Clinical trial results:
Intravenous Ferric Carboxymaltose for improvement of metabolic parameters and vascular function in T2DM patients with iron deficiency

Summary

EudraCT number	2011-005224-18
Trial protocol	DE
Global end of trial date	16 May 2019

Results information

Result version number	v1 (current)
This version publication date	09 June 2022
First version publication date	09 June 2022

Trial information

Trial identification

Sponsor protocol code	CLEVER-2011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01513369
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GWT-TUD GmbH
Sponsor organisation address	Freiberger Str. 33, Dresden, Germany, 01067
Public contact	Medical Consulting, GWT-TUD GmbH, 0049 35125933100, medical.consulting@g-wt.de
Scientific contact	Medical Consulting, GWT-TUD GmbH, 0049 35125933100, medical.consulting@g-wt.de

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	27 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2018
Global end of trial reached?	Yes
Global end of trial date	16 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

reduction in HBA1c-levels between baseline and after 12 weeks of treatment with FCM vs. placebo

Protection of trial subjects:

The conduct of this study was in compliance with the Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study was also carried out in keeping with applicable local law(s) and regulation(s). Participants were monitored for the occurrence of treatment-emergent adverse events and overall health status.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 August 2012
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	Germany: 130
Worldwide total number of subjects	130
EEA total number of subjects	130

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)	0
From 65 to 84 years	130
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From Aug 2012 through Oct 2016, a total of 162 patients were screened at 7 study sites in Germany. Of them, 12 did not meet the eligibilty criteria. In total, 162 patients were screened at 7 study sites in Germany. Of them, 150 met the inclusion criteria and were randomized to receive either IMP Ferinject® (76 pat.) or matching placebo (74 pat.).

Pre-assignment

Screening details:

The PPS comprised all subjects who were treated according to the protocol, had no other major protocol violations, and reached the defined study endpoint. This set was used for all final statistical analysis and included 130 subjects in total, 64 of the FCM group and 66 of the placebo group.

Period 1

Period 1 title	overall period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

The patient was blinded by using a black sheath which was wrapped around the infusion bottle. In addition, a black infusion set was used which conceals the colour of the infused solution to the patient.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental Arm

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ferric carboxymaltose (FCM)
Investigational medicinal product code	
Other name	Ferinject®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

duration of 12 weeks, intravenous via drip infusion
Week 1b (Baseline): 1000mg (exception: with Hb ≥ 14 g/dL and ≤ 15 g/dL only 500mg)
Week 5 (Visit 2a): weight < 70kg & Hb < 10 g/dL: 500mg; weight < 70kg & Hb ≥ 10 g/dL: no dose; weight ≥ 70 kg & Hb < 10 g/dL: 1000mg; weight ≥ 70 kg & Hb ≥ 10 g/dL: 500mg; Any weight & Hb ≥ 14 g/dL and ≤ 15 g/dL: No dose
Week 5+ <=5d (Visit 2b): No dose (exception: Any weight & Hb ≥ 14 g/dL and ≤ 15 g/dL: 500mg, if still iron deficient)

Arm title	Placebo Arm

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

duration of 12 weeks, intravenous via drip infusion
Week 1b (Baseline): 1000mg (exception: with Hb ≥ 14 g/dL and ≤ 15 g/dL only 500mg)
Week 5 (Visit 2a): weight < 70kg & Hb < 10 g/dL: 500mg; weight < 70kg & Hb ≥ 10 g/dL: no dose;

weight ≥ 70 kg & Hb < 10 g/dL: 1000mg; weight ≥ 70 kg & Hb ≥ 10 g/dL: 500mg; Any weight & Hb ≥ 14 g/dL and ≤ 15 g/dL: No dose
Week 5+ <=5d (Visit 2b): No dose (exception: Any weight & Hb ≥ 14 g/dL and ≤ 15 g/dL: 500mg, if still iron deficient)

Number of subjects in period 1	Experimental Arm	Placebo Arm
Started	64	66
Completed	64	66

Baseline characteristics

Reporting groups	
Reporting group title	overall period

Reporting group description: -

Reporting group values	overall period	Total	
Number of subjects	130	130	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	130	130	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66.4		
standard deviation	± 9.2	-	
Gender categorical Units: Subjects			
Female	82	82	
Male	48	48	

End points

End points reporting groups

Reporting group title	Experimental Arm
Reporting group description: -	
Reporting group title	Placebo Arm
Reporting group description: -	

Primary: Change in HbA1c levels

End point title	Change in HbA1c levels
End point description:	
The primary endpoint of this study was the change in HbA1c levels between baseline and after 12 weeks of treatment with FCM or placebo.	
End point type	Primary
End point timeframe:	
between baseline and after 12 weeks	

End point values	Experimental Arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: percent				
arithmetic mean (standard deviation)	-0.19 (± 0.56)	0.04 (± 0.43)		

Statistical analyses

Statistical analysis title	Main analysis set
Statistical analysis description:	
Includes all subjects of the FAS who are without major protocol violations and have data of HbA1c values at V3 .	
Comparison groups	Experimental Arm v Placebo Arm
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 13 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: A total of 150 adverse events (AEs) were recorded in 87 patients. 94 AEs in 48 patients treated with FCM and 56 AEs in 39 patients treated with placebo. 19 out of the 94 AEs (20.2%) reported in experimental group were assessed as likely or possibly related to the IMP, incl. increase in liver enzymes (4), fever (3), nausea (2), increase in ferritin (2), and vertigo, tiredness, headache, worsening of nephropathy, increased CRP, unpleasant aftertaste, Herpes, and elevated erythropoiesis (each 1).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2013	Version 2.4 dated 13.06.2013: multi-site setting (6 new study sites), change of in-/exclusion criteria
06 February 2014	Version 2.5 dated 22.11.2013: changes of in-/exclusion criteria [anemia is not an inclusion criterion anymore IDA ID, serum ferritin < 100 ng/ml or TSAT < 20%, extension of contraindications due to known hypersensitivity reaction (Rote Hand Brief), definition of HbA1c stability, implementation of interim analysis]
15 May 2015	Version 2.6 dated 17.03.2015: changes of inclusion criteria [serum ferritin < 150 ng/mL or TSAT < 25% if Hb < 14 g/dL; serum ferritin < 100 ng/mL or TSAT < 20% if Hb ≥ 14 g/dL and ≤ 15g/dL], changes of exclusion criteria [Hb > 15 g/dL, CRP > 15 mg/L]

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported