Clinical trial results:
A Randomised, Assessor- and Patient-blind, Multicentre, Placebo-controlled Study to Assess the Efficacy and Safety of a Single Administration of Ferric Carboxymaltose in Improving Outcomes in Iron-Deficient Non-anaemic Patients with Restless Legs Syndrome

Summary

EudraCT number	2013-000574-30
Trial protocol	DE FI
Global end of trial date	01 September 2015

Results information

Result version number	v1 (current)
This version publication date	14 September 2016
First version publication date	14 September 2016

Trial information

Trial identification

Sponsor protocol code	VIT-RLS-2012-013

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Vifor (International) Inc.
Sponsor organisation address	Rechenstrasse 37, St. Gallen, Switzerland, 9001
Public contact	Medical Information, Vifor (International) Inc., medinfo@viforpharma.com
Scientific contact	Medical Information, Vifor (International) Inc., medinfo@viforpharma.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	22 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2015
Global end of trial reached?	Yes
Global end of trial date	01 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of ferric carboxymaltose (FCM) versus placebo in the improvement of symptom severity of restless legs syndrome (RLS) as measured by the International Restless Legs Scale (IRLS) rating after 4 weeks.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki including amendments in force up to and including the time the study was conducted. The study was conducted in compliance with the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, Committee for Proprietary Medicinal Products Guideline (CPMP/ICH/135/95), and compliant with the EU Clinical Trial Directive (Directive 2001/20/EC) and/or the Code of Federal Regulations for informed consent and protection of subject rights (21 CFR, Parts 50 and 56).

At the screening visit, subjects were informed about the clinical study. Informed Consent Forms (ICFs) were obtained from the subject according to the regulatory and legal requirements of the participating country, and were retained by the Investigator as part of the study records. Copies of the documents were provided to the subjects. No study specific investigations were conducted until the appropriate valid consent had been obtained. The content of the ICFs was in accordance with the current revision of the Declaration of Helsinki, current International Conference on Harmonisation and Good Clinical Practice guidelines, and Vifor Pharma-Vifor International Inc. policy. The Investigator explained the aims, methods, reasonably anticipated benefits and potential hazards of the study and any potential discomforts. Subjects were informed that their participation in the study was entirely voluntary and would have no effect on clinical care otherwise available, and that they could withdraw consent to participate at any time without penalty or loss of further medical treatment. Subjects were told that Competent Authorities and authorised persons could examine their records but that personal information would be treated as strictly confidential and would not be publicly available.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 April 2014
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	Finland: 36
Country: Number of subjects enrolled	Germany: 70
Country: Number of subjects enrolled	Switzerland: 4
Worldwide total number of subjects	110
EEA total number of subjects	106

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)	76
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 299 subjects were screened of which 189 subjects were screen failures. A total of 110 subjects were randomised into the study, of which 87 subjects completed the study. There were more subjects in the FCM treatment group (59) compared to the placebo treatment group (51). The majority of subjects completed the study (FCM:48; placebo:39).

Pre-assignment

Screening details:

Of the 189 screen failures, 113 subjects failed due to their serumferritin/TSAT results, 51 subjects failed to meet other randomisation criteria, 24 subjects withdrew from the study, and 1 subject was successfully screened but did not attend the study randomisation visit (lost to follow-up).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Subjects were blinded for the study drug administration. 2 Assessors were assigned to administer the subject assessment surveys (RLS-DI and CGI surveys/IRLS, RLS-6, PGI-I, Medical Outcomes Study (MOS) sleep scales and QoL-RLS surveys). Assessors were not allowed to randomise, treat subjects, have access to the treatment information, or be present during the administration. A staff member was appointed to randomise, prepare and administer the study drug (not disclosing such information).

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferric carboxymaltose

Arm description:

A fixed single dose of iron as FCM was to be administered to subjects in the treatment arm. The 20 mL solution of FCM solution was to be diluted in 250 mL sterile 0.9% NaCl solution and administered by IV drip infusion up to a maximum single dose of 20 mL of FCM (1,000 mg of iron) over 15 (±2) minutes.

Arm type	Experimental
Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	
Other name	Ferinject®, FCM
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Fixed single dose of iron as FCM. The 20 mL solution of FCM solution was to be diluted in 250 mL sterile 0.9% NaCl solution and administered by IV drip infusion up to a maximum single dose of 20 mL of FCM (1,000 mg of iron) over 15 (±2) minutes.

Arm title	Placebo

Arm description:

Subjects in the placebo arm were administered a fixed single dose of 250 mL 0.9% NaCl on Day 1 by drip infusion over 15 (±2) minutes.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	NaCl
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
Fixed single dose of 250 mL 0.9% NaCl on Day 1 by drip infusion over 15 (±2) minutes.

Number of subjects in period 1	Ferric carboxymaltose	Placebo
Started	59	51
Completed	48	39
Not completed	11	12
Consent withdrawn by subject	3	8
Physician decision	1	-
Other	1	1
Lost to follow-up	1	-
Lack of efficacy	4	2
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	Ferric carboxymaltose

Reporting group description:

A fixed single dose of iron as FCM was to be administered to subjects in the treatment arm. The 20 mL solution of FCM solution was to be diluted in 250 mL sterile 0.9% NaCl solution and administered by IV drip infusion up to a maximum single dose of 20 mL of FCM (1,000 mg of iron) over 15 (±2) minutes.

Reporting group title	Placebo

Reporting group description:

Subjects in the placebo arm were administered a fixed single dose of 250 mL 0.9% NaCl on Day 1 by drip infusion over 15 (±2) minutes.

Reporting group values	Ferric carboxymaltose	Placebo	Total
Number of subjects	59	51	110
Age categorical			
All randomised patients.			
Units: Subjects			
Adults (18-64 years)	41	35	76
From 65-84 years	18	16	34
Age continuous			
All randomised patients.			
Units: years			
arithmetic mean	53.02	55.45	
standard deviation	± 15.687	± 15.884	-
Gender categorical			
All randomised patients.			
Units: Subjects			
Female	48	42	90
Male	11	9	20

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were randomised to treatment, received at least 1 dose of study medication, and had at least 1 baseline and 1 post-baseline assessment within an analysis visit window for an efficacy parameter before the start of a standard of care treatment if any. There were 110 subjects in the FAS (FCM: 59 subjects, placebo: 51 subjects).

Subject analysis set title	Safety Set (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least 1 dose of study medication.
The subjects in the SS were analysed based on the treatment that they received. In the SS, 58 subjects received FCM and 52 subjects received placebo. One subject was given placebo instead of FCM due to a procedural error. The subject that received placebo instead of FCM was analysed in the placebo treatment group.

Subject analysis set title	Per-Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the FAS who had no major protocol deviations. There were 94 subjects in the PPS (FCM: 52 subjects, placebo: 42 subjects).

Reporting group values	Full Analysis Set (FAS)	Safety Set (SS)	Per-Protocol Set (PPS)
Number of subjects	110	110	94
Age categorical			
All randomised patients.			
Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous			
All randomised patients.			
Units: years			
arithmetic mean	54.1	54.1	54.2
standard deviation	± 15.75	± 15.75	± 15.9
Gender categorical			
All randomised patients.			
Units: Subjects			
Female	90	90	76
Male	20	20	18

End points

End points reporting groups

Reporting group title	Ferric carboxymaltose

Reporting group description:

A fixed single dose of iron as FCM was to be administered to subjects in the treatment arm. The 20 mL solution of FCM solution was to be diluted in 250 mL sterile 0.9% NaCl solution and administered by IV drip infusion up to a maximum single dose of 20 mL of FCM (1,000 mg of iron) over 15 (±2) minutes.

Reporting group title	Placebo

Reporting group description:

Subjects in the placebo arm were administered a fixed single dose of 250 mL 0.9% NaCl on Day 1 by drip infusion over 15 (±2) minutes.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were randomised to treatment, received at least 1 dose of study medication, and had at least 1 baseline and 1 post-baseline assessment within an analysis visit window for an efficacy parameter before the start of a standard of care treatment if any. There were 110 subjects in the FAS (FCM: 59 subjects, placebo: 51 subjects).

Subject analysis set title	Safety Set (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least 1 dose of study medication.
The subjects in the SS were analysed based on the treatment that they received. In the SS, 58 subjects received FCM and 52 subjects received placebo. One subject was given placebo instead of FCM due to a procedural error. The subject that received placebo instead of FCM was analysed in the placebo treatment group.

Subject analysis set title	Per-Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the FAS who had no major protocol deviations. There were 94 subjects in the PPS (FCM: 52 subjects, placebo: 42 subjects).

Primary: Change in the IRLS total score between baseline and Week 4 (Day 29)

End point title	Change in the IRLS total score between baseline and Week 4 (Day 29)

End point description:

The 2 treatment groups (FCM and placebo) were compared with respect to the change in the IRLS total score (gold standard for efficacy evaluation in RLS) between baseline and Week 4 (Day 29). Only IRLS score values collected prior to the use of standard of care therapy were used in the analysis.
The FAS was used as the primary analysis set and, for sensitivity analysis, the PPS was used as a secondary analysis set. For the purpose of the primary efficacy analysis, if a subject discontinued the study before Week 4 (Day 29) or was using a concomitant RLS standard of care at Week 4 (Day 29), the last observation carried forward (LOCF) was used.

End point type	Primary

End point timeframe:

Baseline (Day 1); Week 4 (Day 29).

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[1]	51[2]		
Units: score				
arithmetic mean (standard deviation)	-7.7 (± 10.06)	-5.2 (± 8.72)		

Notes:

[1] - FAS population and LOCF were considered.

[2] - FAS population and LOCF were considered.

Statistical analyses

Statistical analysis title	Primary efficacy analysis (FAS)

Statistical analysis description:

A mixed model with IRLS measure as fixed effects and site as random effect and subsequent contrast tests (t-tests on least squares means) was applied to analyse the IRLS total score at Week 4 (Day 29) (last observation carried forward (LOCF) in dropouts), using the FAS population.

Comparison groups	Placebo v Ferric carboxymaltose
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.163
Method	t-test, 2-sided
Parameter estimate	least squares means
Point estimate	-2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.93
upper limit	1.02
Variability estimate	Standard error of the mean
Dispersion value	1.75

Statistical analysis title	Primary efficacy analysis (PPS)

Statistical analysis description:

A mixed model with IRLS measure as fixed effects and site as random effect and subsequent contrast tests (t-tests on least squares means) was applied to analyse the IRLS total score at Week 4 (Day 29) (last observation carried forward (LOCF) in dropouts), using the PPS population.

Comparison groups	Ferric carboxymaltose v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.237
Method	t-test, 2-sided
Parameter estimate	least squares means
Point estimate	-2.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	1.48
Variability estimate	Standard error of the mean
Dispersion value	1.852

Notes:

[3] - NOTE: Subjects included in this analysis (PPS) were 94 instead of 110.

Secondary: Analysis of change from baseline in IRLS scores over time (from Baseline to Week 1)

End point title	Analysis of change from baseline in IRLS scores over time (from Baseline to Week 1)

End point description:

The analysis of change from baseline in IRLS scores over time is a single analysis that includes together the analysis from baseline to week 1, 4, 8 and 12. As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week). For Week 1, the 2 treatment groups (FCM and placebo) were compared with respect to the change in the IRLS total score (gold standard for efficacy evaluation in RLS) between baseline (Day 1) and Week 1 (Day 8). Only IRLS score values collected prior to the use of standard of care therapy were used in the analysis.
The FAS was used for the secondary efficacy analyses.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Week 1 (Day 8).

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	51		
Units: score				
least squares mean (standard error)	-5.15 (± 1.091)	-4.22 (± 1.174)		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis (FAS)

Statistical analysis description:

The analysis of change from baseline in IRLS scores over time including the analysis from baseline to week 1, 4, 8 and 12 has been populated separately for every time point (week). The analysis was performed using a repeated measures mixed model that includes: score at baseline and serum ferritin level at baseline as fixed effects, visits as repeated measures and centre as a random effect. Treatment groups were compared at each visit through t-test between least squares means within the visit.

Comparison groups	Ferric carboxymaltose v Placebo

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.535
Method	t-test, 2-sided
Parameter estimate	least squares means
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.89
upper limit	2.03
Variability estimate	Standard error of the mean
Dispersion value	1.491

Secondary: Analysis of change from baseline in IRLS scores over time (from Baseline to Week 4)

End point title	Analysis of change from baseline in IRLS scores over time (from Baseline to Week 4)

End point description:

The analysis of change from baseline in IRLS scores over time is a single analysis that includes together the analysis from baseline to week 1, 4, 8 and 12. As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week). For Week 4, the 2 treatment groups (FCM and placebo) were compared with respect to the change in the IRLS total score (gold standard for efficacy evaluation in RLS) between baseline (Day 1) and Week 4 (Day 29). Only IRLS score values collected prior to the use of standard of care therapy were used in the analysis.
The FAS was used for the secondary efficacy analyses.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Week 4 (Day 29).

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	51		
Units: score				
least squares mean (standard error)	-8.13 (± 1.263)	-5.24 (± 1.348)		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis (FAS)

Statistical analysis description:

The analysis of change from baseline in IRLS scores over time including the analysis from baseline to week 1, 4, 8 and 12 has been populated separately for every time point (week). The analysis was performed using a repeated measures mixed model that includes: score at baseline and serum ferritin

level at baseline as fixed effects, visits as repeated measures and centre as a random effect. Treatment groups were compared at each visit through t-test between least squares means within the visit.

Comparison groups	Ferric carboxymaltose v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	t-test, 2-sided
Parameter estimate	least squares means
Point estimate	-2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.37
upper limit	0.59
Variability estimate	Standard error of the mean
Dispersion value	1.752

Secondary: Analysis of change from baseline in IRLS scores over time (from Baseline to Week 8)

End point title	Analysis of change from baseline in IRLS scores over time (from Baseline to Week 8)

End point description:

The analysis of change from baseline in IRLS scores over time is a single analysis that includes together the analysis from baseline to week 1, 4, 8 and 12. As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week). For Week 8, the 2 treatment groups (FCM and placebo) were compared with respect to the change in the IRLS total score (gold standard for efficacy evaluation in RLS) between baseline (Day 1) and Week 8 (Day 57). Only IRLS score values collected prior to the use of standard of care therapy were used in the analysis.
The FAS was used for the secondary efficacy analyses.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Week 8 (Day 57).

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	51		
Units: score				
least squares mean (standard error)	-7.76 (± 1.398)	-4.04 (± 1.522)		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis (FAS)

Statistical analysis description:

The analysis of change from baseline in IRLS scores over time including the analysis from baseline to week 1, 4, 8 and 12 has been populated separately for every time point (week). The analysis was performed using a repeated measures mixed model that includes: score at baseline and serum ferritin level at baseline as fixed effects, visits as repeated measures and centre as a random effect. Treatment groups were compared at each visit through t-test between least squares means within the visit.

Comparison groups	Ferric carboxymaltose v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	t-test, 2-sided
Parameter estimate	least squares means
Point estimate	-3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.66
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	1.982

Secondary: Analysis of change from baseline in IRLS scores over time (from Baseline to Week 12)

End point title	Analysis of change from baseline in IRLS scores over time (from Baseline to Week 12)

End point description:

The analysis of change from baseline in IRLS scores over time is a single analysis that includes together the analysis from baseline to week 1, 4, 8 and 12. As it is not possible to represent it in EudraCT as an unique end point (single analysis model), it has been populated separately for every time point (week). For Week 12, the 2 treatment groups (FCM and placebo) were compared with respect to the change in the IRLS total score (gold standard for efficacy evaluation in RLS) between baseline (Day 1) and Week 12 (Day 85). Only IRLS score values collected prior to the use of standard of care therapy were used in the analysis.
The FAS was used for the secondary efficacy analyses.

End point type	Secondary

End point timeframe:

Baseline (Day 1); Week 12 (Day 85).

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	51		
Units: score				
least squares mean (standard error)	-9.62 (± 1.384)	-4.96 (± 1.524)		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis (FAS)

Statistical analysis description:

The analysis of change from baseline in IRLS scores over time including the analysis from baseline to week 1, 4, 8 and 12 has been populated separately for every time point (week). The analysis was performed using a repeated measures mixed model that includes: score at baseline and serum ferritin level at baseline as fixed effects, visits as repeated measures and centre as a random effect. Treatment groups were compared at each visit through t-test between least squares means within the visit.

Comparison groups	Ferric carboxymaltose v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	t-test, 2-sided
Parameter estimate	least squares means
Point estimate	-4.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.59
upper limit	-0.73
Variability estimate	Standard error of the mean
Dispersion value	1.974

Secondary: Proportion of subjects with an improvement of at least 6 points in IRLS from baseline

End point title	Proportion of subjects with an improvement of at least 6 points in IRLS from baseline

End point description:

Proportion of subjects with an improvement by at least 6 points in the IRLS from baseline at any time during the treatment period. FAS population.

End point type	Secondary

End point timeframe:

Baseline (Day 1); any time during the treatment period.

End point values	Ferric carboxymaltose	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	51		
Units: subjects	43	24		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis (FAS)

Statistical analysis description:

The analysis was performed using a logistic regression model with treatment as a factor and baseline IRLS total score as a covariate. Treatment groups have been compared by the Odds ratio Wald Chi-square test.

Comparison groups	Ferric carboxymaltose v Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Wald Chi-square test
Parameter estimate	Odds ratio (OR)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	6.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from the time of informed consent for the duration of the trial.

Adverse event reporting additional description:

Subjects were to be observed for AEs for at least 30 min. following the infusion.
AEs and SAEs that were ongoing after a subject's last scheduled visit/last contact were followed up until resolution or stabilisation, or the patient was lost to follow-up and could not be contacted.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Ferric carboxymaltose

Reporting group description:

A fixed single dose of iron as FCM was to be administered to subjects in the treatment arm. The 20 mL solution of FCM solution was to be diluted in 250 mL sterile 0.9% NaCl solution and administered by IV drip infusion up to a maximum single dose of 20 mL of FCM (1,000 mg of iron) over 15 (±2) minutes.

Reporting group title	Placebo

Reporting group description:

Subjects in the placebo arm were administered 250 mL 0.9% NaCl on Day 1 by drip infusion over 15 (±2) minutes.

Serious adverse events	Ferric carboxymaltose	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Sleep attacks			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1.72 %

Non-serious adverse events	Ferric carboxymaltose	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 58 (50.00%)	19 / 52 (36.54%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	1 / 58 (1.72%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Influenza like illness			
subjects affected / exposed	1 / 58 (1.72%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Bronchitis chronic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Cough			

subjects affected / exposed	1 / 58 (1.72%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 58 (1.72%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Restlessness			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Investigations			
Blood iron decreased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Serum ferritin decreased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Eye contusion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Procedural pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Dysaesthesia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	7 / 58 (12.07%)	2 / 52 (3.85%)	
occurrences (all)	7	2	
Intercostal neuralgia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Migraine with aura			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Post-traumatic headache			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 58 (1.72%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Erythema of eyelid			

subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Eyelids pruritus			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Scintillating scotoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 58 (1.72%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 58 (1.72%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 58 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 58 (5.17%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Toothache			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Erythema			

subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 58 (1.72%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 58 (5.17%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Back pain			
subjects affected / exposed	2 / 58 (3.45%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Fibromyalgia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Joint stiffness			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	2 / 58 (3.45%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Myalgia			

subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	3 / 58 (5.17%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Influenza			
subjects affected / exposed	3 / 58 (5.17%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
Nasopharyngitis			
subjects affected / exposed	3 / 58 (5.17%)	5 / 52 (9.62%)	
occurrences (all)	4	5	
Sinusitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Tinea versicolour			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 58 (1.72%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 52 (1.92%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2014	The original protocol dated 24 April 2013 was amended on 7 April 2014 to implement the following changes: • A 30-minute waiting period was added following FCM and placebo administration (due to recommendations that subjects should be closely observed for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following each injection of an IV iron medicine). • Clarification that any AEs occurring during the screening visit were also to be recorded. • Clarification of the maintenance of blinding and the process of unblinding. • Clarification that an Investigator who was qualified in medicine and blind to the subjects' study treatment was to make the determination of relationship to investigational product for each AE and SAE. • Correction to the sourcing of placebo (250 mL 0.9% NaCl solution), which was to be provided by participating sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported