



## Clinical trial results:

### A Multicenter, Multinational, Randomized, Active-Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia Summary

EudraCT number	2018-002078-27
Trial protocol	PL
Global end of trial date	22 June 2020

#### Results information

Result version number	v1 (current)
This version publication date	14 November 2021
First version publication date	14 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	1VIT17044
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03523117
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	American Regent, Inc.
Sponsor organisation address	800 Adams Avenue, Suite 200, Norristown, United States, PA 19403
Public contact	Clinical Trial Information, American Regent, Inc., +1 610 650 4200,
Scientific contact	Mark Falone, MD, American Regent, Inc., +1 6317723500,

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	25 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2020
Global end of trial reached?	Yes
Global end of trial date	22 June 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the efficacy and safety of intravenous (IV) ferric carboxymaltose (FCM), compared to oral iron,

Protection of trial subjects:

The parent(s)/guardian(s) and the minors, if appropriate for age, were informed by the Investigator about the nature of the study, along with the aims, methods, anticipated benefits, potential hazards, and discomfort that participation may have entailed. Written informed consent and assent were obtained from the parent(s)/guardian(s) and the minors, if appropriate for age. The study protocol and the informed consent form were submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. The study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2019
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: 9
Country: Number of subjects enrolled	Ukraine: 35
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	79
EEA total number of subjects	9

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)	5

Children (2-11 years)	13
Adolescents (12-17 years)	61
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 30 sites in four countries - Canada, Poland, Ukraine, and US. No subjects were enrolled at the Canadian sites.

### Pre-assignment

Screening details:

The screening period, starting at Day -7 (+1) and following obtainment of informed consent/assent, was of maximum 8 days to allow for all screening results to be obtained and validated.

### 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, Monitor, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort 1

Arm description:

Subjects assigned to Cohort 1 received two doses (on Day 0 and Day 7) of Ferric Carboxymaltose (FCM) at 15 mg/kg to a maximum single dose of 750 mg administered as either an undiluted IV push at a rate of 100 mg (2mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes.

Arm type	Experimental
Investigational medicinal product name	Ferric Carboxymaltose
Investigational medicinal product code	FCM
Other name	Injectafer®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg to a maximum single dose of 750 mg administered as either an undiluted IV push at a rate of 100 mg (2mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes.

<b>Arm title</b>	Cohort 2
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Arm description:

Subjects assigned to Cohort 2 received an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age received 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 received 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) received oral ferrous sulfate drops, while children (ages ≥4 to <12 years) received oral ferrous sulfate elixir. Adolescents (ages ≥12 to 17 years) received an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants was 130 mg of elemental iron.

Arm type	Active comparator
Investigational medicinal product name	Ferrous sulfate monohydrate
Investigational medicinal product code	Ferrous Sulfate Lomapharm
Other name	
Pharmaceutical forms	Film-coated tablet, Oral drops, Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age received 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 received 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) received oral ferrous sulfate drops, while children (ages ≥4 to <12 years) received oral

ferrous sulfate elixir. Adolescents (ages  $\geq 12$  to 17 years) received an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants was 130 mg of elemental iron.

<b>Number of subjects in period 1</b>	Cohort 1	Cohort 2
Started	40	39
Completed	40	39

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Subjects assigned to Cohort 1 received two doses (on Day 0 and Day 7) of Ferric Carboxymaltose (FCM) at 15 mg/kg to a maximum single dose of 750 mg administered as either an undiluted IV push at a rate of 100 mg (2mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes.

Reporting group title	Cohort 2
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Reporting group description:

Subjects assigned to Cohort 2 received an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age received 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 received 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) received oral ferrous sulfate drops, while children (ages ≥4 to <12 years) received oral ferrous sulfate elixir. Adolescents (ages ≥12 to 17 years) received an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants was 130 mg of elemental iron.

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	40	39	79
Age categorical			
Mean age of subjects assigned to Cohort 1 (FCM) was 12.5 years. Mean age of subjects assigned to cohort 2 (Oral ferric sulfate) was 12.8 years.			
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)	3	2	5
Children (2-11 years)	7	6	13
Adolescents (12-17 years)	30	31	61
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	12.5	12.8	
standard deviation	± 4.84	± 4.35	-
Gender categorical			
Units: Subjects			
Female	33	30	63
Male	7	9	16

## End points

### End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Subjects assigned to Cohort 1 received two doses (on Day 0 and Day 7) of Ferric Carboxymaltose (FCM) at 15 mg/kg to a maximum single dose of 750 mg administered as either an undiluted IV push at a rate of 100 mg (2mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes.	
Reporting group title	Cohort 2
Reporting group description:	
Subjects assigned to Cohort 2 received an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age received 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 received 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) received oral ferrous sulfate drops, while children (ages ≥4 to <12 years) received oral ferrous sulfate elixir. Adolescents (ages ≥12 to 17 years) received an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants was 130 mg of elemental iron.	

### Primary: Hemoglobin

End point title	Hemoglobin
End point description:	
End point type	Primary
End point timeframe:	
Baseline	
Day 35	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39		
Units: g/dL				
least squares mean (standard error)	2.22 (± 0.266)	1.92 (± 0.244)		

### Statistical analyses

Statistical analysis title	Hemoglobin
Comparison groups	Cohort 1 v Cohort 2
Number of subjects included in analysis	79
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.88
Variability estimate	Standard error of the mean
Dispersion value	0.293

## Secondary: Ferritin

End point title	Ferritin
End point description:	
End point type	Secondary
End point timeframe:	
Baseline	
Day 35	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39		
Units: ng/mL				
least squares mean (standard error)	132.1 (± 13.38)	11.01 (± 13.368)		

## Statistical analyses

<b>Statistical analysis title</b>	Ferritin
Comparison groups	Cohort 1 v Cohort 2
Number of subjects included in analysis	79
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	121.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	88.93
upper limit	153.24
Variability estimate	Standard error of the mean
Dispersion value	16.137



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**Secondary: Transferrin Saturation**

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End point title	Transferrin Saturation
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End point description:

End point type	Secondary
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End point timeframe:

Baseline

Day 35

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End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39		
Units: %				
least squares mean (standard error)	24.3 ( $\pm$ 2.563)	8.66 ( $\pm$ 2.491)		

**Statistical analyses**

Statistical analysis title	Transferrin Saturation
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Comparison groups	Cohort 1 v Cohort 2
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Number of subjects included in analysis	79
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Analysis specification	Post-hoc
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Analysis type	superiority
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P-value	< 0.0001
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Method	ANCOVA
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Parameter estimate	Mean difference (final values)
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Point estimate	15.64
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	9.59
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upper limit	21.69
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Variability estimate	Standard error of the mean
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Dispersion value	3.037
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**Secondary: Reticulocyte Hemoglobin Content**

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End point title	Reticulocyte Hemoglobin Content
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End point description:

End point type	Secondary
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End point timeframe:

Baseline

Day 35

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: pg				
least squares mean (standard error)	6.95 ( $\pm$ 0.374)	4.9 ( $\pm$ 0.377)		

### Statistical analyses

Statistical analysis title	Reticulocyte Hemoglobin Content
Comparison groups	Cohort 1 v Cohort 2
Number of subjects included in analysis	71
Analysis specification	Post-hoc
Analysis type	superiority
P-value	> 0.0002
Method	mixed Mixed Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	3.12
Variability estimate	Standard error of the mean
Dispersion value	0.533

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 0 to Day 35

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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### Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Subjects assigned to Cohort 1 received two doses (on Day 0 and Day 7) of Ferric Carboxymaltose (FCM) at 15 mg/kg to a maximum single dose of 750 mg administered as either an undiluted IV push at a rate of 100 mg (2mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes.

Reporting group title	Cohort 2
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Reporting group description:

Subjects assigned to Cohort 2 received an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age received 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 received 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) received oral ferrous sulfate drops, while children (ages ≥4 to <12 years) received oral ferrous sulfate elixir. Adolescents (ages ≥12 to 17 years) received an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants was 130 mg of elemental iron.

Serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 38 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 40 (35.00%)	10 / 38 (26.32%)	
Investigations			
Investigations			
subjects affected / exposed	3 / 40 (7.50%)	1 / 38 (2.63%)	
occurrences (all)	3	1	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	1 / 38 (2.63%) 1	
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	0 / 38 (0.00%) 0	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2  0 / 40 (0.00%) 0	1 / 38 (2.63%) 1  5 / 38 (13.16%) 5	
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 38 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	2 / 38 (5.26%) 2	
Metabolism and nutrition disorders Hypophosphatemia subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4	0 / 38 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported