Clinical trial results:
A Randomized, Open-Label, Active-Controlled Study of the Safety, Efficacy, and Pharmacokinetics of Ferumoxytol Compared with Oral Iron for the Treatment of Iron Deficiency Anemia in Pediatric Subjects with Chronic Kidney Disease.

Summary

EudraCT number	2010-019387-37
Trial protocol	DE GB HU ES RO LT BG
Global end of trial date	24 June 2014

Results information

Result version number	v1 (current)
This version publication date	13 December 2017
First version publication date	13 December 2017

Trial information

Trial identification

Sponsor protocol code	AMAG-FER-CKD-251

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01155375
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000373-PIP02-09
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2014
Global end of trial reached?	Yes
Global end of trial date	24 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study (AMAG-FER-CKD-251) was a study evaluating the efficacy and safety of intravenous (IV) ferumoxytol in pediatric participants with dialysis-dependent chronic kidney disease (CKD). Study AMAG-FER-CKD-252 (2010-019388-12) was a study evaluating the efficacy and safety of IV ferumoxytol in pediatric participants with nondialysis-dependent CKD.

Due to significant challenges with enrollment for both studies, Study AMAG-FER-CKD-252 was combined with Study AMAG-FER-CKD-251, and enrollment continued under Study AMAG-FER-CKD-251. The significant challenges with enrollment then led the sponsor to discontinue the combined AMAG FER-CKD-251 and AMAG FER-CKD-252 studies. The analysis of the primary completion data and the results for the combined studies are included in this record. The enrollment number (n=14) includes the number of participants for both AMAG-FER-CKD-251 and AMAG-FER-CKD-252 studies, combined.

Protection of trial subjects:

These studies were conducted according to international standards of Good Clinical Practice, International Conference on Harmonization (ICH), United States Food and Drug Administration regulations, applicable government regulations, and institutional research policies and procedures. AMAG will also continue to support the principles of the Declaration of Helsinki.

All participants were to remain in the clinic for 1 hour following each IV injection of ferumoxytol, with frequent monitoring of vital signs and close observation for adverse events.

Background therapy:

There was no background therapy administered across all participant groups.

Evidence for comparator: -

Actual start date of recruitment	17 October 2011
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	United States: 5
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	14
EEA total number of subjects	3

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)	1
Adolescents (12-17 years)	13
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population will consist of pediatric participants (6 months to <18 years of age) with iron deficiency anemia defined as hemoglobin <12.0 grams/deciliter and with either transferrin saturation ≤40%, or ferritin <100 nanograms/milliliter (mL) and CKD.

Pre-assignment

Screening details:

Screening was to take place within 2 weeks of the start of the study. Screening assessments included review of inclusion/exclusion criteria, signature of informed consent, medical history, vital signs measurement, physical examination, clinical laboratory assessments including iron panel, and start of AE capture.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was a randomized, open-label (not blinded) study. Participants were to be randomized to either IV ferumoxytol or oral iron supplementation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferumoxytol

Arm description:

Participants received 1 of the following 2 ferumoxytol dose regimens:

- Four IV injections of ferumoxytol 3.5 milligrams (mg) oral iron (Fe)/kilogram (kg) (maximum of 255 mg/dose) administered on nonconsecutive days within a 14-day period as follows: Day 1 (dose 1), Days 3* through 10 (dose 2), Days 5 through 12 (dose 3), and Days 7 through 14 (dose 4). *Participants participating in pharmacokinetic (PK) sampling received the second dose on Day 4 after the 72-hour PK sample was collected.

- Two IV injections of ferumoxytol 7.0 mg Fe/kg (maximum of 510 mg/dose), the first administered on Day 1 and the second on Days 3 through 9.

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

Dosage and administration details:

Ferumoxytol for IV injection: Each 20 mL single-use vial contains 17 mL of ferumoxytol that consists of iron, at a concentration of 30 mg Fe/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. Osmolality: 270-330 milliosmoles/kg; pH: 6-8.

Administration was either 4 IV injections of ferumoxytol 3.5 mg Fe/kg (maximum 255 mg/dose) administered on nonconsecutive days within a 14-day period as follows: Day 1 (dose 1), Days 3* through 10 (dose 2), Days 5 through 12 (dose 3), and Days 7 through 14 (dose 4); or 2 IV injections of ferumoxytol 7.0 mg Fe/kg (maximum 510 mg/dose), the first administered on Day 1 and the second on Days 3* through 9.

*Participants participating in PK sampling were to receive the second dose on Day 4 after the 72-hour PK sample was collected.

Arm title	Oral Iron

Arm description:

Participants received oral iron (2.5 mg Fe/kg) twice daily (maximum 100 mg/dose) on Days 1 through 35.

Arm type	Active comparator
Investigational medicinal product name	Ferrous Fumarate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Liquid oral iron preparation (ferrous fumarate) 2.5 mg Fe/kg, administered twice daily (maximum of 100 mg/dose) on Days 1 through 35.

Number of subjects in period 1	Ferumoxytol	Oral Iron
Started	8	6
Received at Least One Dose of Study Drug	8	6
Completed	7	6
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ferumoxytol
Reporting group description:	
Participants received 1 of the following 2 ferumoxytol dose regimens: - Four IV injections of ferumoxytol 3.5 milligrams (mg) oral iron (Fe)/kilogram (kg) (maximum of 255 mg/dose) administered on nonconsecutive days within a 14-day period as follows: Day 1 (dose 1), Days 3* through 10 (dose 2), Days 5 through 12 (dose 3), and Days 7 through 14 (dose 4). *Participants participating in pharmacokinetic (PK) sampling received the second dose on Day 4 after the 72-hour PK sample was collected. - Two IV injections of ferumoxytol 7.0 mg Fe/kg (maximum of 510 mg/dose), the first administered on Day 1 and the second on Days 3 through 9.	
Reporting group title	Oral Iron
Reporting group description:	
Participants received oral iron (2.5 mg Fe/kg) twice daily (maximum 100 mg/dose) on Days 1 through 35.	

Reporting group values	Ferumoxytol	Oral Iron	Total
Number of subjects	8	6	14
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	1	1
Adolescents (12-17 years)	8	5	13
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
12 to <18 years old	0	0	0
6 to <12 years	0	0	0
Age continuous Units: years			
arithmetic mean	15.2	13.8	
standard deviation	± 1.65	± 4.52	-
Gender categorical Units: Subjects			
Female	5	1	6
Male	3	5	8

End points

End points reporting groups

Reporting group title	Ferumoxytol

Reporting group description:

Participants received 1 of the following 2 ferumoxytol dose regimens:

- Four IV injections of ferumoxytol 3.5 milligrams (mg) oral iron (Fe)/kilogram (kg) (maximum of 255 mg/dose) administered on nonconsecutive days within a 14-day period as follows: Day 1 (dose 1), Days 3* through 10 (dose 2), Days 5 through 12 (dose 3), and Days 7 through 14 (dose 4). *Participants participating in pharmacokinetic (PK) sampling received the second dose on Day 4 after the 72-hour PK sample was collected.

- Two IV injections of ferumoxytol 7.0 mg Fe/kg (maximum of 510 mg/dose), the first administered on Day 1 and the second on Days 3 through 9.

Reporting group title	Oral Iron

Reporting group description:

Participants received oral iron (2.5 mg Fe/kg) twice daily (maximum 100 mg/dose) on Days 1 through 35.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population includes all randomized participants who had any exposure to study drug (ferumoxytol or oral iron); the safety analysis is based on actual treatment received. Data are for the combined AMAG-FER-CKD-251 and AMAG-FER-CKD-252 studies.

Subject analysis set title	Intent-to-Treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population included all randomized participants who had received at least one dose of study drug. Sample data were collected, but not run through any analysis to obtain end point data. As such, summary of the data set is not possible.

Subject analysis set title	PK Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK Population included all randomized participants who received at least 1 dose of study drug and consented to PK sampling. Of the 14 participants who participated in the studies, only 1 participated in the PK sampling of the study. Sample data were collected, but not run through any analysis to obtain end point data. As such, summary of the data set is not possible.

Primary: Mean Change In Hemoglobin From Baseline To Week 5

End point title	Mean Change In Hemoglobin From Baseline To Week 5[1]

End point description:

Mean changes in hemoglobin from Baseline to Week 5 were to be presented. Despite efforts to complete the studies as designed, several factors contributed to significant challenges in enrollment and led the sponsor to discontinue the combined AMAG FER-CKD-251 and AMAG FER-CKD-252 studies. Blood samples were collected, but not run through an analysis to obtain outcome measure data. As such, the data set for this primary end point cannot be summarized nor can the statistical analysis, as described in the protocol, be provided in a way that will provide any significant data based upon the limited study datasets.

End point type	Primary

End point timeframe:

Baseline, Week 5

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Sample data were collected, but not run through any analysis to obtain end point data. As such, summary and statistical analysis of the data set is not possible.

End point values	Ferumoxytol	Oral Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: participants				

Notes:

[2] - Sample data were collected, but not run through any analysis to obtain end point data.

[3] - Sample data were collected, but not run through any analysis to obtain end point data.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Area Under The Curve Of Ferumoxytol

End point title	Pharmacokinetics Area Under The Curve Of Ferumoxytol

End point description:

Ferumoxytol concentrations were to be determined using a drug-specific nuclear magnetic resonance assay. Blood samples were to be collected at specified times predose and postdose at the time of the first dose from 6 participants in each age-dose group. Sampling for participants <6 years of age was to be minimized to the fewest number of time points required for population PK analysis based on preliminary PK data from the first two age cohorts. Blood samples were collected, but not run through an analysis to obtain end point data. As such, the data set for this secondary end point cannot be summarized in a way that will provide any significant data based upon the limited study datasets.

End point type	Secondary

End point timeframe:

Baseline, 10, 30, 120, and 360 minutes and 24, 48, and 72 hours postdose

End point values	Ferumoxytol	Oral Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: participants				

Notes:

[4] - No analyses were performed as there was only 1 participant in the PK portion.

[5] - No analyses were performed as there was only 1 participant in the PK portion.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization up to 7 weeks (Follow-up)

Adverse event reporting additional description:

Due to significant challenges with enrollment for both studies, Study AMAG-FER-CKD-251 was combined with Study AMAG-FER-CKD-252 (2010-019388-12) and enrollment continued under Study AMAG-FER-CKD-251. The adverse events for the combined studies are included in this record.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Ferumoxytol

Reporting group description:

Participants received 1 of 2 of the following ferumoxytol dose regimens:

- Four IV injections of ferumoxytol 3.5 mg Fe/kg (maximum of 255 mg/dose) administered on nonconsecutive days within a 14-day period as follows: Day 1 (dose 1), Days 3* through 10 (dose 2), Days 5 through 12 (dose 3), and Days 7 through 14 (dose 4). *Participants participating in PK sampling received the second dose on Day 4 after the 72-hour PK sample was collected.

- Two IV injections of ferumoxytol 7.0 mg Fe/kg (maximum of 510 mg/dose), the first administered on Day 1 and the second on Days 3 through 9.

Reporting group title	Oral Iron

Reporting group description:

Participants received oral iron (2.5 mg Fe/kg) twice daily (maximum 100 mg/dose) on Days 1 through 35.

Serious adverse events	Ferumoxytol	Oral Iron	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Acute gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (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: 5 %

Non-serious adverse events	Ferumoxytol	Oral Iron	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	5 / 6 (83.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Investigations			

Residual urine volume decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Procedural hypotension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Procedural nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Skin injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cardiac disorders			
Ventricular flutter			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pneumonia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Viral pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Hypermagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2013	Major changes included: combined dialysis and nondialysis-dependent participants (nondialysis-dependent participants previously studied separately in CKD-252 were combined with CKD-251); updated total number of participants from 144 to 288; inclusion/exclusion criteria changes; administrative changes. Rationale for changes included: conducting a single protocol in CKD participants aligned with the current approved label (potential efficiencies gained in the conduct of a single protocol); modification of entry criteria based on feedback from physicians regarding iron treatment protocols in this population.
12 July 2013	Major change was the change in comparator sourcing. The rationale for the change was that the original comparator supply (ferrous sulfate) expired on 30-Jun-2013 and was no longer being manufactured. As such, the Sponsor identified a new comparator product (ferrous fumarate) to be used in the clinical study.

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.

While sample data were collected, it was not run through any analysis to obtain the necessary end point data. As such, summary of the data set is not possible.

Notes: