Clinical trial results:
A prospective, multicentre, randomised, double-blind, placebo controlled study with oral ST10-021 for the treatment of iron deficiency anaemia in subjects with quiescent Crohn's Disease where oral ferrous preparations have failed or cannot be used (AEGIS 2)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2010-023589-39
Trial protocol	DE AT GB HU
Global end of trial date	17 October 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016
Summary attachment (see zip file)	AEGIS 1/2 double-blind results publication (Gasche et al - Aegis IBD article 2015.pdf) AEGIS 1/2 long term data publication (Schmidt_et_al-2016-Alimentary_Pharmacology_&_Therapeutics.pdf)

Trial information

Trial identification

Sponsor protocol code	ST10-01-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01352221
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Iron Therapeutics (UK) Ltd
Sponsor organisation address	Northern Design Centre, Baltic Business Quarter, Gateshead Quays, Gateshead, United Kingdom, NE8 3DF
Public contact	Clinical Operations, Iron Therapeutics (Switzerland) AG, 44 191511 8510, jmitchell@shieldtx.com
Scientific contact	Clinical Operations, Iron Therapeutics (Switzerland) AG, 44 191511 8510, 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	02 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2013
Global end of trial reached?	Yes
Global end of trial date	17 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of oral ST10-021 in the treatment of iron deficiency anaemia (IDA), as measured by change in haemoglobin (Hb) concentration from baseline to Week 12, in subjects with quiescent Crohn's Disease (CD) where oral ferrous preparations (OFP) have failed or cannot be used.

Protection of trial subjects:

Subjects were males or females aged ≥18 years with a confirmed diagnosis of CD. All patients were required to be in remission or to have a mild-to-moderate disease activity of CD (as defined by a Crohn’s Disease Activity Index [CDAI] score <220 at randomization). All subjects were required to have mild-to-moderate IDA, as defined by a haemoglobin (Hb) concentration ≥9.5 g/dL and <12.0 g/dL for females and ≥9.5 g/dL and <13.0 g/dL for males (40), as well as serum ferritin levels <30 µg/L at screening. Subjects were also required to have previously failed on treatment with oral ferrous products (OFP) for one or more of the following reasons: 1) adverse drug effects that led to withdrawal from OFP (at least one of: nausea, diarrhea, constipation, abdominal pain, flatulence); 2) deterioration of the primary disease caused by OFP; 3) lack of efficacy; 4) other signs of failure of OFP (or documented reasons why OFP could not be used). Safety assessments conducted throughout the study included adverse event monitoring, routine clinical safety laboratory testing, changes in CDAI and IBDQ (Irritable Bowel Disease Questionnaire). Subjective Quality of Life score was also assessed over the study duration using SF-36.

Background therapy:

Subjects receiving protocol-allowed immunosuppressive and immunomodulatory agents for treatment of IBD (i.e. thiopurines and anti-TNF) at screening were required to have been on a stable dose for ≥4 weeks prior to randomization. Subjects with anaemia unrelated to iron deficiency or who had received depot iron preparations, erythropoietin 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 (e.g. methotrexate, cyclosporin A, tacrolimus); folate deficiency, uncorrected vitamin B12 deficiency; serum creatinine >2.0 mg/dL (176 µmol/L); abnormal liver function tests; and pregnancy.

Evidence for comparator: -

Actual start date of recruitment	01 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Germany: 67

Country: Number of subjects enrolled	Hungary: 26
Worldwide total number of subjects	128
EEA total number of subjects	128

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)	125
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential subjects were selected from the general population attending each centre in UK, DE, AU or HU for routine care of their IBD and anaemia. Individuals interested in participating were invited for the screening visit in order to assess eligibility. Written informed consent was obtained prior to conducting any study specific assessments.

Pre-assignment

Screening details:

Potential subjects were screened for eligibility to participate based on their demographics, medical/surgical history, physical examination, concomitant medications, vital signs, clinical laboratory tests (including pregnancy test for females of child-bearing potential) and current IBD disease status (Crohn's Disease Activity Index [CDAI] score).

Period 1

Period 1 title	Double-blind phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

At randomisation, an Interactive Voice/Web Response System (IXRS) assigned a study drug kit (uniquely numbered; ST10 or placebo kits) to each subject according to the pre-defined randomisation scheme. The site dispensed the appropriate number of study drug bottles at each scheduled study visit, according to the schedule of assessments and IXRS kit number allocation. Randomisation was centrally controlled for all subjects via the IXRS system.

Arms

Are arms mutually exclusive?	Yes
Arm title	ST10

Arm description:

Double-blind phase, 12 week active treatment arm with ST10.

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

Dosage and administration details:

One (1) 30mg capsule taken on an empty stomach morning and evening, with a glass of water.

Arm title	Placebo

Arm description:

Placebo treatment arm for 12 week double-blind phase

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo for ST10
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One (1) capsule taken each morning and evening on an empty stomach, with a glass of water.

Number of subjects in period 1	ST10	Placebo
Started	64	64
Completed	55	53
Not completed	9	11
Consent withdrawn by subject	3	5
Physician decision	-	1
Adverse event, non-fatal	6	4
Protocol deviation	-	1

Period 2	
Period 2 title	Open-label phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	ST10 - open-label continuation from active arm in double-blind

Arm description:

Open-label extension of ST10 active treatment arm from double-blind phase.

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

Dosage and administration details:

One (1) 30mg capsule taken on an empty stomach morning and evening, with a glass of water.

Arm title	Placebo switch to open-label extension ST10 treatment

Arm description:

Open-label extension ST10 treatment arm for placebo subjects completing double-blind phase after 12 weeks.

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

Dosage and administration details:

One (1) 30mg capsule taken on an empty stomach morning and evening, with a glass of water.

Number of subjects in period 2[1]	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment
Started	50	47
Completed	37	36
Not completed	13	11
Physician decision	2	1
Consent withdrawn by subject	1	6
Adverse event, non-fatal	8	4
Worsening of IBD symptoms	1	-
Pregnancy	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only subjects in DE, UK and HU were able to enter the open-label extension; addition of the open-label extension via Protocol Amendment 1 was rejected by the Ethics committee in AU, hence the open-label extension was not conducted in AU; study subjects in AU hence completed only the double- blind portion of the study at Week 12 (or early termination, if applicable).

Baseline characteristics

Reporting groups	
Reporting group title	ST10
Reporting group description:	
Double-blind phase, 12 week active treatment arm with ST10.	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment arm for 12 week double-blind phase	

Reporting group values	ST10	Placebo	Total
Number of subjects	64	64	128
Age categorical			
The study population consisted of males and females, aged 18 years or older at screening and with a current diagnosis of Crohn's Disease and IDA.			
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)	62	63	125
From 65-84 years	2	1	3
85 years and over	0	0	0
Age continuous			
The study population consisted of males and females, aged 18 years or older at screening and with a current diagnosis of Crohn's Disease and IDA.			
Units: years			
arithmetic mean	40.1	38.5	
standard deviation	± 13.52	± 12.3	-
Gender categorical			
Units: Subjects			
Female	40	43	83
Male	24	21	45
Duration of Crohn’s disease (years)			
Duration of Crohn’s disease (years)			
Units: Years			
median	10.12	10.89	
full range (min-max)	0.5 to 40.2	0 to 30.8	-
Time since last IDB flare-up (months)			
Time since last IDB flare-up (months)			
Units: Months			
median	8.71	6.49	
full range (min-max)	0 to 450.4	0 to 258.8	-
Time since last OFP dose (months)			
Time since last prior oral ferrous product (OFP) dose (months)			
Units: Months			

median	21.82	17.4	
full range (min-max)	0.2 to 175.4	0 to 206.8	-
Haemoglobin concentration at baseline			
Haemoglobin concentration at baseline of 12 week double-blind phase			
Units: g/dL			
arithmetic mean	11	11.1	
standard deviation	± 1.027	± 0.851	-
Serum Ferritin concentration at baseline			
Serum Ferritin concentration at baseline of the 12 week double-blind phase			
Units: µg/L			
arithmetic mean	8.6	8.2	
standard deviation	± 6.8	± 6.5	-
Serum TSAT% at baseline			
Serum TSAT% (transferrin saturation %) at baseline of the 12 week double-blind phase			
Units: Percentage			
arithmetic mean	10.6	9.5	
standard deviation	± 11.7	± 7.5	-
Crohn's Disease Activity Index (CDAI) score at baseline			
Crohn's Disease Activity Index (CDAI) score at baseline (randomisation) of the 12-week double-blind phase (in subjects with CD).			
Units: Score			
median	86	109	
full range (min-max)	14 to 199	10 to 220	-
Irritable Bowel Disease Questionnaire (IBDQ) score at baseline			
Irritable Bowel Disease Questionnaire (IBDQ) score at baseline (randomisation) of the 12 week double-blind phase			
Units: Score			
arithmetic mean	5.84	5.65	
standard deviation	± 0.942	± 1.067	-

End points

End points reporting groups

Reporting group title	ST10
Reporting group description:	
Double-blind phase, 12 week active treatment arm with ST10.	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment arm for 12 week double-blind phase	
Reporting group title	ST10 - open-label continuation from active arm in double-blind
Reporting group description:	
Open-label extension of ST10 active treatment arm from double-blind phase.	
Reporting group title	Placebo switch to open-label extension ST10 treatment
Reporting group description:	
Open-label extension ST10 treatment arm for placebo subjects completing double-blind phase after 12 weeks.	

Primary: Change in Haemoglobin Concentration from Baseline to Week 12 (Full Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 12 (Full Analysis Set)

End point description:

Primary efficacy endpoint, defined as the change in Hb concentration from Baseline to Week 12. Baseline was defined as the pre-dose Hb concentration measured at the Randomisation Visit (Week 0). Missing Randomisation Hb values were replaced by Screening Hb values, if the randomisation was within the protocol-specified window. Hb concentration (g/dL) was analysed by a central laboratory from blood samples collected at every clinic visit: Screening, Randomisation (Week 0), Weeks 4, 8, 12, 14, 16, 20, 24, 36, 48, 64, Weeks 14 to 64 were open-label. The baseline, absolute concentration and change from baseline in Hb at all post-randomisation visits were listed and summarised by week using descriptive statistics. An analysis of covariance (ANCOVA) was used to analyse the primary endpoint; this included treatment, gender and disease as factors and baseline Hb as a covariate.

End point type	Primary
End point timeframe:	
Double-blind phase (12 weeks), primary efficacy endpoint of study	

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	53		
Units: g/dL				
arithmetic mean (standard deviation)	2.26 (± 1.184)	0.01 (± 0.764)		

Statistical analyses

Statistical analysis title	ANCOVA - primary endpoint, Full Analysis Set

Statistical analysis description:

ANCOVA for primary endpoint, Change in Hb concentration from Baseline to Week 12 in double-blind phase, Full Analysis Set

Comparison groups	Placebo v ST10
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.18
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	1.81
Variability estimate	Standard error of the mean
Dispersion value	0.19

Secondary: Proportion of subjects that achieved ≥2 g/dL change from baseline in Hb concentration at Week 12 (Full Analysis Set)

End point title	Proportion of subjects that achieved ≥2 g/dL change from baseline in Hb concentration at Week 12 (Full Analysis Set)

End point description:

Logistic regression analysis of proportion of subjects that achieved ≥2 g/dL change from baseline in Hb concentration at Week 12 in the double-blind phase

End point type	Secondary

End point timeframe:

Proportion of subjects that achieved ≥2 g/dL change from baseline in Hb concentration at Week 12 - double-blind phase

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	64		
Units: Subjects				
Yes	36	0		
No	28	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects that achieved Hb concentration within normal range at Week 12 (Full Analysis Set)

End point title	Proportion of subjects that achieved Hb concentration within normal range at Week 12 (Full Analysis Set)

End point description:

Logistic regression analysis of proportion of subjects that achieved Hb concentration within normal range at Week 12 - end of double-blind phase

End point type	Secondary

End point timeframe:

Proportion of subjects that achieved Hb concentration within normal range at Week 12 - end of double-blind phase

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	64		
Units: Subjects				
Yes	42	8		
No	22	56		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects that achieved ≥1 g/dL change from baseline in Hb concentration at Week 12 (Full Analysis Set)

End point title	Proportion of subjects that achieved ≥1 g/dL change from baseline in Hb concentration at Week 12 (Full Analysis Set)

End point description:

Logistic regression analysis of proportion of subjects that achieved ≥1 g/dL change from baseline in Hb concentration at Week 12 in the double-blind phase

End point type	Secondary

End point timeframe:

Subjects that achieved ≥1 g/dL change from baseline in Hb concentration at Week 12 - end of double-blind phase

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	64		
Units: Subjects				
Yes	50	7		
No	14	57		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hb concentration from Baseline to Week 4 (Full Analysis Set)	
End point title	Change in Hb concentration from Baseline to Week 4 (Full Analysis Set)

End point description:

ANCOVA analysis of the change in Hb concentration from Baseline to Week 4 of the double-blind phase - Full Analysis Set, multiple imputation

End point type	Secondary

End point timeframe:

Change in Hb concentration from Baseline to Week 4 of the double-blind phase - Full Analysis Set

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: g/dL				
arithmetic mean (standard deviation)	1.08 (± 0.676)	0 (± 0.67)		

Statistical analyses

Statistical analysis title	Change in Hb concentration from Baseline to Week 4

Statistical analysis description:

ANCOVA analysis of the change in Hb concentration from Baseline to Week 4 of the double-blind phase - Full Analysis Set, multiple imputation

Comparison groups	Placebo v ST10
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.04
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	0.11

Secondary: Change in Hb concentration from Baseline to Week 8 (Full Analysis Set)	
End point title	Change in Hb concentration from Baseline to Week 8 (Full Analysis Set)

End point description:

ANCOVA analysis of Change in Hb concentration from Baseline to Week 8 of double-blind phase - Full Analysis Set, multiple imputation

End point type	Secondary

End point timeframe:

Change in Hb concentration from Baseline to Week 8 of double-blind phase - Full Analysis Set

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	56		
Units: g/dL				
arithmetic mean (standard deviation)	1.79 (± 1.037)	0.04 (± 0.722)		

Statistical analyses

Statistical analysis title	Change in Hb concentration from Baseline to Week 8

Statistical analysis description:

ANCOVA analysis of change in Hb concentration from Baseline to Week 8 of double-blind phase - Full Analysis Set, multiple imputation

Comparison groups	ST10 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.73
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	1.43
Variability estimate	Standard error of the mean
Dispersion value	0.15

Secondary: Change in Haemoglobin Concentration from Baseline to Week 16 (Full Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 16 (Full Analysis Set)

End point description:

Change in Haemoglobin Concentration from Baseline to Week 16 (Full Analysis Set), after 12-week double-blind phase and first 4 weeks of open-label ST10 treatment.

End point type	Secondary

End point timeframe:

Change in Haemoglobin Concentration from Baseline to Week 16 (Full Analysis Set), after 12-week double-blind phase and first 4 weeks of open-label ST10 treatment.

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: g/dL				
arithmetic mean (standard deviation)	2.34 (± 1.281)	1.04 (± 1.023)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Haemoglobin Concentration from Baseline to Week 20 (Full Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 20 (Full Analysis Set)

End point description:

Change in Haemoglobin Concentration from Baseline to Week 20 (Full Analysis Set), after 12-week double-blind phase and then 8 weeks of open-label ST10 treatment.

End point type	Secondary

End point timeframe:

Change in Haemoglobin Concentration from Baseline to Week 20 (Full Analysis Set), after 12-week double-blind phase and then 8 weeks of open-label ST10 treatment.

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: g/dL				
arithmetic mean (standard deviation)	2.45 (± 1.213)	1.46 (± 1.056)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Haemoglobin Concentration from Baseline to Week 24 (Full Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 24 (Full Analysis Set)

End point description:

Change in Haemoglobin Concentration from Baseline to Week 24 (Full Analysis Set), after 12-week double-blind phase and then 12 weeks of open-label ST10 treatment.

End point type	Secondary

End point timeframe:

Change in Haemoglobin Concentration from Baseline to Week 24 (Full Analysis Set), after 12-week double-blind phase and then 12 weeks of open-label ST10 treatment.

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	41		
Units: g/dL				
arithmetic mean (standard deviation)	2.68 (± 1.127)	1.87 (± 1.195)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Haemoglobin Concentration from Baseline to Week 36 (Full Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 36 (Full Analysis Set)

End point description:

Change in Haemoglobin Concentration from Baseline to Week 36 (Full Analysis Set), after 12-week double-blind phase and then 24 weeks of open-label ST10 treatment.

End point type	Secondary

End point timeframe:

Change in Haemoglobin Concentration from Baseline to Week 36 (Full Analysis Set), after 12-week double-blind phase and then 24 weeks of open-label ST10 treatment.

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	36		
Units: g/dL				
arithmetic mean (standard deviation)	2.85 (± 1.227)	2.17 (± 1.048)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Haemoglobin Concentration from Baseline to Week 48 (Full Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 48 (Full Analysis Set)

End point description:

Change in Haemoglobin Concentration from Baseline to Week 48 (Full Analysis Set), after 12-week double-blind phase and then 36 weeks of open-label ST10 treatment.

End point type	Secondary

End point timeframe:

Change in Haemoglobin Concentration from Baseline to Week 48 (Full Analysis Set), after 12-week double-blind phase and then 36 weeks of open-label ST10 treatment.

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	47		
Units: g/dL				
arithmetic mean (standard deviation)	3.09 (± 1.339)	2 (± 1.191)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Haemoglobin Concentration from Baseline to Week 64 (Full Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 64 (Full Analysis Set)

End point description:

Change in Haemoglobin Concentration from Baseline to Week 64 (Full Analysis Set), after 12-week double-blind phase and then 52 weeks of open-label ST10 treatment.

End point type	Secondary

End point timeframe:

Change in Haemoglobin Concentration from Baseline to Week 64 (Full Analysis Set), after 12-week double-blind phase and then 52 weeks of open-label ST10 treatment.

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: g/dL				
arithmetic mean (standard deviation)	3.07 (± 1.457)	2.19 (± 1.605)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Haemoglobin Concentration from Baseline to Week 64 EOS (Full Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 64 EOS (Full Analysis Set)

End point description:

Change in Haemoglobin Concentration from Baseline to Week 64 EOS (Full Analysis Set) - Week 64 was re-categorised as Week 64 EOS for those subjects who withdrew from the study early and the 'Week 64' visit was outside the visit window of 64 weeks ± 2 days

End point type	Secondary

End point timeframe:

Change in Haemoglobin Concentration from Baseline to Week 64 EOS (Full Analysis Set) - Week 64 was re-categorised as Week 64 EOS for those subjects who withdrew from the study early and the 'Week 64' visit was outside the visit window of 64 weeks ± 2 days

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	17		
Units: g/dL				
arithmetic mean (standard deviation)	1.32 (± 1.713)	0.52 (± 1.417)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 16 (Full Analysis Set)

End point title	Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 16 (Full Analysis Set)

End point description:

Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 16 (Full Analysis Set), after 12-week double-blind phase and first 4 weeks of open-label ST10 treatment

End point type	Secondary

End point timeframe:

Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 16 (Full Analysis Set), after 12-week double-blind phase and first 4 weeks of open-label ST10 treatment

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: Number of subjects				
Yes	36	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 36 (Full Analysis Set)

End point title	Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 36 (Full Analysis Set)

End point description:

Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 36 (Full Analysis Set), after 12-week double-blind phase and 24 weeks of open-label ST10 treatment.

End point type	Secondary

End point timeframe:

Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 36 (Full Analysis Set), after 12-week double-blind phase and 24 weeks of open-label ST10 treatment.

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	36		
Units: Number of subjects				
Yes	35	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 64 (Full Analysis Set)

End point title	Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 64 (Full Analysis Set)

End point description:

Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks of open-label ST10 treatment

End point type	Secondary

End point timeframe:

Proportion of subjects that achieved Haemoglobin Concentration within normal range at Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks of open-label ST10 treatment

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: Number of subjects				
Yes	31	30		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Haemoglobin Concentration from Baseline to Week 12 (Per Protocol Analysis Set)

End point title	Change in Haemoglobin Concentration from Baseline to Week 12 (Per Protocol Analysis Set)

End point description:

ANCOVA sensitivity analysis of the Primary efficacy endpoint analysis on the FAS.

End point type	Other pre-specified

End point timeframe:

Change in Hb from Baseline to Week 12 - double-blind phase, per protocol analysis set (PPAS)

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: g/dL				
least squares mean (standard error)	2.23 (± 0.13)	0.05 (± 0.13)		

Statistical analyses

Statistical analysis title	ANCOVA - Change in Hb from Baseline to Wk12 - PPAS
Comparison groups	ST10 v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.18
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	1.87
Variability estimate	Standard error of the mean
Dispersion value	0.17

Other pre-specified: Change in Haemoglobin Concentration from Baseline to Week 12 (Full Analysis Set LOCF)

End point title	Change in Haemoglobin Concentration from Baseline to Week 12 (Full Analysis Set LOCF)

End point description:

ANCOVA sensitivity analysis of the Primary efficacy endpoint using Full Analysis Set - LOCF

End point type	Other pre-specified

End point timeframe:

Change in Hb from Baseline to Week 12 - double-blind phase, FAS LOCF

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	64		
Units: g/dL				
least squares mean (standard error)	2.11 (± 0.12)	-0.03 (± 0.12)		

Statistical analyses

Statistical analysis title	ANCOVA - Change in Hb from Baseline to Wk12 - LOCF
Comparison groups	ST10 v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.15
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	1.82
Variability estimate	Standard error of the mean
Dispersion value	0.16

Other pre-specified: Change in serum Ferritin concentration from Baseline to Week 12 (Full Analysis Set)

End point title	Change in serum Ferritin concentration from Baseline to Week 12 (Full Analysis Set)

End point description:

Change in serum Ferritin concentration from Baseline to Week 12 (Full Analysis Set), after 12-week double-blind phase

End point type	Other pre-specified

End point timeframe:

Change in serum Ferritin concentration from Baseline to Week 12 (Full Analysis Set), after 12-week double-blind phase

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	53		
Units: µg/L				
arithmetic mean (standard deviation)	17.3 (± 28.3)	1.2 (± 7.85)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in serum TSAT% from Baseline to Week 12 (Full Analysis Set)

End point title	Change in serum TSAT% from Baseline to Week 12 (Full Analysis Set)

End point description:

Change in serum TSAT% from Baseline to Week 12 (Full Analysis Set), after 12-week double-blind phase

End point type	Other pre-specified

End point timeframe:

Change in serum TSAT% from Baseline to Week 12 (Full Analysis Set), after 12-week double-blind phase

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	52		
Units: percent				
arithmetic mean (standard deviation)	18 (± 20.17)	-0.4 (± 7.82)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in serum Ferritin concentration from Baseline to Week 64 (Full Analysis Set)

End point title	Change in serum Ferritin concentration from Baseline to Week 64 (Full Analysis Set)

End point description:

Change in serum Ferritin concentration from Baseline to Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks open-label ST10 treatment

End point type	Other pre-specified

End point timeframe:

Change in serum Ferritin concentration from Baseline to Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks open-label ST10 treatment

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: µg/L				

arithmetic mean (standard deviation)	60.4 (± 93.35)	36.6 (± 46.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in serum TSAT% from Baseline to Week 64 (Full Analysis Set)

End point title	Change in serum TSAT% from Baseline to Week 64 (Full Analysis Set)

End point description:

Change in serum TSAT% from Baseline to Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks open-label ST10 treatment

End point type	Other pre-specified

End point timeframe:

Change in serum TSAT% from Baseline to Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks open-label ST10 treatment

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: percent				
arithmetic mean (standard deviation)	18.8 (± 12.46)	17.7 (± 16.2)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Irritable Bowel Disease Questionnaire (IBDQ) score at Week 12 (Full Analysis Set)

End point title	Irritable Bowel Disease Questionnaire (IBDQ) score at Week 12 (Full Analysis Set)

End point description:

Irritable Bowel Disease Questionnaire (IBDQ) score at Week 12 (Full Analysis Set), end of double-blind phase

End point type	Other pre-specified

End point timeframe:

Irritable Bowel Disease Questionnaire (IBDQ) score at Week 12 (Full Analysis Set), end of double-blind phase

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: unit(s)				
arithmetic mean (standard deviation)	178.3 (± 32.36)	176.3 (± 31.5)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Irritable Bowel Disease Questionnaire (IBDQ) score at Week 64 (Full Analysis Set)

End point title	Irritable Bowel Disease Questionnaire (IBDQ) score at Week 64 (Full Analysis Set)

End point description:

Irritable Bowel Disease Questionnaire (IBDQ) score at Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks of open-label ST10 treatment

End point type	Other pre-specified

End point timeframe:

Irritable Bowel Disease Questionnaire (IBDQ) score at Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks of open-label ST10 treatment

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	36		
Units: unit(s)				
arithmetic mean (standard deviation)	180.7 (± 30.14)	177.2 (± 36.97)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in Crohn’s Disease Activity Index (CDAI) score at Week 12 (Full Analysis Set)

End point title	Change from baseline in Crohn’s Disease Activity Index (CDAI) score at Week 12 (Full Analysis Set)

End point description:

Change from baseline in Crohn’s Disease Activity Index (CDAI) score at Week 12 (Full Analysis Set), end of double-blind phase (in subjects with CD)

End point type	Other pre-specified

End point timeframe:

Change from baseline in Crohn’s Disease Activity Index (CDAI) score at Week 12 (Full Analysis Set), end of double-blind phase (in subjects with CD)

End point values	ST10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: unit(s)				
median (full range (min-max))	-24 (-151 to 49)	12.5 (-90 to 124)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in Crohn’s Disease Activity Index (CDAI) score at Week 64 (Full Analysis Set)

End point title	Change from baseline in Crohn’s Disease Activity Index (CDAI) score at Week 64 (Full Analysis Set)

End point description:

Change from baseline in Crohn’s Disease Activity Index (CDAI) score at Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks open-label ST10 treatment (in subjects with CD)

End point type	Other pre-specified

End point timeframe:

Change from baseline in Crohn’s Disease Activity Index (CDAI) score at Week 64 (Full Analysis Set), after 12-week double-blind phase and 52 weeks open-label ST10 treatment (in subjects with CD)

End point values	ST10 - open-label continuation from active arm in double-blind	Placebo switch to open-label extension ST10 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: unit(s)				
median (full range (min-max))	-16.6 (-112 to 54)	-1 (-99 to 58)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were solicited after informed consent and until 4 weeks after the last dose of study drug (at study completion or early termination).

Adverse event reporting additional description:

Subjects were expected to volunteer information about AEs they experienced. The Investigator/designee also questioned the subject at each visit about AEs and recorded these as well as all other AEs apparent. AEs/SAEs were monitored until they were resolved or determined to be due to a subject's on-going condition or inter-current illness.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	ST10 - Safety Set, Double-blind Phase

Reporting group description:

Adverse events reported in the double-blind phase active treatment arm with ST10 (Ferric Maltol).

Reporting group title	Placebo - Safety Set, Double-blind Phase

Reporting group description:

Adverse events reported in the double-blind phase placebo treatment arm.

Reporting group title	ST10 continuation - Safety Set, Open-label Phase

Reporting group description:

Adverse events reported in the open-label extension phase for continuation of active treatment with ST10 (Ferric Maltol) from the double-blind phase active treatment arm.

Reporting group title	Placebo switch to ST10 treatment-Safety Set, Open-label Phase

Reporting group description:

Adverse events reported in the open-label extension phase from those subjects continuing treatment from the double-blind placebo arm; subjects commenced ST10 open-label treatment after completion of the double-blind phase at the Week 12 visit.

Serious adverse events	ST10 - Safety Set, Double-blind Phase	Placebo - Safety Set, Double-blind Phase	ST10 continuation - Safety Set, Open-label Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	8 / 50 (16.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cholesteatoma removal			

subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo switch to ST10 treatment-Safety Set, Open-label Phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 47 (4.26%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cholesteatoma removal			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Hernia			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal abscess			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	ST10 - Safety Set, Double-blind Phase	Placebo - Safety Set, Double-blind Phase	ST10 continuation - Safety Set, Open-label Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 64 (60.94%)	46 / 64 (71.88%)	40 / 50 (80.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 64 (3.13%)	4 / 64 (6.25%)	1 / 50 (2.00%)
occurrences (all)	2	4	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	1 / 50 (2.00%)
occurrences (all)	1	2	1
Fatigue			
subjects affected / exposed	2 / 64 (3.13%)	3 / 64 (4.69%)	0 / 50 (0.00%)
occurrences (all)	2	3	0
Gastrooesophageal reflux disease			

subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences (all)	2	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	2 / 50 (4.00%)
occurrences (all)	0	2	2
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	1 / 50 (2.00%)
occurrences (all)	1	2	1
Rectal haemorrhage			
subjects affected / exposed	3 / 64 (4.69%)	1 / 64 (1.56%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
Nausea			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Haematochezia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	1 / 50 (2.00%)
occurrences (all)	1	1	1
Flatulence			
subjects affected / exposed	4 / 64 (6.25%)	0 / 64 (0.00%)	3 / 50 (6.00%)
occurrences (all)	4	0	3
Abdominal discomfort			
subjects affected / exposed	3 / 64 (4.69%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences (all)	3	0	0
Abdominal distension			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 64 (1.56%)	3 / 64 (4.69%)	1 / 50 (2.00%)
occurrences (all)	1	3	1
Abdominal pain lower			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			

subjects affected / exposed	7 / 64 (10.94%)	5 / 64 (7.81%)	2 / 50 (4.00%)
occurrences (all)	8	6	2
Colitis ulcerative			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	4 / 50 (8.00%)
occurrences (all)	1	2	4
Constipation			
subjects affected / exposed	5 / 64 (7.81%)	1 / 64 (1.56%)	2 / 50 (4.00%)
occurrences (all)	5	1	2
Crohn's disease			
subjects affected / exposed	0 / 64 (0.00%)	4 / 64 (6.25%)	2 / 50 (4.00%)
occurrences (all)	0	4	2
Diarrhoea			
subjects affected / exposed	5 / 64 (7.81%)	4 / 64 (6.25%)	4 / 50 (8.00%)
occurrences (all)	6	5	4
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 64 (0.00%)	3 / 64 (4.69%)	0 / 50 (0.00%)
occurrences (all)	0	3	0
Cough			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Arthralgia			

subjects affected / exposed	3 / 64 (4.69%)	0 / 64 (0.00%)	4 / 50 (8.00%)
occurrences (all)	3	0	4
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	0 / 50 (0.00%)
occurrences (all)	1	2	0
Sinusitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	4 / 64 (6.25%)	8 / 64 (12.50%)	12 / 50 (24.00%)
occurrences (all)	4	8	14
Influenza			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	1 / 50 (2.00%)
occurrences (all)	2	0	1
Gastroenteritis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	2 / 50 (4.00%)
occurrences (all)	0	1	2

Non-serious adverse events	Placebo switch to ST10 treatment-Safety Set, Open-label Phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 47 (74.47%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	3		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Rectal haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Haematochezia			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Abdominal discomfort			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	4		
Abdominal pain lower			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Abdominal pain			

subjects affected / exposed	7 / 47 (14.89%)		
occurrences (all)	8		
Colitis ulcerative			
subjects affected / exposed	6 / 47 (12.77%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Crohn's disease			
subjects affected / exposed	5 / 47 (10.64%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	6 / 47 (12.77%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Arthralgia			

subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	8 / 47 (17.02%)		
occurrences (all)	8		
Influenza			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2012	Global Amendment 1 Changes to study endpoints/statistics: Given the design change to add the open-label extension, additional endpoints and statistical methods were defined in order to assess the long-term safety and efficacy of ST10 in this study. A number of exploratory endpoints were also pre-defined. Details on long-term and exploratory endpoints/methods were provided in the final Statistical Analysis Plan (SAP) for the study. Within the study protocol, sections that described study endpoints and statistical methods were condensed to focus on the evaluation of primary efficacy and safety, which occurred following the Randomised Phase of the study (i.e., the first 12 weeks). Endpoints and methods for the primary and secondary efficacy endpoints and safety endpoints for the pivotal part of the study were unchanged from the original protocol. Additional text relating to sensitivity analysis of secondary endpoints was added.
17 January 2012	Global Amendment 1 Changes to inclusion/exclusion criteria: Several changes to Inclusion and Exclusion Criteria were made, including definition of anaemia (Section 7.5.1); removal of mean corpuscular volume (MCV) criteria for study entry (Section 7.5.1); exclusion on vitamin B12 or folic acid deficiency and associated treatments (Section 7.5.2) and creatinine exclusion criterion 10 (Section 7.5.2). Other sections within the study protocol that were affected by the change to the definition of anaemia included: Section 2, Synopsis, Diagnosis/Inclusion Criteria; Section 5.4.2 Population; Section 7.1 Study Description. Other sections within the study protocol that were affected by the change to MCV criteria included: Section 2, Synopsis, Diagnosis/Inclusion Criteria. Other sections within the study protocol that were affected by the changes to folic acid and vitamin B12 deficiencies include: Section 2, Synopsis, Diagnosis/Exclusion Criteria; Section 7.4.3 Prohibited Concomitant Medication at baseline and during the study; Section 10.2.12 Clinical laboratory. Other sections within the study protocol that were affected by creatinine exclusion changes included: Section 2, Synopsis, Diagnosis/Exclusion Criteria. In summary, these changes were to improve consistency with clinical practice and/or central laboratory results reporting, and to assist with subject recruitment

17 January 2012	Global Amendment 1 Changes to study objectives: Given the design change to add an open-label extension, the secondary study objectives were updated accordingly, to include an examination of longer-term safety and efficacy of ST10 over a treatment duration of up to 64 weeks. Section 6.2 Secondary objectives was thus revised to: To evaluate the safety and tolerability of ST10 in subjects with IDA and CD, where OFP have failed or cannot be used, over a treatment duration of up to 64 weeks. To evaluate long-term efficacy of ST10 in subjects with IDA and UC, where OFP have failed or cannot be used, over a treatment duration of up to 64 weeks.
17 January 2012	Global Amendment 1 Miscellaneous revisions: • Minor administrative changes to wording were made throughout the document in order to improve internal consistency and clarity • The number of study centres was increased to 30-40 • Specific timing for the conduct of this study was removed from the protocol, as this information is subject to change depending upon rates of enrolment • References to the use of a Data and Safety Monitoring Board during this study were removed. Subject safety was monitored during the conduct of the study by the sponsor or an appropriate designee • Transferrin saturation was removed from efficacy variables described in Section 7.3.1 and efficacy assessments in Section 10.1 for clarity. Transferrin saturation was not a component of primary efficacy or safety analyses for this study • References to the Health Resource Utilization Survey and associated analyses were removed. This assessment was to be examined in a separate pharmacoeconomic substudy to the AEGIS 1 and AEGIS 2 studies • The safety reporting contact information provided in Section 10.2.5 was updated • The scope of information collected at baseline for female subjects was revised. The day, month, and year of the last 3 menstrual cycles preceding randomisation was no longer required • In Section 9.2.1, under treatment procedures for the Screening Visit, a sub-bullet was added under instructions for documenting concomitant medications.
17 January 2012	Global Amendment 1 Changes to study design/visit schedule: The study design of ST10-01-302 was modified to include a 52 week open-label extension to further evaluate the safety and efficacy of ST10 in all randomised subjects. Study visits during the first 12 weeks of the pivotal study were unchanged from the original protocol; study procedures during the first 12 weeks were also largely unchanged, with the exception of several additional procedures added to the Week 12 visit, to facilitate the transition of subjects from the randomised phase to the open-label phase of the study. Additional visits and instructions for the open-label period were added. A separate study was originally planned to gather long-term safety data on the use of ST10 in subjects with IBD; for logistical reasons, it was decided to incorporate the long-term extension into the existing study protocol. This amendment was not ethically approved in AU; therefore the open-label extension was only available to study subjects in UK, DE and HU.

17 January 2012	Global Amendment 1 Changes to prohibited medications: Text was revised or added to the instructions on the use of vitamin B12 and folic acid injections or infusions, which were now permitted during study participation. Changes to Inclusion and Exclusion Criteria describe additional rationale regarding the use of these treatments. Text was added to the instructions on the use of immunosuppressants for clarity.
17 January 2012	Global Amendment 1 Changes to subject discontinuation criteria: The concentration of Hb reported in mmol/L that will result in discontinuation of study treatment was reduced to one decimal place to be consistent with values reported out by the central laboratory. It was clarified that CDAI scores of 320 or greater will result in discontinuation of study drug. In addition, due to the addition of the open-label period of the study, study requirements for subjects who discontinue treatment prior to or after Week 12 were delineated and defined. Protocol Section 7.4.5 Individual discontinuation criteria was therefore amended as follows: Treatment will be stopped for any of the following reasons: '…Hb ≤9.0 g/dL (5.6 mmol/L)…' If treatment is discontinued during the first 12 weeks of the study, the subject must be followed for safety for the duration of the Randomised Treatment Period (with the exception of subjects who withdraw consent). Subjects who prematurely discontinue study treatment after Week 12 must return to clinic for an End of Study Visit at the time of discontinuation. Procedures performed will be the same as those for the End of Study Visit at Week 64 for subjects who complete the study.
19 March 2012	Global Amendment 2 Changes to subject discontinuation criteria Section 7.4.5: The lower limit of Hb concentration for treatment continuation was reduced to reflect the reduction in the lower limit for study inclusion from Hb ≥10 to Hb ≥ 9.5 g/dL (Inclusion criterion 4b). A 1 g/dL difference between the lowest concentration of Hb for study entry (≥9.5 g/dL) and mandated study exit (≤ 8.5 g/dL) was maintained to ensure that natural fluctuations in Hb concentration due to either plasma volume changes (dilution effect) or through inherent Hb sample measurement variation did not result in inappropriate study discontinuation. Haematologists and gastroenterologists confirmed that given the controlled nature of the clinical study, the clearly defined limits for study participation and the regular assessments of Hb, the change did not result in a risk to subject safety.

19 March 2012	Global Amendment 2 Changes to exclusion criteria Section 7.4.2: Exclusion Criterion 1 originally provided examples of potential causes of untreated or untreatable severe malabsorption syndromes. However, feedback from AEGIS Investigators indicated that provision of examples created confusion and uncertainty as these clinical examples were not exclusion criteria in their own right. As such, the examples were removed. Exclusion Criterion 10: this exclusion criterion was originally included to exclude subjects with concomitant inflammatory disease due to the potential association of inflammatory disease with anaemia of chronic disease. However, discussion with rheumatologists and haematologists has confirmed that Inclusion Criterion 4c that mandates a ferritin <30 µg/mL at screening will exclude subjects with anaemia of chronic disease. Ferritin <30 µg/mL has a positive predictive value for IDA of 92 to 98% (Weiss 2005). As such, this exclusion criterion was removed. Changes to prohibited concomitant medication Section 7.4.3: following discussion and confirmation with AEGIS Investigators and haematologists, the length of time a subject must be stable on parenteral vitamin B12 was decreased from 6 months to 3 months. Three months of stable parenteral vitamin B12 therapy in the presence of a screening serum vitamin B12 within normal limits effectively rules out vitamin B12 deficiency as well as anaemia secondary to that condition. As such the requirement for 6 months of stable therapy prior to randomisation was reduced to 3 months as the former was considered excessive and beyond the limits of the study. In addition, the wording was revised to increase understanding and reduce the potential for confusion.
19 March 2012	Global Amendment 2 Changes to inclusion criteria Section 7.4.1: The lower limit Hb level for inclusion was lowered from 10.0 g/dL to 9.5 g/dL following discussions with AEGIS Investigators as well as clinicians who routinely treat iron deficiency anaemia in subjects with Crohn’s disease. The firm consensus was that within the controlled environment of a clinical study, oral iron is appropriate in this subject population with Hb of 9.5 g/dL and above, provided that the subject has quiescent disease at study entry. Inclusion Criterion 4a, requiring a CDAI score of <220 at the Randomisation Visit, ensures exclusion of subjects with active disease. In addition, the protocol mandated treatment discontinuation for subjects who have an CDAI score ≥320 at any time during the study. For randomisation, subjects must have had ferritin < 30 µg/L, a normal serum vitamin B12 level and a normal serum folate level at screening. A serum ferritin <30 µg/L, in the absence of vitamin B12 and folate deficiency, is the strongest indicator of IDA in ulcerative colitis with a positive predictive value of 92 to 98% (Weiss 2005). The requirement for TSAT < 16% at screening was therefore considered superfluous. Furthermore TSAT may be reduced in both IDA and anaemia of chronic disease and as such does not confirm the diagnosis of IDA. There is also significant within-person diurnal variation in TSAT measurements, which confounds the result. As such a ferritin level of <30 µg/L was determined to be sufficient to define a study population with iron deficiency anaemia.

27 September 2012	Global Amendment 3 Miscellaneous revisions Minor administrative changes to wording were made throughout the document in order to improve internal consistency and clarity. • The number of study centres was increased to 30 to 50 • Study time periods were clarified with the inclusion of the following definition: For the purposes of this protocol, the following conventions are used: o 1 week equals 7 days o 4 weeks equal 28 days o 12 weeks equal 84 days o 52 weeks equal 364 days.
27 September 2012	Global Amendment 3 Changes to exclusion criteria Section 7.4.2: The AEGIS 1 and AEGIS 2 protocols were designed to exclude subjects with folate deficiency to ensure a study population with iron deficiency anaemia and without another significant haematological confounder. This scientific rationale was discussed with, and accepted as appropriate, by EU competent authorities during scientific advice meetings. The original AEGIS 1 and AEGIS 2 protocols, approved by the competent authorities and by the Ethics Committees, simply referred to 'folate deficiency' as an exclusion criterion to study entry. However, following discussions with study Investigators, the protocol was amended in an attempt to clarify the definition of folate deficiency by referring to a definition used by the central laboratory contracted for the study. It became clear that whilst trying to clarify the definition an error was incorporated into the revised protocol as follows: In redefining the exclusion criteria as 'a subject with a folate level below the lower limit of normal' this moved away from the previous definition (folate deficiency) and critically, this significantly and unnecessarily raised the lower level of serum folate value required by a subject to enter the study. The result of this definition error was a 30% screen failure rate due to folate levels lower than the criterion currently required for study entry. However the vast majority of these screen failure subjects do NOT have a serum folate level that constitutes a defined folate deficiency and therefore would not introduce a significant confounding haematological factor. The Sponsor addressed this error by a further amendment to the protocol to ensure that only subjects with a folate reading below the central laboratory's reference value for folate deficiency were excluded from the study, taking this criterion back to the original protocol, whilst providing the defined value sought by Investigators.

25 July 2013	Global Amendment 5 Changes to the analysis of the study: The protocol was amended to change the primary analysis in ST10-01-301/302 (AEGIS 1 and AEGIS 2) from the non-parametric Wilcoxon-Mann Whitney analysis to an ANCOVA. Missing data was to be imputed using multiple imputation. Sensitivity analyses was also to be performed for the primary endpoint, including an analysis using LOCF and complete case analysis using ANCOVA and a MMRM. The protocol was also amended to allow analysis of the study data from ST10-01-301 (AEGIS 1) and ST10-01-302 (AEGIS 2) as a single integrated data set of target size 120. Rationale for Change in primary analysis methodology No evidence was found in the literature to suggest the distribution of this endpoint was non-normal in similar sized studies. Parametric approaches have also been used in much smaller sized studies. Even if the primary endpoint was non-normal, given that each study has greater than 100 subjects, the central limit theorem should apply, i.e., the sample means should follow the normal distribution even if the endpoint is not normally distributed and the parametric approach to analysis should still be appropriate. This also held true for the proposed integrated analysis. Furthermore, ANCOVA analysis is a more powerful method then the Wilcoxon-Mann Whitney analysis. Finally the use of ANCOVA to analyse the primary endpoint was recommended by the national competent authorities consulted (BfARM and MHRA, Scientific Advice meetings held in Q1 2013).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25545376

http://www.ncbi.nlm.nih.gov/pubmed/27237709