Clinical trial results:
A phase 3b, randomized, controlled, multicentre study with oral ferric maltol (Feraccru) or intravenous iron (ferric carboxymaltose; FCM), for the treatment of iron deficiency anaemia in subjects with inflammatory bowel disease

Summary

EudraCT number	2015-002496-26
Trial protocol	DE BE ES HU
Global end of trial date	02 January 2019

Results information

Result version number	v2 (current)
This version publication date	21 November 2020
First version publication date	18 April 2020
Version creation reason	• New data added to full data set Following a comprehensive review of the previously reported study results, some corrective measures were taken to re-analyse and re-report the data which is reflected in the updated Post-Hoc Analysis Plan. All efficacy analyses for the PP and ITT population were rerun and WHO guidelines were followed for Hb normalisation.

Trial information

Trial identification

Sponsor protocol code	ST10-01-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02680756
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shield TX (UK) Limited
Sponsor organisation address	Nothern Design Centre, Baltic Business Quarter, Gateshead Quays, United Kingdom, NE8 3DF
Public contact	Clinical Operations, Shield TX (UK) Ltd., 44 1915118511, jmitchell@shieldtx.com
Scientific contact	Clinical Operations, Shield TX (UK) Ltd., 44 1915118511, jmitchell@shieldtx.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	25 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of ferric maltol and intravenous iron (FCM) in the treatment and maintenance of iron deficiency anaemia in subjects with IBD

Protection of trial subjects:

Subjects were males or females aged ≥18 years with a confirmed diagnosis of IBD (endoscopic or biopsy). All patients were required to be in remission or to have a mild-to-moderate disease activity of IBD (as defined by a Simple Clinical Colitis Activity Index [SCCAI] >5 or a Crohn's Disease Activity Index [CDAI] score <300 at screening). All subjects were required to have IDA, defined by a haemoglobin (Hb) concentration ≥8.0 g/dL and ≤11.0 g/dL for women OR a Hb ≥8.0 g/dL and ≤12.0 g/dL for men, as well as ferritin levels <30 ng/mL or Ferritin <100 ng/mL with Transferrin saturation (TSAT) <20% at screening. Female subjects of childbearing potential had to agree to use a reliable method of contraception until they had completed the study and for at least 4 weeks following their final study visit. Safety assessments conducted throughout the study included adverse event monitoring, routine clinical safety laboratory testing, changes in CDAI and SCCAI. Subjective Quality of Life score was also assessed over the study duration using SF-36.

Background therapy:

The following concomitant medications were allowed at baseline and during the study:
• ESAs, but the subject had to have been on a stable dose for the preceding 3 months before randomisation
• Vitamin B12 and folic acid supplements/replacement
• Immunosuppressants, including variations to dosing at the discretion of the investigator, so long as there was no clinical evidence or suspicion of the immunosuppressant contributing to the subject's anaemia or affecting erythropoiesis.
Subjects with anaemia unrelated to iron deficiency or who had received depot iron preparations within 8 weeks of screening or blood transfusions within 12 weeks of screening were excluded. Other reasons for exclusion were: oral iron treatment within 4 weeks of randomization; treatment with immunosuppressants known to induce anemia; uncorrected folate or vitamin B12 deficiency; and pregnancy.

Evidence for comparator: -

Actual start date of recruitment	21 December 2015
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	Spain: 39
Country: Number of subjects enrolled	United States: 65
Country: Number of subjects enrolled	Belgium: 1

Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 69
Country: Number of subjects enrolled	Hungary: 53
Worldwide total number of subjects	250
EEA total number of subjects	185

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)	228
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening assessments included demographics, medical history, concomitant medication, physical examination, vital signs, clinical laboratory tests (including liver function, iron markers and pregnancy test for women of childbearing potential), status of their disease using SSCAI or CDAI.

Period 1

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferric Maltol

Arm description:

Ferric maltol 30mg BID

Arm type	Experimental
Investigational medicinal product name	Ferric maltol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One capsule (30mg) taken bid, first thing in the morning at least 1 hour before food and concomitant medications, and last thing at night before bed at least 2 hours after food and concomitant medications. Capsules had to be taken on an empty stomach with water only with at least 8 hours between doses.

Arm title	IV Iron

Arm description:

IV iron, ferric carboxymaltose

Arm type	Active comparator
Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	
Other name	FCM
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects randomised to IV iron received FCM in accordance with the dosing instructions as per the local SmPC/PI. A copy of the relevant local SmPC/PI for FCM is available in the TMF. Initial dosing and the number of IV iron doses administered were calculated based on the subject’s starting Hb and weight. For ongoing treatment decisions, ferritin was measured at Visit 4 (Week 12) and Visits 5 and 6 (Week 24, and Week 36) for subjects prior to protocol amendment 7.0. Subjects continuing after Week 12 who were iron deficient (ferritin below 100 ng/mL) at any of Visits 4-6 received additional FCM doses according to the formula in the local SmPC/PI.

Number of subjects in period 1	Ferric Maltol	IV Iron
Started	125	125
Completed Wk 12	109	118
Completed Wk 24	79 [1]	89 [2]
Completed Wk 36	57 [3]	64 [4]
Completed Wk 52/ET	64 [5]	63 [6]
Completed Wk 54	98	96 [7]
Completed	93	106
Not completed	32	19
Consent withdrawn by subject	5	5
Physician decision	4	1
Protocol violation	1	-
Adverse event, non-fatal	10	2
Blood transfusion during study treatment period	-	1
Death	1	-
Other	3	2
Hb <7.5 g/dL	-	2
Lost to follow-up	7	6
TSAT above 60 % or ferritin above 800 mg/ml	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects includes those who had discontinued but come back for follow-up visit

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects includes those who had discontinued but come back for follow-up visit

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects includes those who had discontinued but come back for follow-up visit

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects includes those who had discontinued but come back for follow-up visit

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects includes those who had discontinued but come back for follow-up visit

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects includes those who had discontinued but come back for follow-up visit

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects includes those who had discontinued but come back for follow-up visit

Baseline characteristics

Reporting groups	
Reporting group title	Ferric Maltol
Reporting group description: Ferric maltol 30mg BID	
Reporting group title	IV Iron
Reporting group description: IV iron, ferric carboxymaltose	

Reporting group values	Ferric Maltol	IV Iron	Total
Number of subjects	125	125	250
Age categorical			
The subject population consists of male and female aged 18 or older with a confirmed diagnosis of IBD.			
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)	115	113	228
From 65-84 years	10	12	22
85 years and over	0	0	0
Age continuous			
The study population consisted of male and female subjects aged 18 or over with a confirmed diagnosis of IBD			
Units: years			
arithmetic mean	40.0	40.4	
standard deviation	± 14.58	± 15.54	-
Gender categorical Units: Subjects			
Female	68	77	145
Male	57	48	105
Screening Hb for randomisation Units: Subjects			
<10 g/dL Female or <11 g/dL Male	67	67	134
≥10 g/dL Female or ≥11 g/dL Male	58	58	116
Baseline Hb Units: Subjects			
< 9.5g/dL	38	35	73
>= 9.5g/dL	87	90	177
IBD Subgroup Units: Subjects			
Crohn's disease	79	79	158
Ulcerative Colitis	46	46	92

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population included all subjects who were randomised.

Reporting group values	ITT population		
Number of subjects	250		
Age categorical			
The subject population consists of male and female aged 18 or older with a confirmed diagnosis of IBD.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	228		
From 65-84 years	22		
85 years and over	0		
Age continuous			
The study population consisted of male and female subjects aged 18 or over with a confirmed diagnosis of IBD			
Units: years			
arithmetic mean	40.2		
standard deviation	± 15.04		
Gender categorical			
Units: Subjects			
Female	145		
Male	105		
Screening Hb for randomisation			
Units: Subjects			
<10 g/dL Female or <11 g/dL Male	134		
≥10 g/dL Female or ≥11 g/dL Male	116		
Baseline Hb			
Units: Subjects			
< 9.5g/dL	73		
>= 9.5g/dL	177		
IBD Subgroup			
Units: Subjects			
Crohn's disease	158		
Ulcerative Colitis	92		

End points

End points reporting groups

Reporting group title	Ferric Maltol
Reporting group description: Ferric maltol 30mg BID	
Reporting group title	IV Iron
Reporting group description: IV iron, ferric carboxymaltose	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intention-to-treat (ITT) population included all subjects who were randomised.	

Primary: Proportion of subjects achieving either a 2 g/dL increase in Hb or normalisation of Hb (>=12 g/dL women, >=13 g/dL men) at Week 12 - re-evaluated PP

End point title	Proportion of subjects achieving either a 2 g/dL increase in Hb or normalisation of Hb (>=12 g/dL women, >=13 g/dL men) at Week 12 - re-evaluated PP
End point description: The primary efficacy endpoint was the proportion of subjects achieving either a 2 g/dL increase in Hb or normalisation of Hb (>=12 g/dL women, >=13 g/dL men) at Week 12 in the re-evaluated PP population	
End point type	Primary
End point timeframe: 12 weeks (primary efficacy endpoint of study)	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	88		
Units: Subjects				
Responder	53	75		
Non-responder	25	13		

Statistical analyses

Statistical analysis title	Statistical testing Hb responder rate at 12 weeks
Comparison groups	Ferric Maltol v IV Iron
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.341
Method	t-test, 2-sided
Parameter estimate	Risk difference (RD)
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.05
Variability estimate	Standard deviation

Notes:

[1] - The null hypothesis for the primary efficacy analysis will be rejected (i.e., ferric maltol will be deemed non-inferior to IV Iron), if the LCL of the 95% CI for the difference (ferric maltol – IV Iron) in proportions of Hb responders at Week 12 is ≥ -20% for both the ITT analysis and the re-evaluated PP analysis. The p-value in testing the aforementioned hypotheses will be equal to one minus the confidence
coefficient corresponding to the CI for the risk difference whose LCL equals -20%.

Primary: Proportion of subjects achieving either a 2 g/dL increase in Hb or normalisation of Hb (>=12 g/dL women, >=13 g/dL men) at Week 12 - ITT

End point title	Proportion of subjects achieving either a 2 g/dL increase in Hb or normalisation of Hb (>=12 g/dL women, >=13 g/dL men) at Week 12 - ITT

End point description:

The primary efficacy endpoint was the proportion of subjects achieving either a 2 g/dL increase in Hb or normalisation of Hb (>=12 g/dL women, >=13 g/dL men) at Week 12 in ITT (MI) population

End point type	Primary

End point timeframe:

12 weeks (primary efficacy endpoint of study)

End point values	Ferric Maltol	IV Iron	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	125	125	250	
Units: Subjects				
Responder	84	105	189	
Non-responder	41	20	61	

Statistical analyses

Statistical analysis title	Statistical testing Hb responder rate at 12 weeks

Statistical analysis description:

ITT (MI)

Comparison groups	Ferric Maltol v IV Iron
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.298
Method	t-test, 2-sided
Parameter estimate	Risk difference (RD)
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	-0.06
Variability estimate	Standard deviation

Notes:

[2] - The null hypothesis for the primary efficacy analysis will be rejected (i.e., ferric maltol will be deemed non-inferior to IV Iron), if the LCL of the 95% CI for the difference (ferric maltol – IV Iron) in proportions of Hb responders at Week 12 is ≥ -20% for both the ITT analysis and the re-evaluated PP analysis. The p-value in testing the aforementioned hypotheses will be equal to one minus the confidence
coefficient corresponding to the CI for the risk difference whose LCL equals -20%.

Secondary: Change from Baseline in Haemoglobin Concentration Over 12 weeks

End point title	Change from Baseline in Haemoglobin Concentration Over 12 weeks

End point description:

The key secondary efficacy endpoint was change from baseline in Hb concentration at Week 12.
The change from baseline in Hb concentration was analysed using an ANCOVA model adjusted for treatment group, baseline Hb, and IBD subgroup and was based on ITT(MI).

End point type	Secondary

End point timeframe:

12 weeks

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	125		
Units: g/dL				
arithmetic mean (standard deviation)	2.45 (± 1.449)	3.04 (± 1.576)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hb concentration from baseline to Week 4

End point title	Change in Hb concentration from baseline to Week 4

End point description:

ITT (MI)

End point type	Secondary

End point timeframe:

At week 4

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: g/dL				
arithmetic mean (standard deviation)	1.27 (± 0.974)	2.19 (± 1.133)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hb concentration from baseline to Week 4 in subjects with baseline Hb <9.5 g/dL

End point title	Change in Hb concentration from baseline to Week 4 in subjects with baseline Hb <9.5 g/dL

End point description:

Change in Hb concentration from baseline to Week 4 in subjects with a baseline Hb <9.5 g/dL - ITT (MI) population

End point type	Secondary

End point timeframe:

At week 4

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	33		
Units: g/dL				
arithmetic mean (standard deviation)	1.35 (± 0.993)	2.99 (± 1.092)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hb concentration from baseline at Week 12 in subjects with baseline Hb <9.5 g/dL

End point title	Change in Hb concentration from baseline at Week 12 in subjects with baseline Hb <9.5 g/dL

End point description:

ITT (MI)

End point type	Secondary

End point timeframe:

At 12 weeks

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: g/dL				
arithmetic mean (standard deviation)	2.83 (± 1.493)	4.18 (± 1.686)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who experience a change from baseline (CFB) in Hb concentration ≥1.0 g/dL at Week 12

End point title	Proportion of subjects who experience a change from baseline (CFB) in Hb concentration ≥1.0 g/dL at Week 12
End point description:	
ITT (MI)	
End point type	Secondary
End point timeframe:	
At week 12	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	125		
Units: Subjects				
Responder	107	111		
Non-responder	18	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with baseline Hb <9.5 g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 12

End point title	Proportion of subjects with baseline Hb <9.5 g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 12
End point description:	
ITT (MI)	
End point type	Secondary
End point timeframe:	
At 12 weeks	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Subjects				
Responder	35	32		
Non-responder	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who experience a CFB in Hb concentration ≥2.0 g/dL at Week 12

End point title	Proportion of subjects who experience a CFB in Hb concentration ≥2.0 g/dL at Week 12
End point description:	
ITT (MI)	
End point type	Secondary
End point timeframe:	
At week 12	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	125		
Units: Subjects				
Responder	76	96		
Non-responder	49	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with baseline Hb <9.5 g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 12

End point title	Proportion of subjects with baseline Hb <9.5 g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 12
End point description:	
ITT (MI)	
End point type	Secondary
End point timeframe:	
At week 12	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Subjects				
Responder	26	30		
Non-responder	12	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who experience a CFB in Hb concentration ≥1.0 g/dL at Week 4

End point title	Proportion of subjects who experience a CFB in Hb concentration ≥1.0 g/dL at Week 4

End point description:

End point type	Secondary

End point timeframe:

At week 4

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	125		
Units: Subjects				
Responder	75	105		
Non-responder	50	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with baseline Hb <9.5 g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 4

End point title	Proportion of subjects with baseline Hb <9.5 g/dL that achieve an increase in Hb concentration of ≥1 g/dL at Week 4

End point description:

End point type	Secondary

End point timeframe:
At week 4

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Subjects				
Responder	23	33		
Non-responder	15	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who experience a CFB in Hb concentration ≥2.0 g/dL at Week 4

End point title	Proportion of subjects who experience a CFB in Hb concentration ≥2.0 g/dL at Week 4

End point description:
ITT (MI)

End point type	Secondary

End point timeframe:
At week 4

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	125		
Units: Subjects				
Responder	26	75		
Non-responder	99	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with baseline Hb <9.5 g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 4

End point title	Proportion of subjects with baseline Hb <9.5 g/dL that achieve an increase in Hb concentration of ≥2 g/dL at Week 4

End point description:
ITT (MI)

End point type	Secondary
End point timeframe: At week 4	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Subjects				
Responder	5	28		
Non-responder	33	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with Hb concentration within normal limits at Week 12

End point title	Proportion of subjects with Hb concentration within normal limits at Week 12
End point description: ITT (MI)	
End point type	Secondary
End point timeframe: At week 12	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	125		
Units: Subjects				
Responder	69	101		
Non-responder	56	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 12

End point title	Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 12

End point description: ITT (MI)	
End point type	Secondary
End point timeframe: At week 12	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Subjects				
Responder	12	28		
Non-responder	26	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with Hb concentration within normal limits at Week 4

End point title	Proportion of subjects with Hb concentration within normal limits at Week 4
End point description: ITT (MI)	
End point type	Secondary
End point timeframe: At week 4	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	125		
Units: Subjects				
Responder	31	60		
Non-responder	94	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with baseline Hb concentration <9.5 g/dL that is within normal limits at Week 4

End point title	Proportion of subjects with baseline Hb concentration <9.5

	g/dL that is within normal limits at Week 4
End point description: ITT (MI)	
End point type	Secondary
End point timeframe: At week 4	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Subjects				
Responder	2	15		
Non-responder	36	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ferritin concentration from baseline to Week 12

End point title	Change in ferritin concentration from baseline to Week 12
End point description: ITT (OC)	
End point type	Secondary
End point timeframe: At week 12	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	112		
Units: ng/ml				
arithmetic mean (standard deviation)	16.15 (± 21.721)	129.64 (± 170.154)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Long term efficacy endpoints, Anaemic status at Week 24

End point title	Long term efficacy endpoints, Anaemic status at Week 24

End point description:

Number of subjects with non-anaemic status at week 24 in population ITT (OC)

End point type	Other pre-specified

End point timeframe:

At week 24

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	85		
Units: Subjects				
anamic	28	27		
non-anaemic	52	58		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Long term efficacy endpoint, normal ferritin levels at Week 24

End point title	Long term efficacy endpoint, normal ferritin levels at Week 24

End point description:

ITT (OC)

End point type	Other pre-specified

End point timeframe:

At week 24

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	86		
Units: Subjects				
responder	56	60		
non-responder	21	26		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Quality of life - Medical outcome study SF-36

End point title	Quality of life - Medical outcome study SF-36

End point description:

Changes from baseline in physical component (PCS) and mental component (MCS) for SF-36

questionnaires. Data is from the last observation carried forward

End point type	Other pre-specified

End point timeframe:
At week 12

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: Score				
arithmetic mean (standard deviation)				
PCS - week 12	3.4 (± 6.04)	2.3 (± 6.34)		
PCS - week 24	3.6 (± 6.86)	2.7 (± 6.75)		
PCS - week 36	3.3 (± 7.43)	2.5 (± 6.78)		
PCS week 52/ET	3.0 (± 7.62)	2.5 (± 7.52)		
MCS - week 12	3.8 (± 6.69)	2.6 (± 6.65)		
MCS - week 24	4.1 (± 7.85)	3.1 (± 6.86)		
MCS - week 36	3.6 (± 8.19)	3.0 (± 7.04)		
MCS - week 52/ET	3.3 (± 8.32)	2.6 (± 7.60)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Long-term efficacy endpoint, anaemic status at Week 36

End point title	Long-term efficacy endpoint, anaemic status at Week 36

End point description:
ITT (OC)

End point type	Other pre-specified

End point timeframe:
Week 36

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	62		
Units: subjects				
anaemic	16	15		
non-anaemic	39	47		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Long-term efficacy endpoint, anaemic status at Week 52/ET

End point title	Long-term efficacy endpoint, anaemic status at Week 52/ET
End point description: ITT (OC)	
End point type	Other pre-specified
End point timeframe: Week 52/Early Termination	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	56		
Units: subjects				
anaemic	24	20		
non-anaemic	37	36		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Long term efficacy endpoint, normal ferritin levels at Week 36

End point title	Long term efficacy endpoint, normal ferritin levels at Week 36
End point description: ITT (OC)	
End point type	Other pre-specified
End point timeframe: Week 36	

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	62		
Units: subjects				
responder	43	37		
non-responder	11	25		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Long term efficacy endpoint, normal ferritin levels at Week 52/ET

End point title	Long term efficacy endpoint, normal ferritin levels at Week 52/ET

End point description:

ITT (OC)

End point type	Other pre-specified

End point timeframe:

At Week 52/Early Termination

End point values	Ferric Maltol	IV Iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	56		
Units: subjects				
responder	39	39		
non-responder	19	17		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The analysis of AEs focuses on TEAEs, which were defined as any AE that occurred on or worsened after the first dose of IMP and up to 14 days after the last dose of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Ferric maltol - Safety data set

Reporting group description:

Treatment Emergent Adverse Events (TEAEs) reported in the treatment arm with Ferric Maltol

Reporting group title	IV Iron - Safety dataset

Reporting group description:

Treatment Emergent Adverse Events (TEAEs) reported in the treatment arm with IV Ironl

Serious adverse events	Ferric maltol - Safety data set	IV Iron - Safety dataset	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 127 (9.45%)	4 / 120 (3.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 127 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic stenosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper limb fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (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			
Purpura non-thrombocytopenic			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (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			
Death			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			

subjects affected / exposed	0 / 127 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory bowel disease			
subjects affected / exposed	0 / 127 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 127 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (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	0 / 127 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mania			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (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			
Cellulitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (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 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 127 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Ferric maltol - Safety data set	IV Iron - Safety dataset	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 127 (49.61%)	39 / 120 (32.50%)	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 127 (0.79%)	1 / 120 (0.83%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 127 (3.15%)	1 / 120 (0.83%)	
occurrences (all)	4	1	
Migraine			
subjects affected / exposed	1 / 127 (0.79%)	0 / 120 (0.00%)	
occurrences (all)	4	0	
Dizziness			
subjects affected / exposed	2 / 127 (1.57%)	0 / 120 (0.00%)	
occurrences (all)	2	0	
Presyncope			
subjects affected / exposed	0 / 127 (0.00%)	2 / 120 (1.67%)	
occurrences (all)	0	2	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	1 / 127 (0.79%)	4 / 120 (3.33%)	
occurrences (all)	1	4	
Asthenia			
subjects affected / exposed	3 / 127 (2.36%)	1 / 120 (0.83%)	
occurrences (all)	3	1	
Chest pain			
subjects affected / exposed	0 / 127 (0.00%)	2 / 120 (1.67%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 127 (1.57%)	0 / 120 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 127 (9.45%)	3 / 120 (2.50%)	
occurrences (all)	13	3	
Nausea			
subjects affected / exposed	6 / 127 (4.72%)	2 / 120 (1.67%)	
occurrences (all)	8	5	
Abdominal pain upper			
subjects affected / exposed	7 / 127 (5.51%)	2 / 120 (1.67%)	
occurrences (all)	7	2	
Colitis ulcerative			
subjects affected / exposed	4 / 127 (3.15%)	4 / 120 (3.33%)	
occurrences (all)	4	4	
Crohn's disease			
subjects affected / exposed	3 / 127 (2.36%)	4 / 120 (3.33%)	
occurrences (all)	3	5	
Constipation			
subjects affected / exposed	5 / 127 (3.94%)	1 / 120 (0.83%)	
occurrences (all)	5	2	
Diarrhoea			
subjects affected / exposed	6 / 127 (4.72%)	1 / 120 (0.83%)	
occurrences (all)	6	1	
Faeces discoloured			

subjects affected / exposed	4 / 127 (3.15%)	0 / 120 (0.00%)	
occurrences (all)	4	0	
Flatulence			
subjects affected / exposed	4 / 127 (3.15%)	0 / 120 (0.00%)	
occurrences (all)	4	0	
Vomiting			
subjects affected / exposed	1 / 127 (0.79%)	3 / 120 (2.50%)	
occurrences (all)	1	3	
Abdominal distension			
subjects affected / exposed	3 / 127 (2.36%)	0 / 120 (0.00%)	
occurrences (all)	3	0	
Mouth ulceration			
subjects affected / exposed	2 / 127 (1.57%)	0 / 120 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 127 (1.57%)	1 / 120 (0.83%)	
occurrences (all)	2	1	
Alopecia			
subjects affected / exposed	1 / 127 (0.79%)	1 / 120 (0.83%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 127 (3.15%)	1 / 120 (0.83%)	
occurrences (all)	4	1	
Back pain			
subjects affected / exposed	1 / 127 (0.79%)	1 / 120 (0.83%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	2 / 127 (1.57%)	0 / 120 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 127 (7.87%)	4 / 120 (3.33%)	
occurrences (all)	11	6	
Cellulitis			

subjects affected / exposed	2 / 127 (1.57%)	0 / 120 (0.00%)	
occurrences (all)	4	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 127 (0.79%)	3 / 120 (2.50%)	
occurrences (all)	1	3	
Urinary tract infection			
subjects affected / exposed	2 / 127 (1.57%)	2 / 120 (1.67%)	
occurrences (all)	2	2	
Clostridium difficile infection			
subjects affected / exposed	1 / 127 (0.79%)	2 / 120 (1.67%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	3 / 127 (2.36%)	0 / 120 (0.00%)	
occurrences (all)	3	0	
Gastroenteritis viral			
subjects affected / exposed	2 / 127 (1.57%)	1 / 120 (0.83%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	2 / 127 (1.57%)	1 / 120 (0.83%)	
occurrences (all)	2	1	
Pharyngitis			
subjects affected / exposed	1 / 127 (0.79%)	2 / 120 (1.67%)	
occurrences (all)	1	2	
Respiratory tract infection			
subjects affected / exposed	2 / 127 (1.57%)	1 / 120 (0.83%)	
occurrences (all)	2	1	
Gastrointestinal infection			
subjects affected / exposed	1 / 127 (0.79%)	1 / 120 (0.83%)	
occurrences (all)	1	1	
Herpes zoster			
subjects affected / exposed	2 / 127 (1.57%)	0 / 120 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2015	Global Amendment 1 (protocol version 3.0). MAJOR CHANGES: 1. Addition of secondary endpoints to give specific information on the efficacy in population with baseline Hb concentration < 9.5g/dL. 2. Update to Primary objective wording to include only subjects with IBD in whom other oral iron therapies have failed. 3. Changes to inclusion criteria, to include subjects with Hb >= 8.0 g/dL and Ferritin <30 ng/ml or Ferritin <100 ng/ml an to clarify the wording for female with childbearing potential. 4. Changes to exclusion criteria, to clarify the permitted use of some immunosuppressant; to exclude patient who received oral iron supplementation within 4 weeks, to broaden the IBD population by changing the SCCAI and CDAI score for exclusion; to clarify exclusion for allergy sufferers; to only exclude patients with serious adverse reactions with IV iron from the trial. 5. Changes to concomitant medications to clarify the permitted use of immunosuppressant. 6. Addition of advice regarding ptential ferric maltol drug interactions. 7. Changes to individual discontinuation criteria, to discontinue patients from the study in case of use of prohibited co-medications, blood transfusions, change in immunosuppressant route. 8. Changes to the non-inferiority margin to 20% and the power of the study to 90%. this increased the number of required subjects to 108 per arm (121 to allow for protocol deviations). Various minor / administrative changes.
08 July 2016	Global Amendment 2 (protocol version 4.0). MAJOR CHANGES. 1. Addition of secondary endpoints related to Hb concentration at week 4. 2. Change to primary objective to clarify the population also includes patients for whom other oral iron therapies are not considered suitable. 3. Expansion of the study to US as well as in the EU. Various minor / administrative changes to reflect the change of the name of the sponsor (from Iron therapeutics to Shield TX, legal entity remains the same) and include background to reflect the extension of the study to the US.
04 January 2017	Global Amendment 3 (protocol version 5.0). MAJOR CHANGES. 1 and 2. Change in primary objective and inclusion criteria to include OFP-naive patients, and not only following OFP failure or unsuitability. 3. Small widening of the iron deficiency anaemia definition from <11 or 12 g/dL to <= 11 or 12 g/dL. 4 and 16. Clarification of permitted changes in the immunosuppressnt co-medication. 5. Clarification to refer to ferric carboxymaltose as intravenous iron in the exclusion criteria to ensure consistency for all countries. 6. Vitamin B12 or folic acid deficiency definition as an exclusion criteria is to be determined by the central laboratory screening results only and no longer by the investigator. 7. the exclusion criteria regarding subject with severe renal impairment is mentioned as applicable to US sites only. 8. Change to the discontinuation criteria for TSAT to above 60%, as it happens in the study population and is not indicative of iron overload. 9 to 15. Change in the dosing requirement of ferric maltol to clarify timing of administration of concomitant medication and introducing a 8-hour gap between doses. This change is implemented at each visit for compliance check and as a dosing reminder for patients. 11. and 15. Patients will be given 3 bottles of study drug (instead of 4) at visit 2 (randomisation) that will cover the 12 weeks of treatment before the next visit, and 4 bottles at visit 5 (week 36) that will cover for the final 16 weeks of treatment. Patients will be reminded at each visit that the number of bottle they are given (3 or 4) are sufficient for the treatment until the next visit. 17. Secondary endpoints regarding increase of Hb concentration of 1g/dL and 2g/dL have been split into two separate endpoints. Various minor / administrative changes, including an update to the number of sites in US and EU.

11 July 2017	Global Amendment 4 (protocol version 6.0). MAJOR CHANGES. 1, 2 and 6. Change in the exclusion criteria to allow dose change in immunosuppressant co-medication. This would reflect the current practice and also help to address low recruitment rates. 3. dosing information added in the previous amendment have been added to the section regarding interaction for consistency. 4. Changes in the discontinuation criteria to clarify the definition of transient rise or TSAT or ferritin and to allow immunosuppressent dose change as per amended exclusion criteria (see 1.). 5. Administration of IV iron at week 4 should only be done if clinically required. Various minor / administrative changes to correct spelling.
30 April 2018	Global amendment 5 (Protocol v7.0). MAJOR CHANGES. The study duration change from 52 weeks to 12 weeks (for new patients, existing patients will continue until their next scheduled visit) in an effort to improve recruitment rate. this change is reflected in various sections of the protocol: study design (5.4.3), dose selection (5.5), discontinuation criteria (7.4.6), IMP (8.1), clinical laboratory (10.2.12). The schedule of assessment for visit 4 and after have been revised in line with the amended study duration (patient's next visit after visit 4 will be the end of treatment visit). Various minor / administrative changes for consistency with protocol changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported