Clinical trial results:
The effectiveness and tolerability of GlobiFer Forte (haem iron) tablets compared to ferrous sulphate tablets in inflammatory bowel disease: a randomised-controlled trial.

Summary

EudraCT number	2008-004277-17
Trial protocol	GB
Global end of trial date	06 May 2015

Results information

Result version number	v1 (current)
This version publication date	08 February 2020
First version publication date	08 February 2020
Summary attachment (see zip file)	End of Trial Report summary (End of Trial report summary - GlobiFer IBD_draft 01.03.2016.pdf) report (Clinical Study Report - GlobiFer IBD_draft 2015-11-13.pdf)

Trial information

Trial identification

Sponsor protocol code	2008/2

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlobiFer Intl.
Sponsor organisation address	Satenrozen 6A unit 002, Kontich/Antwerp, Belgium, 2550
Public contact	General Manager, Patrick Swolfs, 38808772 38808772, ps@globiferintl.be
Scientific contact	General Manager, Patrick Swolfs, 38808772 38808772, ps@globiferintl.be
Sponsor organisation name	GlobiFer Intl
Sponsor organisation address	Satenrozen 6A unit 002, Kontich/Antwerp, Belgium, 2550
Public contact	Product Manager, Rabia Sarroukh , 0032 38808772, rs@globiferintl.be
Scientific contact	Product Manager, Rabia Sarroukh , 0032 38808772, rs@globiferintl.be

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	13 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate if oral haem iron supplementation is more effective and better tolerated than non-haem iron in patients with inflammatory bowel disease over 12 weeks
The current study aims to evaluate the effectiveness and acceptability of a new form of iron supplement GlobiFer (haem iron) against iron sulphate. GlobiFer Forte, the test preparation, is an iron supplement to offer both haem iron (protein-based iron) and non-haem iron (plant-based iron). Unlike other iron supplements, GlobiFer Forte provides two types of iron in one tablet for maximum absorption with virtually no gastric side effects. Iron can be enterically absorbed in haem or non-haem forms. Because haem iron uptake is thought to be less susceptible to inflammatory downregulation and less irritant to enterocytes, haem iron products are absorbed four times more efficiently and are better tolerated than non-haem preparations in healthy individuals.

Protection of trial subjects:

GlobiFer Forte (active ingredient: Iron integrated haemolysed haemoglobin powderequal to 18 mg Fe++/tablet) was supplied as 900 mg tablets for oral intake twice daily with sufficient liquid.
Batch Nos.: 911183, 102029, 320030, 320030, 420010
The main safety variables were the incidence and the severity of possible or probable adverse events and evaluation of laboratory tests.
The analysis considered all events as documented in the CRFs.
Symptoms and side effects are assessed using a weekly diary card for the duration of the active treatment and the number of serious side effects were recorded i.e. death, GI side effect, increased disease activity. Adverse events will be recorded form the first intake of the study drug and serious events will be followed up for 30 days after the last intake of study drug

Background therapy:

An alternative approach to correcting iron deficiency anaemia is by the intravenous route. Iron sucrose has been extensively studied in patients with IBD and this has been found to be both safe and efficacious both alone and in combination with EPO. However, the use of intravenous iron is inconvenient, involving extra hospitals visits and can be uncomfortable.

Evidence for comparator:

This above mentioned study was designed to test an alternative therapy for a better tolerated, safe and more effective iron supplementation than that which is currently available for IBD patients.
The standard treatment for this (iron sulphate tablets) is commonly associated with gastro-intestinal side effects such as nausea, pain, diarrhoea or constipation. Oral non-haem iron supplementation is difficult in the context of IBD because patients with colitis seem to suffer the common gastrointestinal side effects of this medicine (nausea, bloating, pain, diarrhoea) more than iron deficient subjects without GI disease.
Ferrous sulphate was supplied as 200 mg tablets for oral intake twice daily with sufficient liquid. In addition.
Batch Nos.: FL2061, FM28, FM66, FT6, FT30, FT25

Actual start date of recruitment	19 May 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 Kingdom: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	18
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was stopped due to unscheduled low recruitment.

Pre-assignment

Screening details:

Patients with established inactive or mild to moderately active IBD.

Period 1

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

Blinding implementation details:

Patient have been provided with blister strips in numbered boxes by the manufacturer of GlobiFer forte who organized the randomization. Investigators and patient were not blinded to the treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	GlobiFer forte

Arm description:

active ingredient: Iron integrated haemolysed haemoglobin powder equal to 18 mg elemental iron per tablet

Arm type	Experimental
Investigational medicinal product name	GlobiFer forte
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

36 mg elemental iron was supplied as 900 mg tablets for oral intake twice daily with sufficient liquid. Batch Nos.: 911183, 102029, 320030, 320030, 420010

Arm title	Ferrous Sulfate

Arm description:

Ferrous iron equal to 65 mg elemental iron per tablet

Arm type	Active comparator
Investigational medicinal product name	Ferrous sulfate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

130 mg of ferrous sulfate was supplied as 200 mg tablets for oral intake twice daily with sufficient liquid. Batch Nos.: FL2061, FM28, FM66, FT6, FT30, FT25

Number of subjects in period 1	GlobiFer forte	Ferrous Sulfate
Started	11	10
Completed	9	9
Not completed	2	1
Adverse event, non-fatal	1	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	21	21	
Age categorical Units: Subjects			
16-29 years	9	9	
30-39 years	3	3	
40-49 years	1	1	
50-59 years	5	5	
>59 years	3	3	
Gender categorical Units: Subjects			
Female	9	9	
Male	12	12	
Race			
Part of the demographic data collected			
Units: Subjects			
Black-African	1	1	
White	14	14	
Asian	5	5	
Other	1	1	

End points

End points reporting groups

Reporting group title	GlobiFer forte

Reporting group description:

active ingredient: Iron integrated haemolysed haemoglobin powder equal to 18 mg elemental iron per tablet

Reporting group title	Ferrous Sulfate

Reporting group description:

Ferrous iron equal to 65 mg elemental iron per tablet

Subject analysis set title	Primary Efficacy criteria
Subject analysis set type	Full analysis

Subject analysis set description:

GlobiFer arm :
Achievement a 1g/dl increase in haemoglobin over baseline at 12weeks 56%
no achievement a 1 g/dl increase in haemoglobin aver baseline at 12 weeks 44%
Ferrous sulphate arm :
Achievement a 1g/dl increase in haemoglobin over baseline at 12weeks 100%
no achievement a 1 g/dl increase in haemoglobin aver baseline at 12 weeks 0%

Subject analysis set title	Secondary efficacy criteria
Subject analysis set type	Full analysis

Subject analysis set description:

GlobiFer arm :
Achievement a 1g/dl increase in haemoglobin over baseline at 24 weeks 100%
no achievement a 1 g/dl increase in haemoglobin aver baseline at 24 weeks 0%

Ferrous sulphate arm :
Achievement a 1g/dl increase in haemoglobin over baseline at 24 weeks 88%
no achievement a 1 g/dl increase in haemoglobin aver baseline at 24 week 13%

Subject analysis set title	Tolerance of study medication over baselines 24 weeks
Subject analysis set type	Full analysis

Subject analysis set description:

GlobiFer arm :
Patient with AE - possible related 27.3%
Patient without AE-possible related 72.7%
Patient with AE - propable related 0%
Patient without AE-probalbe related 100%
Ferrous sulphate arm :
Patient with AE - possible related 0%
Patient without AE-possible related 100%
Patient with AE - propable related 30%
Patient without AE-probalbe related 100%

Subject analysis set title	Secondary efficacy criteria-AE over baselines at 24 weekds
Subject analysis set type	Full analysis

Subject analysis set description:

GlobiFer arm :
Patient with AE 100%
Patient without AE 0%
Patient with AE - not related 100%
Patient without AE-not related 0%
Patient with AE - possible related 27.3%
Patient without AE-possible related 72.7%
Patient with AE - probable related 0%
Patient without AE-probable related 100%
Ferrous sulphate arm :
Patient with AE 80%
Patient without AE 20%
Patient with AE - not related 50%
Patient without AE-not related 50%
Patient with AE - possible related 0%

Patient without AE-possible related 100%
Patient with AE - probable related 30%
Patient without AE-probable related 70%

Subject analysis set title	Adherence over baseline at 12 weeks
Subject analysis set type	Full analysis

Subject analysis set description:

All patients n=21 97% SD 4%
GlobiFer n= 9 95%
Ferrous sulphate n=8 98%

Subject analysis set title	Resolution of anemia over baselines 12 weeks
Subject analysis set type	Full analysis

Subject analysis set description:

all patients
increase of haemoglobine (g/dl) 2.3 SD 1.4
GlobiFer
increase of haemoglobine (g/dl) 1.5 SD 1.3
Ferrous sulphate
increase of haemoglobine (g/dl) 3.1 SD 0.9

Primary: Proportion of patients in each of the patient groups whoachieveda 1g/dl increase in haemoglobin over baseline at 12 weeks

End point title	Proportion of patients in each of the patient groups whoachieveda 1g/dl increase in haemoglobin over baseline at 12 weeks

End point description:

End point type	Primary

End point timeframe:

12weeks

End point values	GlobiFer forte	Ferrous Sulfate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: number of person	5	8		

Statistical analyses

Statistical analysis title	No statistical analysis

Statistical analysis description:

due to the small number of patients and the inhomogeneous data situation does not allow a statement to compare the efficacy of the two drugs.

Comparison groups	GlobiFer forte v Ferrous Sulfate
Number of subjects included in analysis	17
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	≤ 0 [2]
Method	not applicable
Parameter estimate	not applicable
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	95

Notes:

[1] - not applicable

[2] - target not met, no statistical analysis done

Secondary: Sustainability of 1g/dl increase in haemoglobin (baseline to 12 weeks) at 24 weeks

End point title	Sustainability of 1g/dl increase in haemoglobin (baseline to 12 weeks) at 24 weeks

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	GlobiFer forte	Ferrous Sulfate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: patient number	5	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: weekly assessment	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	no found
Reporting groups	
Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)		
Gastrointestinal disorders			
Abdominal pain lower	Additional description: The subject present nausea and vomiting , headache syndromes, tinnitus , dizziness and giddiness experienced R sided abdominal pain and constipation, 57 days after receiving Globifer. The patient was treated for pain and constipation-faecal loading		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2010	inclusion of colonic microbiota- stool sample added to study design treatment 36 weeks to 24 weekds
05 August 2011	Study design per PI request to increase recruitment
09 December 2011	protocol to increase patient recruitment
22 May 2013	Inclusion criteria changes
26 February 2014	Sponsor contact changes
01 April 2014	enrollment is very low; protocol amended to increase the enrolment rate inclusion criteria exclusion criteria rescreening Trial design

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 May 2015	Study was prematuraly ended because of recruitment status very low	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was stopped due to unscheduled low recruitment. Due to the inhomogeneity of the patient population and the very low number of patients no statistical analysis was performed.

Notes: