Clinical trial results:
A Phase 1, Open-Label, Randomized, Repeat Dose, Parallel Group Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ferric Maltol at Three Dosage Levels in Paediatric Subjects Aged 10-17 Years of Age with Iron Deficiency (with or without Anaemia)

Summary

EudraCT number	2016-002192-10
Trial protocol	GB
Global end of trial date	28 March 2018

Results information

Result version number	v1 (current)
This version publication date	14 October 2018
First version publication date	14 October 2018

Trial information

Trial identification

Sponsor protocol code	ST10-01-103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03181451
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shield TX (UK) Limited
Sponsor organisation address	Northern Design Centre, Baltic Business Quarter, Gateshead Quays,, Gateshead, United Kingdom, NE8 3DF
Public contact	Clinical Operations, Shield TX (UK) Limited, 44 1915118500, clinicalsupport@shieldtherapeutics.com
Scientific contact	Clinical Operations, Shield TX (UK) Limited, 44 1915118500, clinicalsupport@shieldtherapeutics.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001195-PIP01-11
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 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2018
Global end of trial reached?	Yes
Global end of trial date	28 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the pharmacokinetics (PK) and iron uptake of ferric maltol (ST10) in children and adolescents (aged 10 to 17 years) after twice daily (BID) oral doses of 7.8 mg, 16.6 mg, or 30 mg for 9 days (Days 1 to 9) and a single morning dose on Day 10 through measurement of serum iron, transferrin saturation (TSAT), and plasma concentrations of maltol and maltol glucuronide

Protection of trial subjects:

Routine recording of treatment-emergent AEs and changes in vital signs (blood pressure and heart rate) and 12-lead ECGs was conducted at study visits and clinical laboratory safety blood testing was conducted at screening and Day 10. In addition urine pregnancy testing was conducted at screening and at study visits, for females of child bearing potential.

Background therapy:

There was no background therapy administered across all subject groups.

Evidence for comparator:

No comparators were used in this trial.

Actual start date of recruitment	05 April 2017
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: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	3

Adolescents (12-17 years)	34
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential patients were selected from the general population attending centres for routine care of their iron deficiency/anaemia; those interested in participating were invited for the screening visit in order to assess eligibility. Written informed consent/assent was obtained from parent/guardian & patient prior to undergoing any study procedure.

Pre-assignment

Screening details:

Subject eligibility for the study was assessed at the Screening Visit (conducted within 14 days prior to the planned Ferric Maltol dosing period for each subject).

Pre-assignment period milestones

Number of subjects started	44[1]
Number of subjects completed	37

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen faiilures: 7

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Provides details of all subjects screened in total (44); 7 subjects were ineligible for the trial after Screening, so 37 were enrolled.

Period 1

Period 1 title	Ferric Maltol treatment period Days 1-10 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferric Maltol 7.8mg BID

Arm description:

Cohort received 7.8mg iron as Ferric Maltol BID for 9 days and a single 7.8mg dose on Day 10

Arm type	Experimental
Investigational medicinal product name	Ferric Maltol 7.8mg
Investigational medicinal product code	ST10
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort received 7.8mg iron as Ferric Maltol BID for 9 days and a single 7.8mg dose on Day 1

Arm title	Ferric Maltol 16.6mg BID

Arm description:

Cohort received 16.6mg iron as Ferric Maltol BID for 9 days and a single 16.6mg dose on Day 10

Arm type	Experimental
Investigational medicinal product name	Ferric Maltol 16.6mg
Investigational medicinal product code	ST10
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort received 16.6mg iron as Ferric Maltol BID for 9 days and a single 7.8mg dose on Day 1

Arm title	Ferric Maltol 30.0mg BID

Arm description:

Cohort received 30.0mg iron as Ferric Maltol BID for 9 days and a single 30.0mg dose on Day 1

Arm type	Experimental
Investigational medicinal product name	Ferric Maltol 30.0mg
Investigational medicinal product code	ST10
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cohort received 30.0mg iron as Ferric Maltol BID for 9 days and a single 30.0mg dose on Day 10.

Number of subjects in period 1	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID
Started	12	13	12
Completed	12	11	12
Not completed	0	2	0
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Ferric Maltol treatment period Days 1-10

Reporting group description: -

Reporting group values	Ferric Maltol treatment period Days 1-10	Total	
Number of subjects	37	37	
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)	3	3	
Adults (18-64 years)	34	34	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	14.0		
standard deviation	± 1.8	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	13	13	

Subject analysis sets

Subject analysis set title	PPK Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS/ ITT Population included all subjects who took at least 1 dose of study drug and had at least 1 evaluable postdose PK sample. This population was used in the PPK analysis.

Reporting group values	PPK Analysis		
Number of subjects	37		
Age categorical 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)	3		

Adolescents (12-17 years)	34		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	14.0		
standard deviation	± 1.8		
Gender categorical Units: Subjects			
Female	24		
Male	13		

End points

End points reporting groups

Reporting group title	Ferric Maltol 7.8mg BID
Reporting group description:	
Cohort received 7.8mg iron as Ferric Maltol BID for 9 days and a single 7.8mg dose on Day 10	
Reporting group title	Ferric Maltol 16.6mg BID
Reporting group description:	
Cohort received 16.6mg iron as Ferric Maltol BID for 9 days and a single 16.6mg dose on Day 10	
Reporting group title	Ferric Maltol 30.0mg BID
Reporting group description:	
Cohort received 30.0mg iron as Ferric Maltol BID for 9 days and a single 30.0mg dose on Day 1	
Subject analysis set title	PPK Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS/ ITT Population included all subjects who took at least 1 dose of study drug and had at least 1 evaluable postdose PK sample. This population was used in the PPK analysis.	

Primary: Cmax Day 1 for Maltol Glucuronide

End point title	Cmax Day 1 for Maltol Glucuronide[1]
End point description:	
End point type	Primary
End point timeframe:	
Measured after first dose of Ferric Maltol on Day 1	
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: As per the statistical analysis plan (SAP), only summary descriptive statistics were derived for this end point from population PK analysis; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.	

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: mg/L				
arithmetic mean (standard deviation)	0.5299 (± 0.5295)	1.1632 (± 0.184)	2.451 (± 2.2351)	

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - Change from Cmax to Ctrough on Day 1

End point title	Serum Iron - Change from Cmax to Ctrough on Day 1[2]
End point description:	
End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1.

Notes:

[2] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: mg/L				
arithmetic mean (standard deviation)	0.2715 (± 0.11873)	0.4102 (± 0.22155)	0.6169 (± 0.3230)	

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - AUC0-6h Day 1

End point title	Serum Iron - AUC0-6h Day 1[3]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1

Notes:

[3] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: h.mg/L				
arithmetic mean (standard deviation)	3.928 (± 1.1318)	5.963 (± 1.7793)	6.711 (± 2.5721)	

Attachments (see zip file)	Serum Iron PPK - Day 1/Serum Iron-Day 1.PNG

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - CL/F Day 1

End point title	Serum Iron - CL/F Day 1[4]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1

Notes:

[4] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: L/h				
arithmetic mean (standard deviation)	0.324 (± 0.1517)	0.654 (± 0.2441)	1.321 (± 0.6945)	

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - V/F Day 1

End point title	Serum Iron - V/F Day 1[5]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1

Notes:

[5] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: Litres				
arithmetic mean (standard deviation)	10.462 (± 3.1033)	14.244 (± 4.8183)	22.114 (± 7.2315)	

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - Change from Cmax to Ctrough on Day 10

End point title	Serum Iron - Change from Cmax to Ctrough on Day 10[6]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10

Notes:

[6] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: mg/L				
arithmetic mean (standard deviation)	0.2551 (± 0.08)	0.3625 (± 0.153)	0.5486 (± 0.323)	

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - Cave (0-6h) Day 10

End point title	Serum Iron - Cave (0-6h) Day 10[7]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10.

Notes:

[7] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: mg/L				
arithmetic mean (standard deviation)	0.9748 (± 0.39783)	0.9557 (± 0.2964)	1.1667 (± 0.6142)	

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - AUC0-6h Day 10

End point title	Serum Iron - AUC0-6h Day 10[8]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10.

Notes:

[8] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: h.mg/L				
arithmetic mean (standard deviation)	5.849 (± 2.38)	5.734 (± 1.78)	7.00 (± 3.69)	

Attachments (see zip file)	Serum Iron PPK - Day 10/Serum Iron-Day 10.PNG

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - CLss/F Day 10

End point title	Serum Iron - CLss/F Day 10[9]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10

Notes:

[9] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: L/h				
arithmetic mean (standard deviation)	0.898 (± 0.31)	1.757 (± 0.6673)	3.264 (± 2.2297)	

Statistical analyses

No statistical analyses for this end point

Primary: Serum Iron - RAUC(0-6h) Day 10/Day 1

End point title	Serum Iron - RAUC(0-6h) Day 10/Day 1[10]

End point description:

End point type	Primary

End point timeframe:

Measured after first and last dose of Ferric Maltol on Day 1 & Day 10

Notes:

[10] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: Ratio - AUC(0-6h) first / last dose				
arithmetic mean (standard deviation)	1.529 (± 1.4673)	1.020 (± 0.3170)	1.038 (± 0.3973)	

Statistical analyses

No statistical analyses for this end point

Primary: Transferrin Saturation (TSAT%) Day 1, baseline

End point title	Transferrin Saturation (TSAT%) Day 1, baseline[11]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1

Notes:

[11] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered

inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: percent				
arithmetic mean (standard deviation)	11.5 (± 5.66)	16.8 (± 9.25)	15.8 (± 9.31)	

Statistical analyses

No statistical analyses for this end point

Primary: Transferrin Saturation (TSAT%) Day 1, maximum response (%)

End point title	Transferrin Saturation (TSAT%) Day 1, maximum response (%)[12]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1

Notes:

[12] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: percent				
arithmetic mean (standard deviation)	18.68 (± 7.13)	28.261 (± 8.4784)	32.845 (± 10.5913)	

Statistical analyses

No statistical analyses for this end point

Primary: Transferrin Saturation (TSAT%) Day 1, time to maximum response Tmax (h).

End point title	Transferrin Saturation (TSAT%) Day 1, time to maximum response Tmax (h).[13]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1.

Notes:

[13] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: hour				
median (full range (min-max))	4.00 (2.00 to 4.00)	3.00 (2.00 to 4.00)	3.00 (3.00 to 5.00)	

Statistical analyses

No statistical analyses for this end point

Primary: Transferrin Saturation (TSAT%) Day 1, AUC0-6h (h.%)

End point title	Transferrin Saturation (TSAT%) Day 1, AUC0-6h (h.%)[14]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1.

Notes:

[14] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: h.%				
arithmetic mean (standard deviation)	104.5 (± 41.009)	158.21 (± 50.723)	179.47 (± 60.259)	

Statistical analyses

No statistical analyses for this end point

Primary: Transferrin Saturation (TSAT%) Day 10, maximum response (%)

End point title	Transferrin Saturation (TSAT%) Day 10, maximum response (%)[15]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10.

Notes:

[15] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: percent				
arithmetic mean (standard deviation)	27.779 (± 13.86)	27.214 (± 6.699)	33.524 (± 13.633)	

Statistical analyses

No statistical analyses for this end point

Primary: Transferrin Saturation (TSAT%) Day 10, time to maximum response Tmax (h).

End point title	Transferrin Saturation (TSAT%) Day 10, time to maximum response Tmax (h).[16]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10.

Notes:

[16] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: hour				
median (full range (min-max))	3.00 (0.00 to 4.00)	3.00 (0.00 to 4.00)	3.00 (0.00 to 4.00)	

Statistical analyses

No statistical analyses for this end point

Primary: Transferrin Saturation (TSAT%) Day 10, AUC0-6h (h.%).

End point title	Transferrin Saturation (TSAT%) Day 10, AUC0-6h (h.%).[17]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10.

Notes:

[17] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: h.%				
arithmetic mean (standard deviation)	157.43 (± 81.693)	149.40 (± 37.8)	180.14 (± 76.19)	

Statistical analyses

No statistical analyses for this end point

Primary: Cmax Day 10 for Maltol Glucuronide

End point title	Cmax Day 10 for Maltol Glucuronide[18]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10

Notes:

[18] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: mg/L				
arithmetic mean (standard deviation)	0.9926 (± 0.023)	2.1028 (± 0.133)	4.2355 (± 0.781)	

Statistical analyses

No statistical analyses for this end point

Primary: Tmax Day 1 for Maltol Glucuronide

End point title	Tmax Day 1 for Maltol Glucuronide[19]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1

Notes:

[19] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: hour				
median (full range (min-max))	1.00 (1.0 to 1.00)	1.00 (0.75 to 1.00)	1.00 (0.75 to 1.00)	

Statistical analyses

No statistical analyses for this end point

Primary: Tmax Day 10 for Maltol Glucuronide

End point title	Tmax Day 10 for Maltol Glucuronide[20]

End point description:

Measured after last dose of Ferric Maltol on Day 10.

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10.

Notes:

[20] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: hour				
median (full range (min-max))	0.75 (0.75 to 0.75)	0.75 (0.75 to 0.75)	0.75 (0.75 to 0.75)	

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-6h Day 1 for Maltol Glucuronide

End point title	AUC0-6h Day 1 for Maltol Glucuronide[21]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1.

Notes:

[21] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: h.mg/L				
arithmetic mean (standard deviation)	2.585 (± 0.0968)	5.613 (± 0.7589)	11.09 (± 3.9033)	

Attachments (see zip file)	Maltol Glucuronide PPK - Day 1/Maltol Glucuronide-Day 1.PNG

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-6h Day 10 for Maltol Glucuronide

End point title	AUC0-6h Day 10 for Maltol Glucuronide[22]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10.

Notes:

[22] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: h.mg/L				
arithmetic mean (standard deviation)	5.016 (± 0.1133)	10.518 (± 0.5277)	20.511 (± 1.7997)	

Attachments (see zip file)	Maltol Glucuronide PPK - Day 10/Maltol Glucuronide-Day 10.

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-inf Day 1 for Maltol Glucuronide

End point title	AUC0-inf Day 1 for Maltol Glucuronide[23]

End point description:

End point type	Primary

End point timeframe:

Measured after first dose of Ferric Maltol on Day 1

Notes:

[23] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: h.mg/L				
arithmetic mean (standard deviation)	8.590 (± 0.2025)	17.862 (± 0.9328)	34.372 (± 4.5052)	

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-tau Day 10 for Maltol Glucuronide

End point title	AUC0-tau Day 10 for Maltol Glucuronide[24]

End point description:

End point type	Primary

End point timeframe:

Measured after last dose of Ferric Maltol on Day 10.

Notes:

[24] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: h.mg/L				
arithmetic mean (standard deviation)	8.59 (± 0.2024)	17.862 (± 0.9327)	34.368 (± 4.4981)	

Statistical analyses

No statistical analyses for this end point

Primary: RAUC(0-6h) Maltol Glucuronide Day 10/Day 1

End point title	RAUC(0-6h) Maltol Glucuronide Day 10/Day 1[25]

End point description:

End point type	Primary

End point timeframe:

Ratio AUC0-6h measured after last dose of Ferric Maltol on Day 10 vs first dose Day 1.

Notes:

[25] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: Ratio AUC(0-6h) Day 10/Day 1				
arithmetic mean (standard deviation)	1.942 (± 0.0582)	1.899 (± 0.2286)	2.030 (± 0.6695)	

Statistical analyses

No statistical analyses for this end point

Primary: RCmax Maltol Glucuronide Day 10/Day 1

End point title	RCmax Maltol Glucuronide Day 10/Day 1[26]

End point description:

End point type	Primary

End point timeframe:

Ratio Cmax measured after last dose of Ferric Maltol on Day 10 vs first dose Day 1.

Notes:

[26] - 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: As per the study statistical analysis plan, only summary descriptive statistics were derived for this population PK endpoint; between dose-group statistical comparisons were considered inappropriate for the study design and sample size.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: Ratio Cmax Day 10/Day 1				
arithmetic mean (standard deviation)	1.875 (± 0.0537)	1.836 (± 0.2109)	1.956 (± 0.6210)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Day 10 in Haemoglobin Concentration

End point title	Change from Baseline to Day 10 in Haemoglobin Concentration

End point description:

End point type	Secondary

End point timeframe:

Change calculated as difference in values measured at Screening (Baseline) and on Day 10

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: g/dL				
arithmetic mean (standard deviation)	-0.45 (± 0.301)	-0.33 (± 1.097)	-0.03 (± 0.789)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Day 10 in Absolute Reticulocyte Count

End point title	Change from Baseline to Day 10 in Absolute Reticulocyte Count

End point description:

End point type	Secondary

End point timeframe:

Change calculated as difference in values measured at Screening (Baseline) and on Day 10.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	10	5	
Units: 10^12/L				
arithmetic mean (standard deviation)	0.016 (± 0.0358)	-0.001 (± 0.0218)	0.036 (± 0.0114)	

Statistical analyses

No statistical analyses for this end point

Secondary: Negative and Positive Non-Transferrin Bound Iron [NTBI] tests on Day 10, predose

End point title	Negative and Positive Non-Transferrin Bound Iron [NTBI] tests on Day 10, predose

End point description:

End point type	Secondary

End point timeframe:

Measured prior to last dose of Ferric Maltol on Day 10

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	11	12	
Units: subjects				
Negative	10	11	11	
Positive	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Negative and Positive Non-Transferrin Bound Iron [NTBI] tests on Day 1, predose

End point title	Negative and Positive Non-Transferrin Bound Iron [NTBI] tests on Day 1, predose

End point description:

End point type	Secondary

End point timeframe:

Measured prior to first dose of Ferric Maltol on Day 1.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: subjects				
Negative	12	13	12	
Positive	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Ferritin - change from Baseline to Day 10, predose

End point title	Ferritin - change from Baseline to Day 10, predose

End point description:

End point type	Secondary

End point timeframe:

Change calculated as difference in values measured at Day 1, predose (Baseline) and on Day 10, predose.

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	12	
Units: µg/L				
arithmetic mean (standard deviation)	0.5 (± 4.95)	4.1 (± 3.73)	7.3 (± 8.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: TIBC - change from Baseline to Day 10, predose

End point title	TIBC - change from Baseline to Day 10, predose

End point description:

End point type	Secondary

End point timeframe:

Change calculated as difference in values measured at Day 1, predose (Baseline) and on Day 10, predose

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	10	
Units: umol/L				
arithmetic mean (standard deviation)	1.13 (± 4.452)	-3.11 (± 3.201)	-2.12 (± 3.406)	

Statistical analyses

No statistical analyses for this end point

Secondary: UIBC - change from Baseline to Day 10, predose

End point title	UIBC - change from Baseline to Day 10, predose

End point description:

End point type	Secondary

End point timeframe:

Change calculated as difference in values measured at Day 1, predose (Baseline) and on Day 10, predose

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	11	
Units: umol/L				
arithmetic mean (standard deviation)	-4.49 (± 8.343)	-2.33 (± 5.525)	-2.10 (± 7.775)	

Statistical analyses

No statistical analyses for this end point

Secondary: Transferrin - change from Baseline to Day 10, predose

End point title	Transferrin - change from Baseline to Day 10, predose

End point description:

End point type	Secondary

End point timeframe:

Change calculated as difference in values measured at Day 1, predose (Baseline) and on Day 10, predose

End point values	Ferric Maltol 7.8mg BID	Ferric Maltol 16.6mg BID	Ferric Maltol 30.0mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	11	
Units: g/L				
arithmetic mean (standard deviation)	0.032 (± 0.2275)	-0.147 (± 0.1419)	-0.085 (± 0.151)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were solicited at each study visit after informed consent at Screening; AEs/SAEs that occurred throughout the study, up to 2 weeks after last dose of study drug (SAEs only) were recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Ferric Maltol 7.8mg BID - Safety Population

Reporting group description:

Safety population adverse events for Ferric Maltol 7.8mg BID treatment arm.

Reporting group title	Ferric Maltol 16.6mg BID - Safety Population

Reporting group description: -

Reporting group title	Ferric Maltol 30.0mg BID - Safety Population

Reporting group description: -

Serious adverse events	Ferric Maltol 7.8mg BID - Safety Population	Ferric Maltol 16.6mg BID - Safety Population	Ferric Maltol 30.0mg BID - Safety Population
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Ferric Maltol 7.8mg BID - Safety Population	Ferric Maltol 16.6mg BID - Safety Population	Ferric Maltol 30.0mg BID - Safety Population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	7 / 13 (53.85%)	7 / 12 (58.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)	3 / 13 (23.08%)	5 / 12 (41.67%)
occurrences (all)	1	3	5
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Faeces discoloured			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	3 / 12 (25.00%)
occurrences (all)	1	1	3
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2017	Protocol Version 3, dated 08 Feb 2017 MAJOR CHANGES 1. Changes to Inclusion Criteria (Section 7.3.1) Inclusion Criterion 5 Now reads: Where appropriate, female subjects of childbearing potential must agree to use a reliable method of contraception until study completion and for at least 4 weeks following their final study visit. Reliable contraception is defined as a method which results in a low failure rate, i.e., less than 1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), complete sexual abstinence, a vasectomized partner and oral contraceptive medications. Rationale: Based on the initial review of MHRA on the protocol, the less than 1% per year failure rate considered to be highly effective method, therefore required to be listed in the protocol. The acceptable contraceptive methods are now listed and in line with the Clinical Trials Facilitation Group (CTFG) guidance document. Other sections within the study protocol that are affected by these changes include: Section 4, Synopsis, Inclusion Criteria. 2. Changes to Continuation of Treatment (Section 8.8) Now reads: No further provisions are made for access to the study treatment under this protocol following Visit 3, Day 10. Rationale: Further to internal discussions, Shield concluded that it is not beneficial to continue treatment with the lower dose strengths for which no data is available and efficacy unknown. This is a phase 1 study designed to establish the PK using the approved 30mg capsules and 2 lower doses. The data will be used to select the dose for a subsequent Phase 3 paediatric study which will be conducted for a longer duration.

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.

None specified.

Notes: