Clinical trial results:
A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Ferumoxytol for the Treatment of Iron Deficiency Anemia

Summary

EudraCT number	2011-001865-42
Trial protocol	LV HU PL
Global end of trial date	22 October 2012

Results information

Result version number	v1 (current)
This version publication date	21 November 2018
First version publication date	21 November 2018

Trial information

Trial identification

Sponsor protocol code	AMAG-FER-IDA-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01114139
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	22 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 October 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of a 1.02 grams (g) course of intravenous (IV) ferumoxytol, administered as 2 doses of 510 milligrams (mg) each, compared with placebo (normal saline) for the treatment of iron deficiency anemia (IDA).

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	19 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Latvia: 27
Country: Number of subjects enrolled	Canada: 55
Country: Number of subjects enrolled	India: 112
Country: Number of subjects enrolled	United States: 587
Worldwide total number of subjects	808
EEA total number of subjects	54

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)	733
From 65 to 84 years	65
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

The study was open to enrollment for adult participants with IDA, defined as hemoglobin <10.0 g/deciliter (dL) and transferrin saturation (TSAT) <20%, 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 up to 2 weeks (14 days) prior to the start of dosing with study drug (either ferumoxytol or placebo). Medical history was obtained, and clinical laboratory tests, a physical examination, and vital signs evaluations conducted to determine eligibility for inclusion in the study.

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

Blinding implementation details:

This study was double-blinded with respect to treatment assignment administration of study drug and relevant laboratory parameters. All study participants, study staff (including the physician and all non-study individuals), with the exception of the test article administrator and the unblinded monitor, were blinded to the treatment assigned and administered to each participant.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferumoxytol

Arm description:

Participants received a total of 2 doses of IV ferumoxytol 510 mg (17 milliliters [mL]). The first IV 510 mg dose was administered on Day 1 (Baseline) and second dose 2 to 8 (5±3) days after the first dose, for a total cumulative dose of 1.02 g.

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

Dosage and administration details:

Each 20 mL single-use vial contains 17 mL of ferumoxytol that consists of iron at a concentration of 30 mg of iron/mL, and mannitol, at a concentration of 44 mg/mL, in a black to reddish brown, sterile, aqueous, colloidal, isotonic solution. The product contains no preservatives.

Intravenous injection of ferumoxytol, 510 mg (17 mL) at Baseline (Day 1) with a second dose 2 to 8 days after Dose 1, for a total cumulative dose of 1.02 g.

Arm title	Placebo

Arm description:

Participants received a total of 2 doses of IV saline (17 mL). The first IV dose was administered on Day 1 (Baseline) and second dose 2 to 8 (5±3) days after the first dose.

Arm type	Placebo

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vials contained sterile saline from which 17 mL were drawn for injection.

Intravenous injection of 17 mL of normal saline at Baseline (Day 1) with a second injection 2 to 8 days after the first.

Number of subjects in period 1	Ferumoxytol	Placebo
Started	608	200
Received at Least 1 Dose of Study Drug	608	200
Completed	569	187
Not completed	39	13
Other-Out Of Window For Study Drug Dose	1	-
Consent withdrawn by subject	17	6
Other-Physician Changed Treatment	1	-
Other-Participant Falsified Records	-	1
Other-Participant Went On Hospice	-	1
Adverse event, non-fatal	3	2
Other-Protocol Violation	1	-
Lost to follow-up	15	3
Other-Missed 1 Visit	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ferumoxytol
Reporting group description:	
Participants received a total of 2 doses of IV ferumoxytol 510 mg (17 milliliters [mL]). The first IV 510 mg dose was administered on Day 1 (Baseline) and second dose 2 to 8 (5±3) days after the first dose, for a total cumulative dose of 1.02 g.	
Reporting group title	Placebo
Reporting group description:	
Participants received a total of 2 doses of IV saline (17 mL). The first IV dose was administered on Day 1 (Baseline) and second dose 2 to 8 (5±3) days after the first dose.	

Reporting group values	Ferumoxytol	Placebo	Total
Number of subjects	608	200	808
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)	554	179	733
From 65-84 years	48	17	65
85 years and over	6	4	10
Age continuous			
Units: years			
arithmetic mean	44.8	46.0	
standard deviation	± 13.82	± 13.58	-
Gender categorical			
Units: Subjects			
Female	542	178	720
Male	66	22	88

End points

End points reporting groups

Reporting group title	Ferumoxytol
Reporting group description:	
Participants received a total of 2 doses of IV ferumoxytol 510 mg (17 milliliters [mL]). The first IV 510 mg dose was administered on Day 1 (Baseline) and second dose 2 to 8 (5±3) days after the first dose, for a total cumulative dose of 1.02 g.	
Reporting group title	Placebo
Reporting group description:	
Participants received a total of 2 doses of IV saline (17 mL). The first IV dose was administered on Day 1 (Baseline) and second dose 2 to 8 (5±3) days after the first dose.	
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 (ferumoxytol or placebo) and was based upon randomized treatment assignment.	

Primary: Participants Who Achieved A ≥2.0 g/dL Increase In Hemoglobin At Any Time From Baseline To Week 5

End point title	Participants Who Achieved A ≥2.0 g/dL Increase In Hemoglobin At Any Time From Baseline To Week 5
End point description:	
Participants who achieved a ≥2.0 g/dL increase in hemoglobin at any time from Baseline up to Week 5 are presented. Increase in hemoglobin at any time from Baseline up to Week 5 was calculated for each participant based on: Hemoglobin Change = Hemoglobin (Week X) – Hemoglobin (Baseline), where Week X was any post-Baseline visit up to and including Week 5. 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. Participants with no post-Baseline hemoglobin values were classified as not achieving a ≥2.0 g/dL increase. Statistical analysis was performed for data up to Week 5 only.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) through Week 5	

End point values	Ferumoxytol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608[1]	200[2]		
Units: Number of Participants				
number (not applicable)				
Up to Week 2	252	5		
Up to Week 3	386	7		
Up to Week 4	460	8		
Up to Week 5	493	11		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	A ≥2.0 g/dL Increase In Hemoglobin

Statistical analysis description:

Participants Who Achieved A ≥2.0 g/dL Increase In Hemoglobin At Any Time From Baseline To Week 5

Comparison groups	Ferumoxytol v Placebo
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	75.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	71.15
upper limit	80.02

Notes:

[3] - Participants who achieved a ≥2.0 g/dL increase in hemoglobin from Baseline up to Week 5 were analyzed. Statistical comparison was performed for data up to Week 5 only. 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.

[4] - The p-value is the result of the Cochran-Mantel-Haenszel test, adjusted for Baseline hemoglobin level and underlying condition.

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 X) – Hemoglobin (Baseline), where Week X was any post-Baseline visit up to and including Week 5. 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. If the Week 5 hemoglobin value was missing, the change from Baseline was imputed to be zero. Participants without any post-Baseline hemoglobin values were treated as non-responders.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 5

End point values	Ferumoxytol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608[5]	200[6]		
Units: Mean				
number (not applicable)	2.6	0.1		

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Achieving A Hemoglobin Level ≥12.0 g/dL At Any Time From Baseline To Week 5

End point title	Participants Achieving A Hemoglobin Level ≥12.0 g/dL At Any Time From Baseline To Week 5

End point description:

Participants who achieved a ≥12.0 g/dL hemoglobin level at any time from Baseline up to Week 5 are presented. Increase in hemoglobin at any time from Baseline up to Week 5 was calculated for each participant based on:
Hemoglobin Change = Hemoglobin (Week X) – Hemoglobin (Baseline), where Week X was any post-Baseline visit up to and including Week 5. 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. Participants without any post-Baseline hemoglobin values were treated as non-responders.

End point type	Secondary

End point timeframe:

Baseline (Day 1) through Week 5

End point values	Ferumoxytol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608[7]	200[8]		
Units: Count of Participants				
Up to Week 2	33	3		
Up to Week 3	131	5		
Up to Week 4	240	5		
Up to Week 5	307	6		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change In TSAT From Baseline To Week 5

End point title	Mean Change In TSAT From Baseline To Week 5

End point description:

Mean change in TSAT from Baseline to Week 5 was calculated for each participant as: TSAT Change = TSAT (Week 5) – TSAT (Baseline).
TSAT, measured as a percentage, was part of the iron panel laboratory evaluations. Of the transferrin available to bind iron, this value indicates how much serum iron is bound. For example, a value of 20% means that 20% of iron-binding sites of transferrin are being occupied by iron. 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. If the Week 5 TSAT value was missing, the change from Baseline was imputed to be zero.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 5

End point values	Ferumoxytol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608[9]	200[10]		
Units: Mean (Standard Deviation)				
number (not applicable)	11.4	0.4		

Notes:

[9] - ITT Population

[10] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change In Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue Score From Baseline To Week 5

End point title	Mean Change In Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue Score From Baseline To Week 5

End point description:

The FACIT-Fatigue questionnaire is a 13-item questionnaire designed and validated to specifically assess the presence and impact of treatment on fatigue and related symptoms, such as tiredness, on health-related quality of life in anemic participants with cancer. The questionnaire has 13 items, each measured on a 4-point Likert scale. Scoring ranges from 0 (the most fatigued) to 52 (the least fatigued) points, with higher scores representing better functioning or less fatigue.
Mean change in FACIT-Fatigue Score from Baseline to Week 5 was calculated for each participant as: FACIT-Fatigue Score Change = FACIT-Fatigue Score (Week 5) – FACIT-Fatigue Score (Baseline). Baseline was defined as the Day 1 value (prior to first dose of study drug).The screening or most recent value prior to Day 1 was used for any participant with missing Day 1 information. If the Week 5 FACIT-Fatigue Score value was missing, the change from Baseline was imputed to be zero.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 5

End point values	Ferumoxytol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608[11]	200[12]		
Units: Mean				
number (not applicable)	11.7	6.8		

Notes:

[11] - ITT Population

[12] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Hemoglobin Increase Of ≥2.0 g/dL Or A Hemoglobin Value Of ≥12.0 g/dL From Baseline

End point title	Time To Hemoglobin Increase Of ≥2.0 g/dL Or A Hemoglobin Value Of ≥12.0 g/dL From Baseline

End point description:

The time to hemoglobin increase of ≥2.0 g/dL or hemoglobin value of ≥12.0 g/dL was defined as the days from Baseline (Day 1) to the first time the participant had an increase in hemoglobin of ≥2.0 g/dL or hemoglobin value of ≥12.0 g/dL, and was calculated using a Kaplan-Meier curve. Participants who did

not have a hemoglobin increase of ≥2.0 g/dL or to a hemoglobin level ≥12.0 g/dL were censored at their last visit day. Participants without any post-Baseline study visits were not included.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 5

End point values	Ferumoxytol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	608[13]	200[14]		
Units: Mean				
number (not applicable)	23.5	42.5		

Notes:

[13] - ITT Population

[14] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening Period (1-14 days before Day 1) through Week 5 (35 ± 2 days post Day 1)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	Ferumoxytol
Reporting group description:	
Participants received a total of 2 doses of IV ferumoxytol 510 mg (17 mL). The first IV 510 mg dose was administered on Day 1 (Baseline) and second dose 2 to 8 (5±3) days after the first dose, for a total cumulative dose of 1.02 g.	
Reporting group title	Placebo
Reporting group description:	
Participants received a total of 2 doses of IV saline (17 mL). The first IV dose was administered on Day 1 (Baseline) and second dose 2 to 8 (5±3) days after the first dose.	

Serious adverse events	Ferumoxytol	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 608 (2.63%)	6 / 200 (3.00%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 608 (0.00%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Small intestine carcinoma			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (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	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	3 / 608 (0.49%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed[1]	0 / 542 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (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			
Convulsion			

subjects affected / exposed	0 / 608 (0.00%)	1 / 200 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 608 (0.16%)	3 / 200 (1.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (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			
Nephrolithiasis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (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			
Gastroenteritis			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 608 (0.16%)	0 / 200 (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.

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

Non-serious adverse events	Ferumoxytol	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 608 (32.57%)	56 / 200 (28.00%)	
Injury, poisoning and procedural complications			

Skin laceration			
subjects affected / exposed	0 / 608 (0.00%)	3 / 200 (1.50%)	
occurrences (all)	0	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 608 (1.48%)	0 / 200 (0.00%)	
occurrences (all)	10	0	
Hypotension			
subjects affected / exposed	8 / 608 (1.32%)	1 / 200 (0.50%)	
occurrences (all)	8	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 608 (3.95%)	7 / 200 (3.50%)	
occurrences (all)	28	7	
Dysgeusia			
subjects affected / exposed	9 / 608 (1.48%)	1 / 200 (0.50%)	
occurrences (all)	10	1	
Headache			
subjects affected / exposed	35 / 608 (5.76%)	12 / 200 (6.00%)	
occurrences (all)	41	13	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 608 (1.97%)	3 / 200 (1.50%)	
occurrences (all)	16	3	
Oedema Peripheral			
subjects affected / exposed	10 / 608 (1.64%)	1 / 200 (0.50%)	
occurrences (all)	10	1	
Pyrexia			
subjects affected / exposed	7 / 608 (1.15%)	1 / 200 (0.50%)	
occurrences (all)	9	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 608 (1.81%)	5 / 200 (2.50%)	
occurrences (all)	11	7	
Abdominal pain upper			

subjects affected / exposed	7 / 608 (1.15%)	1 / 200 (0.50%)	
occurrences (all)	7	1	
Constipation			
subjects affected / exposed	10 / 608 (1.64%)	3 / 200 (1.50%)	
occurrences (all)	11	4	
Diarrhoea			
subjects affected / exposed	17 / 608 (2.80%)	6 / 200 (3.00%)	
occurrences (all)	20	6	
Nausea			
subjects affected / exposed	28 / 608 (4.61%)	5 / 200 (2.50%)	
occurrences (all)	32	5	
Toothache			
subjects affected / exposed	5 / 608 (0.82%)	3 / 200 (1.50%)	
occurrences (all)	5	4	
Vomiting			
subjects affected / exposed	12 / 608 (1.97%)	2 / 200 (1.00%)	
occurrences (all)	14	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 608 (1.15%)	1 / 200 (0.50%)	
occurrences (all)	7	1	
Dyspnoea			
subjects affected / exposed	9 / 608 (1.48%)	4 / 200 (2.00%)	
occurrences (all)	9	7	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 608 (0.49%)	3 / 200 (1.50%)	
occurrences (all)	3	3	
Rash			
subjects affected / exposed	12 / 608 (1.97%)	0 / 200 (0.00%)	
occurrences (all)	12	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 608 (1.48%)	5 / 200 (2.50%)	
occurrences (all)	11	5	
Back pain			

subjects affected / exposed	10 / 608 (1.64%)	2 / 200 (1.00%)	
occurrences (all)	10	2	
Muscle spasms			
subjects affected / exposed	7 / 608 (1.15%)	2 / 200 (1.00%)	
occurrences (all)	9	2	
Pain in extremity			
subjects affected / exposed	7 / 608 (1.15%)	1 / 200 (0.50%)	
occurrences (all)	8	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 608 (2.63%)	4 / 200 (2.00%)	
occurrences (all)	17	4	
Upper respiratory tract infection			
subjects affected / exposed	8 / 608 (1.32%)	2 / 200 (1.00%)	
occurrences (all)	8	2	
Urinary Tract Infection			
subjects affected / exposed	17 / 608 (2.80%)	6 / 200 (3.00%)	
occurrences (all)	19	7	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	9 / 608 (1.48%)	0 / 200 (0.00%)	
occurrences (all)	9	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2011	• A formal interim statistical analysis of efficacy data was not planned, but could be performed if requested by regulatory authorities. • For IV administration of the study drug, the use of a winged IV needle (also known as a "butterfly") was prohibited. For participants in whom a portacath or peripherally inserted central catheter line was utilized for administration, initiation of an additional peripheral IV (such as a catheter, 18 gauge or larger when possible) was advisable. Intravenous fluid could be administered at a slow rate (such as <30 cubic centimeters/hour) to keep the line open. • Cognitive function testing and exercise tolerance testing were added to the study per the United States Food and Drug Agency's recommendation to include additional measures of clinical benefit outcomes following improvement in hemoglobin/anemia. • Addition of background information on the potential risks of performing a 6-minute walk test provided for Investigators to make informed decision regarding safety of the procedure. • To ensure participant safety and increase efficiency, Principle Investigators will be notified directly of any potentially concerning changes in hemoglobin.

Notes:

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/23983177