to placebo, the effect of IV

FCM on:

* The composite of recurrent CV hospitalisations and CV death up to 52 weeks

after randomisation.

* HF hospitalisations up to 52 weeks after randomisation (analysed as recurrent

event).

* CV mortality analysed as time to first event at 52 weeks after randomisation.

* The composite of HF hospitalisations or CV death analysed as time to first

event at 52 weeks after randomisation.

* Days lost due to HF hospitalisations or CV death at 52 weeks after randomization.

Other Endpoints

The other endpoints will evaluate, relative to placebo, the effect of IV FCM on:

* The composite of recurrent HF hospitalisations and CV death up to 30 days after randomisation.
* The composite of recurrent CV hospitalisations and CV death up to 30 days after randomisation.
* The composite of HF hospitalisations or CV death analysed as time to first event at 30 days after randomisation.
* The composite of CV hospitalisations or CV death analysed as time to first event at 30 days after randomisation.
* HF hospitalisations up to 30 days after randomisation (analysed as recurrent event).
* HF hospitalisations up to 30 days and 52 weeks after randomisation (analysed as time to first event).
* CV hospitalisations up to 30 days and 52 weeks after randomisation (analysed as recurrent event and time to first event).
* The composite of CV hospitalisations or CV death analysed as time to first event at 30 days and 52 weeks after randomisation
* CV mortality analysed as time to first event at 30 days after randomisation.
* All-cause mortality analysed as time to first event at 30 days and 52 weeks after randomisation.

* Proportion of patients with an event (HF hospitalisations, CV hospitalisations, CV mortality; composite and individual categories).

* Change from baseline in NYHA functional class as assessed at 6, 12, 24 and 52 weeks after randomisation.

* Change from baseline in the Kansas City Cardiomyopathy Questionnaire-12 up to 52 weeks after randomisation.

* Change from baseline in the European quality of life * 5 dimensions questionnaire up to 52 weeks after randomisation.

* Days lost due to HF hospitalisations or CV death at 30 days after randomization.

Safety Endpoints:

* Summary of adverse events (AEs): by system organ class and preferred term (Medical Dictionary for Regulatory Activities (MedDRA) coded term), by severity and relation to study product.

* Summary of serious adverse events (SAEs) by study treatment group presented by system organ class and preferred terms (MedDRA coded term).

* Summary of clinical laboratory panels and cardiac biomarkers (absolute and change from baseline).

Study description

Background summary

Acute heart failure (AHF) constitutes a clinically and economically challenging problem. The prognosis of these patients remains poor, and so far, major clinical trials have failed to improve outcomes in these patients. The current treatment of AHF remained virtually unchanged in recent decades. iron

deficiency (ID) is frequent among patients with HF and predicts poor outcome. Although, there are premises that correction of ID in AHF patients could improve clinical outcomes, it has not been investigated to date.
Sponsor aims to investigate the effect of intravenous Ferric carboxymaltose (IV FCM), relative to placebo on recurrent HF hospitalisations and CV death up to 52 weeks after randomisation in iron deficient subjects hospitalised for AHF.

Study objective

Primary Objective(s)
* To evaluate, relative to placebo, the effect of intravenous (IV) FCM on repeated heart failure (HF) hospitalisations and cardiovascular (CV) death.
Secondary Objective(s)
* To evaluate, relative to placebo, the effect of IV FCM on:
* HF hospitalisations, CV hospitalisations, CV mortality and all-cause mortality.
* Quality of life and New York Heart Association Classification (NYHA).
* Tolerability and safety.

Study design

Multicentre, randomised, double-blind prospective, parallel-group, placebo-controlled, trial with a fixed follow-up of 52 weeks per patient after randomization.

Eligible subjects will be randomised (1:1) to either FCM or placebo using a validated centralised procedure (Interactive Voice response System (IVRS) or Interactive Web-based Randomisation System (IWRS)).
* Active treatment arm: IV FCM
* Control treatment arm: IV NaCl 0.9%

Intervention

- dosing of drug
- venipuncture
- 12-lead Electrocardiogram
- Quality of Life questionnaires

Study burden and risks

In this clinical study the investigational product is ferric carboxymaltose. Ferric carboxymaltose has been on the market since 2007 and over 7,300 patients have already received this medication in clinical studies. There are known side effects that have been seen in patients receiving ferric carboxymaltose. The side effects may be temporary or have permanent consequences.
Known side effects which may occur during ferric carboxymaltose administration

or after having received ferric carboxymaltose include:
- Common side effects (may affect up to 1 in 10 people): headache, dizziness, high blood pressure, nausea, feeling hot (flushing), and reactions around the site of injection such as irritation, pain, bruising or potentially long-lasting brownish discolouration following the leakage of the injection into the skin.
- Uncommon side effects (may affect up to 1 in 100 people): allergic reactions, numbness, tingling or prickling sensation on the skin, a change in your taste sensation, high heart rate, low blood pressure, difficulty breathing, vomiting, indigestion, stomach pain, constipation, diarrhoea, itching, hives, redness of the skin, rash, muscle-, joint -and/or back pain, pain in extremities, muscle spasms, fever, tiredness, chest pain, swelling of the hands and/or the feet, and chills.
- Rare side effects (may affect up to 1 in 1,000 people): severe allergic reactions (symptoms like rash, hives, itching, difficulty breathing, wheezing and/or swelling of the lips, tongue, throat or body), general feeling of discomfort, loss of consciousness, anxiety, fainting, feeling faint, paleness, swelling of the face, and flu-like symptoms like fever, headache and/or feeling ill.

Changes in blood values may occur. The following changes have been reported in clinical trials as side effects:

* Common: decrease in blood phosphorus
* Uncommon: increase in certain liver enzymes called aspartate aminotransferase, gamma-glutamyltransferase, alanine aminotransferase and alkaline phosphatase, and increase in an enzyme called lactate dehydrogenase

Iron medication given directly into a vein can cause severe allergic reactions, which may be potentially fatal. You will therefore be asked to remain in the clinic for observation for 30 minutes after the end of your intravenous injection

Electrocardiogram (ECG)
You can experience skin irritation from the Electrocardiogram (ECG) electrode pads or brief itching when removing then.
Blood drawing procedure
Blood samples will be drawn from a vein in your arm at the scheduled visits by a healthcare professional. Some known risks, although rare, can be associated with the blood drawing procedure: pain at the injection site, bleeding, a burning sensation, dizziness, fainting, a bruise or an infection at the site where the needle was inserted to take the blood could occur. The maximum total amount of blood to be drawn for study purposes is 50 mL/ approx. 10 teaspoons for 5 samples

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 Currently hospitalised for an episode of acute heart failure (AHF) where AHF was the primary reason for hospitalisation. All of the following (i.e., items a to d) must apply:;a. Upon admission for the AHF episode, persistent dyspnoea at rest in a recumbent sitting position (30-45°) or with minimal exertion;b. Upon or during the AHF admission, at least two (2) of the following clinical findings were present:;i. Congestion on chest x-ray;ii. Rales on chest auscultation;iii. Oedema *1+ on a 0-3+ scale, indicating indentation of skin with mild digital pressure that requires 10 or more seconds to resolve in any dependent area including extremities or sacral region;iv. Elevated jugular venous pressure (*8 cm H2O);c Natriuretic peptide levels, measured *24 hours of the AHF admission must have been:;i. Brain natriuretic peptide (BNP) *400 pg/mL or N-terminal-pro-brain natriuretic peptide (NT-proBNP) *1,600 pg/mL or ;ii. BNP *600 pg/mL or NT-proBNP *2,400 pg/mL for subjects presenting with atrial fibrillation when the blood sample was taken;d AHF episode treated with minimally 40 mg of

IV furosemide (or equivalent IV loop diuretic defined as 20 mg of torsemide or 1 mg of bumetanide);2. Subject is iron deficient defined as serum ferritin <100 ng/mL or 100 ng/mL * serum ferritin *299 ng/mL if TSAT <20%.;3. Left ventricular ejection fraction <50% (assessed and documented within 12 months prior to randomisation).;4. Male or female aged *18 years old.;5. Subject (or legally acceptable representative)* has provided the appropriate written informed consent. Subject must provide written informed consent before any study-specific procedures are performed. *Following section in Italics are applicable for the Netherlands only (NL only): The option that legally accepted representatives of subjects can sign the written informed consent is not valid for sites in the Netherlands

Exclusion criteria

1. Dyspnoea due to non-cardiac causes such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, acute bronchitis, pneumonia, primary pulmonary hypertension).;2. Temperature >38°C (oral or equivalent), active infective endocarditis, sepsis, systemic inflammatory response syndrome, or any other active infection requiring anti-microbial treatment at any time during an Index hospitalisation.;3. Clinical evidence of acute coronary syndrome, transient ischemic attack or stroke, within the last 30 days prior randomisation.;4. Coronary-artery bypass graft, cardiac resynchronisation therapy device implantation, percutaneous intervention (e.g., cardiac, cerebrovascular, aortic; diagnostic catheters are allowed) or major surgery that led to significant blood loss, including thoracic and cardiac surgery, within the last 3 months prior to randomisation.;5. Subject has a body weight <35 kg at randomisation.;6. Subject at an immediate need of transfusion or with a Hb <8 g/dL* or with a Hb >15 g/dL.;7. Subject with a known anaemia not attributed to ID (e.g., other microcytic anaemia) or with an evidence of iron overload (e.g., haemochromatosis) or disturbances in the utilisation of iron.;8. Subject has known hypersensitivity to any of the study products to be administered or known serious hypersensitivity to other parenteral iron products.;9. Renal dialysis (previous, current or planned within the next 6 months).;10. Chronic liver disease (including active hepatitis) and/or alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range.;11. Subjects with known hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity.;12. Subject is pregnant (e.g., positive human chorionic gonadotropin
test) or breast feeding.;*Following section in Italics are applicable for the Netherlands only (NL only): The lower threshold of Hb values is set to 10 g/dL.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-06-2017
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	0.9 % sodium chloride = normal saline
Generic name:	0.9 % sodium chloride = normal saline
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ferinject
Generic name:	FERRIC CARBOXYMALTOSE
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	29-11-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	21-03-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-06-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2016-001467-36-NL
ClinicalTrials.gov	NCT02937454
CCMO	NL59598.100.16

Study results

First publication
05-03-2021