



Clinical trial results:

A Phase III, Randomized, Multicenter, Double-Blind, Safety Study of Ferumoxytol Compared to Ferric Carboxymaltose for the Treatment of Iron Deficiency Anemia (IDA)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-000831-41 |
| Trial protocol | HU LV LT PL |
| Global end of trial date | 17 July 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 29 November 2018 |
| First version publication date | 29 November 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | AMAG-FER-IDA-304 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02694978 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AMAG Pharmaceuticals, Inc. |
| Sponsor organisation address | 1100 Winter Street, Waltham, United States, 02451 |
| Public contact | Medical Information, AMAG Pharmaceuticals, Inc., +1 877-411-2510, amag@druginfo.com |
| Scientific contact | Medical Information, AMAG Pharmaceuticals, Inc., +1 877-411-2510, amag@druginfo.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 January 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 January 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 July 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of 1.020 grams (g) of intravenous (IV) ferumoxytol compared to 1.500 g of IV ferric carboxymaltose (FCM).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 29 February 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Poland: 34 |
| Country: Number of subjects enrolled | Hungary: 34 |
| Country: Number of subjects enrolled | Latvia: 122 |
| Country: Number of subjects enrolled | Lithuania: 111 |
| Country: Number of subjects enrolled | United States: 1661 |
| Country: Number of subjects enrolled | Canada: 35 |
| Worldwide total number of subjects | 1997 |
| EEA total number of subjects | 301 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |

| | |
|----------------------|------|
| Adults (18-64 years) | 1343 |
| From 65 to 84 years | 553 |
| 85 years and over | 101 |

Subject disposition

Recruitment

Recruitment details:

Participants with IDA, <12.0 g per deciliter (dL) for females and <14.0 g/dL for males within 60 days of dosing and transferrin saturation <20% or Ferritin ≤100 nanograms per milliliter (mL) within 60 days of dosing and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used.

Pre-assignment

Screening details:

Participants were screened for inclusion in this study either on or up to 30 days prior to the start of dosing with study drug (either ferumoxytol or FCM).

Period 1

| | |
|------------------------------|--|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind ^[1] |
| Roles blinded | Subject, Data analyst, Carer, Assessor |

Blinding implementation details:

This study was double blind with respect to treatment assignment; all study participants (study participant, study staff, including the physician, and all non-study individuals) with the exception of the test article preparer and the unblinded monitor were blinded to the treatment assigned to each participant.

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ferumoxytol |

Arm description:

Participants received an IV infusion of ferumoxytol 510 milligrams (mg) diluted (17 mL) in 233 mL 0.9% sodium chloride injection, United States Pharmacopeia (USP) (normal saline) (final volume 250 mL) over at least 15 minutes with a second dose 7-8 days after the first dose, for a total cumulative dose of 1.020 g.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ferumoxytol |
| Investigational medicinal product code | Feraheme |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Intravenous infusion of ferumoxytol 510 mg diluted (17 mL) in 233 mL 0.9% sodium chloride injection, USP (normal saline) to a final volume of 250 mL, over at least 15 minutes with a second dose 7-8 days after Dose 1, for a total cumulative dose of 1.020 g.

| | |
|------------------|-----------------------------|
| Arm title | Ferric Carboxymaltose (FCM) |
|------------------|-----------------------------|

Arm description:

Participants received an IV infusion of FCM 750 mg diluted (15 mL) in 235 mL 0.9% sodium chloride injection, USP (normal saline) (final volume 250 mL) over at least 15 minutes with a second dose 7-8 days after the first dose, for a total cumulative dose of 1.500 g.

| | |
|--|-----------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Ferric Carboxymaltose |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Intravenous infusion of FCM 750 mg diluted (15 mL) in 235 mL 0.9% sodium chloride injection, USP (normal saline) to a final volume 250 mL, over at least 15 minutes with a second dose 7-8 days after Dose 1, for a total cumulative dose of 1.500 g.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: This study was double blind with respect to treatment assignment; all study participants (study participant, study staff, including the physician, and all non-study individuals) with the exception of the test article preparer and the unblinded monitor were blinded to the treatment assigned to each participant.

| Number of subjects in period 1 | Ferumoxytol | Ferric Carboxymaltose (FCM) |
|--|-------------|-----------------------------|
| | | |
| Started | 997 | 1000 |
| Received at Least 1 Dose of Study Drug | 997 | 1000 |
| Completed | 935 | 948 |
| Not completed | 62 | 52 |
| Adverse event, serious fatal | 4 | 1 |
| Consent withdrawn by subject | 22 | 19 |
| Other-Decision of Participant | 6 | 1 |
| Adverse event, non-fatal | 10 | 9 |
| Other-Unable To Be Reached | - | 1 |
| Other-Investigator's Decision | 1 | - |
| Other-Personal Reasons | 3 | 3 |
| Other-Protocol Noncompliant | 2 | 1 |
| Lost to follow-up | 14 | 17 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Ferumoxytol |
|-----------------------|-------------|

Reporting group description:

Participants received an IV infusion of ferumoxytol 510 milligrams (mg) diluted (17 mL) in 233 mL 0.9% sodium chloride injection, United States Pharmacopeia (USP) (normal saline) (final volume 250 mL) over at least 15 minutes with a second dose 7-8 days after the first dose, for a total cumulative dose of 1.020 g.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Ferric Carboxymaltose (FCM) |
|-----------------------|-----------------------------|

Reporting group description:

Participants received an IV infusion of FCM 750 mg diluted (15 mL) in 235 mL 0.9% sodium chloride injection, USP (normal saline) (final volume 250 mL) over at least 15 minutes with a second dose 7-8 days after the first dose, for a total cumulative dose of 1.500 g.

| Reporting group values | Ferumoxytol | Ferric Carboxymaltose (FCM) | Total |
|--|-------------|-----------------------------|-------|
| Number of subjects | 997 | 1000 | 1997 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 657 | 686 | 1343 |
| From 65-84 years | 286 | 267 | 553 |
| 85 years and over | 54 | 47 | 101 |
| Age continuous Units: years | | | |
| arithmetic mean | 55.6 | 54.8 | |
| standard deviation | ± 17.30 | ± 17.02 | - |
| Gender categorical Units: Subjects | | | |
| Female | 743 | 776 | 1519 |
| Male | 254 | 224 | 478 |

End points

End points reporting groups

| | |
|---|----------------------------------|
| Reporting group title | Ferumoxytol |
| Reporting group description: Participants received an IV infusion of ferumoxytol 510 milligrams (mg) diluted (17 mL) in 233 mL 0.9% sodium chloride injection, United States Pharmacopeia (USP) (normal saline) (final volume 250 mL) over at least 15 minutes with a second dose 7-8 days after the first dose, for a total cumulative dose of 1.020 g. | |
| Reporting group title | Ferric Carboxymaltose (FCM) |
| Reporting group description: Participants received an IV infusion of FCM 750 mg diluted (15 mL) in 235 mL 0.9% sodium chloride injection, USP (normal saline) (final volume 250 mL) over at least 15 minutes with a second dose 7-8 days after the first dose, for a total cumulative dose of 1.500 g. | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Any randomized participant who received any amount of study drug. Treatment group was based on actual treatment. | |
| Subject analysis set title | Intent-to-treat (ITT) Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Any randomized participant who had any exposure to study drug, based on randomized treatment assignment. | |

Primary: Participants With Treatment-Emergent (TE) Moderate To Severe Hypersensitivity Reactions (Rxns), Including Anaphylaxis, Or Moderate To Severe Hypotension

| | |
|--|--|
| End point title | Participants With Treatment-Emergent (TE) Moderate To Severe Hypersensitivity Reactions (Rxns), Including Anaphylaxis, Or Moderate To Severe Hypotension |
| End point description: All IV iron formulations carry some risk of serious hypersensitivity reactions or anaphylaxis. Signs and symptoms potentially representing hypersensitivity were recorded and adjudicated by a blinded Clinical Events Committee (CEC). Hypotension is defined as a >30% drop in systolic blood pressure from baseline or decrease of >20 mmHg for systolic blood pressure. Statistical analysis was only performed on composite data. A summary of serious and all other non-serious adverse events regardless of causality is located in the Reported Adverse Events module. | |
| End point type | Primary |
| End point timeframe: Day 1 (after first dosing) through Week 5 | |

| End point values | Ferumoxytol | Ferric Carboxymaltose (FCM) | | |
|------------------------------------|--------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 997 ^[1] | 1000 ^[2] | | |
| Units: Participants | | | | |
| Moderate hypersensitivity reaction | 3 | 6 | | |
| Severe hypersensitivity reaction | 1 | 0 | | |
| Anaphylaxis | 0 | 0 | | |
| Moderate hypotension | 2 | 1 | | |

| | | | | |
|--|---|---|--|--|
| Severe hypotension | 0 | 0 | | |
| Any TE moderate to severe hypersensitivity rxn | 6 | 7 | | |

Notes:

[1] - Safety Population

[2] - Safety Population

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Ferumoxytol/Ferric Carboxymaltose (FCM) |
| Statistical analysis description: | |
| Statistical analysis was only performed on composite reaction data (that is, the "Any TE moderate to severe hypersensitivity rxn" row in the data table) | |
| Comparison groups | Ferumoxytol v Ferric Carboxymaltose (FCM) |
| Number of subjects included in analysis | 1997 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.0001 |
| Method | Wald large sample assumption |
| Parameter estimate | Treatment difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.61 |

Secondary: Participants With Moderate To Severe Hypersensitivity Reactions, Including Anaphylaxis, Serious Cardiovascular Events, And Death

| | |
|---|--|
| End point title | Participants With Moderate To Severe Hypersensitivity Reactions, Including Anaphylaxis, Serious Cardiovascular Events, And Death |
| End point description: | |
| All IV iron formulations carry some risk of serious hypersensitivity reactions or anaphylaxis. Signs and symptoms potentially representing hypersensitivity were recorded and adjudicated by a blinded CEC. A summary of serious and all other non-serious adverse events regardless of causality is located in the Reported Adverse Events module. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 (after first dosing) through Week 5 | |

| End point values | Ferumoxytol | Ferric Carboxymaltose (FCM) | | |
|------------------------------------|--------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 997 ^[3] | 1000 ^[4] | | |
| Units: Participants | | | | |
| Moderate hypersensitivity reaction | 3 | 6 | | |
| Severe hypersensitivity reaction | 1 | 0 | | |

| | | | | |
|---|----|----|--|--|
| Anaphylaxis | 0 | 0 | | |
| Serious cardiovascular event | 6 | 13 | | |
| Death | 4 | 2 | | |
| Any moderate to severe hypersensitivity rxn | 13 | 20 | | |

Notes:

[3] - Safety Population

[4] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change In Hemoglobin From Baseline To Week 5

| | |
|-----------------|---|
| End point title | Mean Change In Hemoglobin From Baseline To Week 5 |
|-----------------|---|

End point description:

Mean change in hemoglobin from Baseline to Week 5 was calculated for each participant as: Hemoglobin Change = Hemoglobin (Week 5) – Hemoglobin (Baseline). Baseline was defined as the Day 1 value (prior to injection of study drug). The screening or most recent value prior to Day 1 was used for any participant with missing Day 1 information.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Week 5

| End point values | Ferumoxytol | Ferric Carboxymaltose (FCM) | | |
|---|--------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 997 ^[5] | 1000 ^[6] | | |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change In Hemoglobin From Baseline To Week 5 | 1.38 (± 1.351) | 1.63 (± 1.535) | | |

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change In Hemoglobin Per Gram Of Iron Administered From Baseline To Week 5

| | |
|-----------------|---|
| End point title | Mean Change In Hemoglobin Per Gram Of Iron Administered From Baseline To Week 5 |
|-----------------|---|

End point description:

Mean change in hemoglobin per g of iron administered from Baseline (Day 1) to Week 5 was calculated for each participant as: Hemoglobin Change = Hemoglobin (Week 5) – Hemoglobin (Baseline). Baseline was defined as the Day 1 value (prior to injection of study drug). The screening or most recent value prior to Day 1 was used for any participant with missing Day 1 information.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Week 5

| End point values | Ferumoxytol | Ferric Carboxymaltose (FCM) | | |
|--|--------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 997 ^[7] | 1000 ^[8] | | |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change In Hemoglobin Per Gram Of Iron Adminis | 1.35 (± 1.353) | 1.10 (± 1.050) | | |

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (after first dosing) through Week 5

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Ferumoxytol |
|-----------------------|-------------|

Reporting group description:

Participants received an IV infusion of ferumoxytol 510 mg diluted (17 mL) in 233 mL 0.9% sodium chloride injection, USP (normal saline) (final volume 250 mL) over at least 15 minutes with a second dose 7-8 days after the first dose, for a total cumulative dose of 1.020 g.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Ferric Carboxymaltose (FCM) |
|-----------------------|-----------------------------|

Reporting group description:

Participants received an IV infusion of FCM 750 mg diluted (15 mL) in 235 mL 0.9% sodium chloride injection, USP (normal saline) (final volume 250 mL) over at least 15 minutes with a second dose 7-8 days after the first dose, for a total cumulative dose of 1.500 g.

| Serious adverse events | Ferumoxytol | Ferric Carboxymaltose (FCM) | |
|---|------------------|-----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 36 / 997 (3.61%) | 35 / 1000 (3.50%) | |
| number of deaths (all causes) | 4 | 2 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Metastatic uterine cancer | | | |
| subjects affected / exposed ^[1] | 0 / 743 (0.00%) | 1 / 776 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mixed hepatocellular cholangiocarcinoma | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive emergency | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed ^[2] | 1 / 743 (0.13%) | 0 / 776 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ectopic pregnancy | | | |
| subjects affected / exposed ^[3] | 1 / 743 (0.13%) | 0 / 776 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Anastomotic ulcer | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intentional overdose | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|------------------|--|
| Post-procedural haemorrhage subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris subjects affected / exposed | 0 / 997 (0.00%) | 2 / 1000 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation subjects affected / exposed | 0 / 997 (0.00%) | 2 / 1000 (0.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure chronic subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive subjects affected / exposed | 1 / 997 (0.10%) | 3 / 1000 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiorespiratory arrest subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Left ventricular failure | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | 3 / 1000 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia vitamin B12 deficiency | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Ascites | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroduodenal ulcer | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|------------------|--|
| Hepatitis acute | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculopapular | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| End stage renal disease | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Anal abscess | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint abscess | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis chronic | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 997 (0.20%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis syndrome | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 1 / 1000 (0.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 997 (0.10%) | 0 / 1000 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only female participants in both arms were exposed to this adverse event.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only female participants in both arms were exposed to this adverse event.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only female participants in both arms were exposed to this adverse event.

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Ferumoxytol | Ferric Carboxymaltose (FCM) | |
|---|--------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 186 / 997 (18.66%) | 245 / 1000 (24.50%) | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 11 / 997 (1.10%) | 16 / 1000 (1.60%) | |
| occurrences (all) | 11 | 16 | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 997 (0.70%) | 15 / 1000 (1.50%) | |
| occurrences (all) | 7 | 15 | |

| | | | |
|--|-----------------------------|------------------|-------------------|
| Nervous system disorders | | | |
| | Dizziness | | |
| | subjects affected / exposed | 25 / 997 (2.51%) | 40 / 1000 (4.00%) |
| | occurrences (all) | 31 | 40 |
| | Headache | | |
| | subjects affected / exposed | 60 / 997 (6.02%) | 82 / 1000 (8.20%) |
| | occurrences (all) | 70 | 90 |
| General disorders and administration site conditions | | | |
| | Chest discomfort | | |
| | subjects affected / exposed | 8 / 997 (0.80%) | 11 / 1000 (1.10%) |
| | occurrences (all) | 9 | 11 |
| | Chest pain | | |
| | subjects affected / exposed | 10 / 997 (1.00%) | 4 / 1000 (0.40%) |
| | occurrences (all) | 10 | 4 |
| | Fatigue | | |
| | subjects affected / exposed | 30 / 997 (3.01%) | 36 / 1000 (3.60%) |
| | occurrences (all) | 32 | 38 |
| | Pyrexia | | |
| | subjects affected / exposed | 7 / 997 (0.70%) | 22 / 1000 (2.20%) |
| | occurrences (all) | 7 | 23 |
| Gastrointestinal disorders | | | |
| | Abdominal pain | | |
| | subjects affected / exposed | 17 / 997 (1.71%) | 21 / 1000 (2.10%) |
| | occurrences (all) | 18 | 23 |
| | Constipation | | |
| | subjects affected / exposed | 14 / 997 (1.40%) | 13 / 1000 (1.30%) |
| | occurrences (all) | 14 | 13 |
| | Diarrhoea | | |
| | subjects affected / exposed | 29 / 997 (2.91%) | 33 / 1000 (3.30%) |
| | occurrences (all) | 29 | 37 |
| | Nausea | | |
| | subjects affected / exposed | 35 / 997 (3.51%) | 60 / 1000 (6.00%) |
| | occurrences (all) | 39 | 69 |
| | Vomiting | | |
| | subjects affected / exposed | 11 / 997 (1.10%) | 13 / 1000 (1.30%) |
| | occurrences (all) | 11 | 15 |

| | | | |
|---|------------------|-------------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 15 / 997 (1.50%) | 13 / 1000 (1.30%) | |
| occurrences (all) | 17 | 14 | |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 997 (1.10%) | 18 / 1000 (1.80%) | |
| occurrences (all) | 11 | 19 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 12 / 997 (1.20%) | 11 / 1000 (1.10%) | |
| occurrences (all) | 15 | 11 | |
| Urticaria | | | |
| subjects affected / exposed | 3 / 997 (0.30%) | 13 / 1000 (1.30%) | |
| occurrences (all) | 3 | 13 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 14 / 997 (1.40%) | 12 / 1000 (1.20%) | |
| occurrences (all) | 16 | 12 | |
| Back pain | | | |
| subjects affected / exposed | 19 / 997 (1.91%) | 16 / 1000 (1.60%) | |
| occurrences (all) | 23 | 16 | |
| Metabolism and nutrition disorders | | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 997 (0.00%) | 18 / 1000 (1.80%) | |
| occurrences (all) | 0 | 18 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---------------|
| None reported |
|---------------|

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29417614>

<http://www.ncbi.nlm.nih.gov/pubmed/29033620>